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A CRUMBLING INFRASTRUCTURE: QUESTIONING THE STABILITY OF ACCESS TO ANTIBIOTICS NEW AND OLD

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Erin L. PATERSON

Sciences Humaines & Sociales — Perspectives Européennes

A CRUMBLING INFRASTRUCTURE: QUESTIONING THE STABILITY OF ACCESS TO ANTIBIOTICS NEW AND OLD

Résume en Français

Grâce à leur capacité à traiter une série d'affections allant des infections respiratoires courantes aux soins post-opératoires, les antibiotiques peuvent être considérés comme une « infrastructure » qui contribue au maintien du bien-être de la société. Bien que cette infrastructure comporte de nombreux éléments qui lui permettent de fonctionner, cette thèse n'en évalue que trois : la composante antibactérienne de la liste des médicaments essentiels de l'OMS (qui sert de moyen d'accès à des antibiotiques efficaces), la filière des antibiotiques en tant que facette de la création de nouveaux antibiotiques et de leur distribution éventuelle, et enfin la chaîne d'approvisionnement en antibiotiques en tant que méthode distincte garantissant que la distribution a lieu. Cette thèse analyse la manière dont ces trois éléments font partie de cette infrastructure, leur évolution historique depuis les années 1980 et leur état de fonctionnement actuel à l'horizon 2023.

Mots-clés : histoire de la médecine, antibiotiques, infrastructure, histoire contemporaine, produits pharmaceutiques

Abstract in English

Thanks to the ability of antibiotics in addressing a range of ailments from common respiratory infections through post-operative care, antibiotics may be considered as an 'infrastructure' that contributes to holding up societal well-being. Although there are many components to this infrastructure that enable it to function, this dissertation assesses only three: the WHO's antibacterial component of their Essential Medicines List (which serves as an access vehicle for effective antibiotics, the antibiotic pipeline as a facet of new antibiotic creation and eventual distribution, and finally: the antibiotic supply chain as a distinct method of ensuring that distribution take place. This dissertation analyzes how these three components serve as parts of this infrastructure, how they have historically evolved since the 1980s, and what their current state of functioning is as of 2023.

Key words: history of medicine, antibiotics, infrastructure, contemporary history, pharmaceuticals

This dissertation is dedicated to me. For setting out to reach a goal, and achieving it even if it seemed nearly impossible.

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This dissertation contains many appendices. As I was unable to depend on external archival support, I needed to generate my own datasets and organizational metrics. To that end, I have included the most comprehensive of my compilations within a series of annexes to assist in ease of reading and understanding. The appendices in full include:

Appendix 1: The antibiotics section of the collected 1977-2021 World Health Organization Essential Medicines List (EML), set side by side for easy visual comparison and reflection.

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Appendix 6: Preliminary Analysis of New Zealand Supply Chain Frailty

Appendix 7: List of interviews conducted in chronological order.

Abstract

Thanks to the ability of antibiotics in addressing a range of ailments from common respiratory infections through post-operative care, antibiotics may be considered as an 'infrastructure' that contributes to holding up societal well-being. For this to be the case, antibiotics themselves must be supported by their own infrastructure. Although there are many components that would be able to support antibiotics in this way, this dissertation assesses only three: the WHO's antibacterial component of their Essential Medicines List (which serves as an access vehicle for access to effective antibiotics), the antibiotic pipeline as a facet of new antibiotic creation and eventual distribution, and finally: the antibiotic supply chain as a distinct method of ensuring that distribution take place. This dissertation analyzes how these three areas act as parts of the infrastructure that allow antibiotics to serve as a key component of global health care, how they have historically evolved since the 1980s, and what their current state of functioning is as of 2023. It then suggests that these support pillars, are struggling, and have been in decline for decades. Although increased attention since 2016 has been placed on the development of new antibiotics in the "dry antibiotic pipeline," addressing only this section of the infrastructure will likely not solve the overall problems facing antibiotic access and distribution. Wholistic attention to the different ways that antibiotics are used, regulated, and transmitted must be taken into account. By framing antibiotics and the structures that allow them to function within a metaphor of an overarching infrastructure, this dissertation asks whether that infrastructure is stable, and where historically the need for maintenance has become more distinct.

Acronyms and Abbreviations

AB	Antibiotic
AFSSAPS	Anti-Infectieux de l'agence française de sécurité sanitaire des produits de santé
AMR	Antimicrobial Resistance
ASPR	Administration for Strategic Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BI	Bamako Initiative
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
GARDP	Global Antibiotic Research & Development Partnership
CDC	Center for Disease Control and Prevention
CEDR	Center for Drug Evaluation and Research
CFP	Call for Projects
CIA	Critically Important Antibiotics
CIRR	Committee on Industrial Research Relations
DHHS	United States Department of Health and Human Services
DNDi	Drugs for Neglected Diseases Initiative
Dry AP	Dry Antibiotic Pipeline
EFPIA	European Federation of Pharmaceutical Industries and Associates
EML	Essential Medicines List
EUFEPS	European Federation for Pharmaceutical Sciences
FDA	(United States) Food and Drug Administration
FDC	Fixed Dose Combination
GARDP	Global Antibiotic Research & Development Partnership
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
HIC	High-Income Countries
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IHI	Innovative Health Initiative
IMF	International Monetary Fund
IMI	Innovative Medicines Initiative
IMI1	Specifically, the first Innovative Medicines Initiative (Launched in 2008)
IMI2	Innovative Medicines Initiative 2 (The second initiative launched in 2013)
IPM	International Partnership for Microbicides

J&J	Johnson & Johnson
KEI	Knowledge Ecology International
LIC	Low-Income Countries
LMIC	Low-Middle-Income Countries
MDRTB	Multiple-Drug Resistant Tuberculosis
MER	Market Entry Rewards
MIC	Middle-Income Countries
MSF	Médecins Sans Frontières (Doctors Without Borders)
ND4BB	New Drugs for Bad Bugs
NIAD	National Institute of Allergy and infectious Diseases
NIH	National Institute of Health
NME	New Molecular Entity
ODA	Orphan Drug Act
PDP	Product Development Partnership
PDUFA	Prescription Drug User Fee Act
PID	Pelvic Inflammatory Disease
PMR	Priority Medicines for Europe and the world (Report)
PPP	Public Private Partnership
SAP	Structural Adjustment Policies
SME	Small and Medium-sized Enterprise
SPHC	Selective Primary Health Care
SRA	Strategic Research Agenda
STI	Sexually Transmitted Infection
TB	Tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
TRL	Technology Readiness Level
UNICEF	United Nations International Children's Emergency Fund
WHA	World Health Assembly
WHO	World Health Organization
XDRTB	Extensively Drug Resistant Tuberculosis (i.e.: no efficacious drugs available)

General Introduction

"Antibiotics are a crucial part of modern medicine, but they have become victims of their own success. As a result of over-use and misuse of antibiotics by both doctors and patients, antibiotic resistance is a now a gravely serious global health problem." – Dr. Bernhard Schwartländer, WHO Representative in China.[1]

"It was very disturbing to see how few generic medicines actually had any access strategy associated with them…These medicines weren't getting into these low- and middle-income countries, where there was a very dire need."– Fatema Rafiqi, PhD. Access to Medicine Foundation research program manager.[2]

"Where you live may dictate the antibiotics you have access to, which may mean that the treatment you receive might not be the best indicated or available for your condition…This fuels resistance, in turn increasing morbidity and mortality." –Francesca Chiara, PhD, MPH, Antimicrobial Stewardship Program Director.[3]

Antibiotics are a modern health marvel whose impact and importance can scarce be denied. They are used in almost every part of the health care system, ensuring that everything from food poisoning to cancer or amputations can be treated in a way that ensures greater health outcomes. So prevalent is their use, and their impact on the quality of health worldwide, that in 2019 medical anthropologist Clare Chandler published an article in Palgrave Communications describing antibiotics as a form of systemic and structural infrastructure that braces and supports society.[4] As Chandler writes, "whilst retaining their mystique and desire as powerful substances… antimicrobials [are] seen [as] essential to human life with access to these medicines enshrined as primary health care in the declaration signed by 134 countries from around the world at Alma Ata in 1978."[5] Without these drugs, primary health care as a whole is at risk.

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[1] World Health Organization, "Action Needed Now to Prevent a Post-Antibiotic Future: WHO," News Release (blog), November 16, 2015, https://www.who.int/hongkongchina/news/detail/16-11-2015-action-needed-now-to-prevent-a-post-antibiotic-future-who.
[2] Chris Dall, "For Poorer Countries, Lack of Access to Antibiotics Worsens Resistance," News, *CIDRAP*, June 9, 2022, https://www.cidrap.umn.edu/poorer-countries-lack-access-antibiotics-worsens-resistance.
[3] Dall, "For Poorer Countries, Lack of Access to Antibiotics Worsens Resistance."
[4] Clare I. R. Chandler, "Current Accounts of Antimicrobial Resistance: Stabilisation, Individualisation and Antibiotics as Infrastructure," *Palgrave Communications* 5, no. 1 (May 21, 2019): 1-13. https://doi.org/10.1057/s41599-019-0263-4.
[5] Chandler, "Current Accounts of Antimicrobial Resistance," 9.

Infrastructure is a term used to denote anything that supports the physical and organizational abilities of a society or enterprise to flourish. It is predominantly used to describe practical physical constructs such as buildings, roads, or oil pipeline, but as Chandler has shown: the term can also be used as an analytical or metaphorical tool to describe intangible support systems as well. However, in order for antibiotics to be an infrastructure in of themselves, there is also an infrastructure that allows them to exist in the first place. Something supports antibiotics in their effort to *be* an infrastructure. This something, is what sociologist Susan Leigh Star describes as a nesting-doll of infrastructures, or an "embeddedness" where multiple infrastructures interweave and intersect in order to support multiple outputs at the same time.[6] This dissertation examines the infrastructure that allows antibiotics to serve their role as a health care infrastructure and analyses the ways in which these different support systems interact.

Access to antibiotics, thus becomes a key component of this discussion. If an infrastructure is required to enable antibiotics to serve as the support system upholding global health care, then that infrastructure must ensure those antibiotics are accessible to those in need. If patients cannot access the drugs (either for availability *or* affordability reasons), then antibiotics will fail to support the health care system, and the infrastructure maintaining antibiotics in that space has failed. For some individuals, this is a present-day reality. And for others, it is a future that is nearing at an accelerated rate.

Due to antimicrobial resistance, there has been an increased discussion about a potential post-antibiotic era where antibiotics cease to function.[7] This fear mongering, may

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[6] Susan Leigh Star, "The Ethnography of Infrastructure," *American Behavioral Scientist* 43, no. 3 (1999): 381-82. https://doi.org/10.1177/00027649921955326.

[7] For extended commentary on the potential for a post antibiotic era, please review:
Kristofer Hansson and Adam Brenthel, "Imagining a Post-Antibiotic Era: A Cultural Analysis of Crisis and Antibiotic Resistance," *Medical Humanities* 48, no. 3 (2022): 381–88. https://doi.org/10.1136/medhum-2022-012409.
Dominik Koesling and Claudia Bozzaro, "The Post-Antibiotic Era: An Existential Threat for Humanity," *Intergenerational Justice Review*, August 31, 2023, Vol. 8 No. 2 (2022): Existential and unknown risks for future generations (II), https://doi.org/10.24357/IGJR.8.2.1230.

not be wholly without cause, as rates of resistance continue to rise. Therefore, looking into what inhibits access to effective antibiotics and what diminishes the success of antibiotics as a healthcare infrastructure is both timely and essential.

This dissertation focuses on the infrastructure that enables antibiotics to *be* the infrastructure Chandler describes. It highlights the need for access to effective antibiotics as a built-in component of this infrastructure as a whole, and analyzes the history of this infrastructure since 1977. As infrastructures are support systems, this dissertation also uses the philosophy of technology regarding maintenance studies, published by Jérôme Denis, Bruno Latour, David Pontille, Susan Leigh Star, and Mark Thomas Young as a framework for conceptualizing how this infrastructure has been maintained over this time period. And, lastly, it identifies where this infrastructure is "crumbling" as a result of marketing, manufacturing, and regulatory changes that have taken place since 1977.

I. Construction of the Project

I have conducted this research in tandem with four other work packages in an international research project funded by the Research Council of Norway. This team consists of University of Oslo, University of Copenhagen, University College of Dublin, and the Consejo Superior de Investigaciones Científicas in Madrid, and was brought together under the key question "How did the antibiotic pipeline run dry?" The antibiotic pipeline, to be discussed later in this dissertation, is a metaphor used to describe the steps in which an antibiotic makes it through the various product development stages from first conception of an idea through to marketing. The *dry* pipeline, serves as an indication that antibiotics are *not* proceeding effectively through this process. This research project was founded to determine

Sara Reardon. "WHO Warns against 'post-Antibiotic' Era," *Nature*, April 30, 2014, https://doi.org/10.1038/nature.2014.15135.

how this took place, and each axis of this "Dry AP" project sought to investigate different parts of the antibiotic pipeline's framing and story, ranging from the gender of scientists in laboratories, to institutional experiences and governmental regulations.

Initially, my axis of this project was entitled "Global Policy Laboratory (1980-2010)," and was devoted specifically to the policies and regulations that have impacted antibiotic development between those years. However, as I began to collect documentation and conduct interviews with key stakeholders, I felt that focusing solely on the development of new antibiotics (and the antibiotic pipeline on its own) would be disingenuous to the larger picture that was emerging via my research. Deeply inspired by Chandler's discussion of antibiotics as an infrastructure that supported global health care needs, how is this infrastructure constructed?

After much consideration, I hypothesized that if antibiotics were an infrastructure in their own right, then the goal of the infrastructure that supported it needed to be access to antibiotics. If a patient is unable to receive their requisite antibiotic in their time of need, then they never gain access to the health care that they are meant to have. While the dry pipeline can explain a lack of new antibiotics, it does not account for *old* antibiotics. Those drugs had already moved through the research and development pipeline and were now already on the market. To measure their place in the infrastructure, I turned to two different pathways. The first: the World Health Organization (WHO)'s Essential Medicines List which recommends and encourages access to the most essential drugs on the market. This list helps pave the way for countries to gain access to needed medication, and the WHO continually supports efforts to see that happen. The second pathway was that of the antibiotic supply chain. How are the drugs actively making their way from point of creation to point of sale?

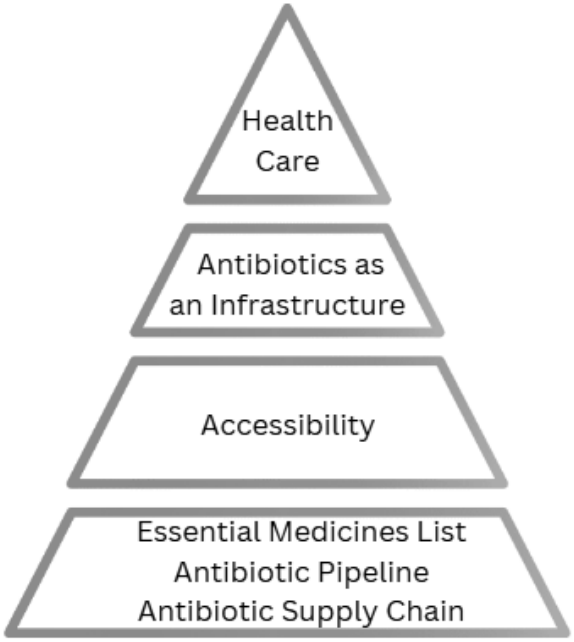

Figure 1 Example of the supporting infrastructures leading to healthcare

Figure 1 visually depicts this thought process. The bottom of the pyramid is the base infrastructure that has an end goal of antibiotic accessibility, by virtue of being accessible: antibiotics can then serve as an infrastructure which leads to effective global healthcare. While there are certainly other factors or components that would support the accessibility of antibiotics, I chose to focus on the Essential Medicines List, pipeline, and supply chain as three distinct areas that offer unique but often interrelated areas of observation. These three areas intersect with one another and support one another, making them clear and practical examples to explore this conceptualization of Chandler's antibiotic infrastructure's infrastructure.

A. The meaning of antibiotic infrastructure and maintenance

In their work on maintenance and what it means to take care of things, Jérôme Denis and David Pontille discuss infrastructure in terms of its indispensability.[8] For Chandler,

[8] Jérôme Denis and David Pontille, *Le Soin de Choses : Politiques de La Maintenance,* (Paris : La Découverte, 2022) 54.

antibiotics are wholly indispensable from a health care perspective.[9] It is why they serve as a key component of a health care infrastructure. But what of the infrastructure that supports antibiotics? And how can that infrastructure insure that antibiotics remain capable of addressing health care needs in the future?

No infrastructure is built to last for eternity. Regardless of field or domain, once something has been developed it requires maintenance to ensure its continued functionality. In the philosophy of technology and science, discussions about maintenance are rare. The field, if it can be called as such, is emerging and has been steadily since roughly the 2000s. Maintenance regarding drugs or drug pipelines has not yet been studiously reviewed. Rather, maintenance seems largely to be discussed in terms of engineering, technological constructs (such as motorcycles or computers), and other such practical aspects.[10] Pipelines, in this case oil or gas pipelines, do receive similar levels of attention, particularly in regards to when and how to initiate repairs and how best to optimize sales outputs when there is a delay in service as a result of maintenance practices.[11] And, in this area, it is important to note that repairs differ from maintenance. Denis and Pontille describe this difference by indicating that repairs are judged by their ability to fix something and have that thing never again require adjustment, where *maintenance* is a noun connected to the present-tense conjugated verb *to maintain,* where the action is considered continuous and ever present.[12] All this said, and despite this lack of direct comparison between drug pipelines and infrastructure and

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[9] Chandler, "Current Accounts of Antimicrobial Resistance," 9.

[10] Some works that specifically discuss the philosophy of maintenance include:
Stephen Graham and Nigel Thrift, "Out of Order: Understanding Repair and Maintenance," *Theory, Culture & Society* 24, no. 3 (2007): 1–25, https://doi.org/10.1177/0263276407075954.
Mark Thomas Young and Mark Coeckelbergh, eds., *Maintenance and Philosophy of Technology: Keeping Things Going,* Routledge Studies in Contemporary Philosophy, (New York, United States: Taylor & Francis Group, 2024).
Mark Thomas Young, "Maintenance," In *The Routledge Handbook of the Philosophy of Engineering*, edited by Diane P. Michelfelder and Neelke Doorn, 356–68, Routledge Handbooks in Philosophy, (New York, United States: Taylor & Francis, 2021).

[11] P.K. Dey, "Decision Support System for Inspection and Maintenance: A Case Study of Oil Pipelines," *IEEE Transactions on Engineering Management* 51, no. 1 (2004): 47–56, https://doi.org/10.1109/TEM.2003.822464.

[12] Denis and Pontille, *Le Soin de Choses,* 56.

maintenance studies as a whole, this analytical framework of understanding does lend itself well to Chandler's use of the term infrastructure, as does the specific terminology that can appear within these philosophical discussions.

One such term is Bruno Latour's use of the word "blackboxing" to identify a kind of spatial blindness that occurs when technology is working effectively. He describes a scenario in which a lecture is provided via projector. So long as the projector is functioning, no one truly notices its use or purpose because it is doing what it is meant to be doing. But if, mid-lecture, that projector should cease functioning: now attention is drawn to its existence in the first place.[13] In this way, the infrastructure that allows for antibiotics to exist is often consigned to a black box. The pills themselves are the most essential component, the output that is evident and tangible. They are able to provide health care miracles because they exist in a necessary and physical form that is easy to understand.[14] However, how they *get* to that patient is, for the most part, invisible.

This dissertation looks at the WHO's Essential Medicines list (EML), the research and development pipeline, and the supply chain as parts of this invisible infrastructure. Most individuals, if asked, would not know what the EML is at all, and while some understanding may be expected for the general concept of a pipeline or supply chain, the complexities within are not public knowledge. Each of these components is influenced, of course, by their own infrastructures. Financial and budgetary constraints are familiar concerns in each branch, as are operating and business decisions that are at the surface level unrelated to the notions of antibiotics from the start. This persistent "embeddedness" continues to justify their notion of

[13] Bruno Latour, *Pandora's Hope: Essays on the Reality of Science Studies,* (Cambridge, Massachusetts: Harvard University Press, 1999): 183.

[14] This commentary is nuanced, of course. Not knowing the differences between antibiotics can lead to individuals believing that any antibiotic can cure any bacterial infection, and an over reliance on antibiotics can make them seem more miraculous than they actually are. This conversation is not dedicated to breaking down the ways in which antibiotics as an infrastructure itself can be blackboxed (that is a discussion for another time) but rather focus on the infrastructure supporting antibiotics first and foremost.

being infrastructures in the first place, but it also makes tracking their histories and impacts difficult.

The EML, a list generated by the WHO in an effort to assist hospital and government formularies when it comes to knowing which drugs are of most importance to suit health care needs is the core focus of Chapter Two. This list is not strictly dedicated to antibiotics. However, antibacterials are a feature of the EML, and they undergo a particular transition over time as a result of the rise of antimicrobial resistance and the need changes of those utilizing the list as a support structure. When looking at the infrastructure that allows for antibiotics *to be* an infrastructure, the EML exemplifies both how these systems intersect, but also how particular aspects of these systems may need additional support (or maintenance) over time.

The research and development pipeline for all drugs has changed over the past fifty years or so, but the antibiotic pipeline is a unique situation where the initial products developed were so effective that creating new and competitive products whose on-patent price can be justified in the face of a wide assortment of off-patent medications is challenging. Chapters Three and Four highlight how this component of the infrastructure that allow for antibiotics to be a global health care infrastructure has struggled and what maintenance efforts have been put in place in an attempt to fix it.

The supply chain has its own unique trend where knowing which antibiotics should be developed, where profit margins lie, and how accessibility can be ensured despite fluctuations of the availability and affordability of these drugs has gone through great changes. Chapter Five grows off of the discussion on developing new drugs in the preceding two chapters by focusing the distribution system.

All three of these subjects are components of a Latourian black box where one does not need to know how something works in order for it to be effective. For the purposes of this

dissertation: one does not need to know how antibiotics arrive in someone's hand – only that it does. So long as these domains function and do their job: access to effective antibiotics is a smooth process that receives no attention. But once parts of that infrastructure start fragmenting or breaking down (the rise of antimicrobial resistance outpacing the production of new antibiotics, unsuccessful funding initiatives, or supply chain disruptions – for instance), the infrastructure itself is now more evident than ever before.

The same year that Latour published his thoughts regarding blackboxing, the sociologist Susan Leigh Star published her own work on the "Ethnography of Infrastructure." While embeddedness has already been mentioned, there are eight other key components of infrastructure, summarized below:

> *Embeddedness.* Infrastructure is sunk into and inside of other structures, social arrangements, and technologies.
>
> *Transparency.* Infrastructure is transparent to use, in the sense that it does not have to be reinvented each time or assembled for each task, but invisibly supports those tasks.
>
> *Reach or scope.* This may be either spatial or temporal—infrastructure has reach beyond a single event or one-site practice.
>
> *Learned as part of membership.* The taken-for-grantedness of artifacts and organizational arrangements.
>
> *Links with conventions of practice.* Infrastructure both shapes and is shaped by the conventions of a community of practice.
>
> *Embodiment of standards.* Modified by scope and often by conflicting conventions, infrastructures takes on transparency by plugging into other infrastructures and tools in a standardized fashion.
> *Built on an installed base.* Infrastructure does not grow *de novo,* it wrestles with the inertia of the installed base and inherits strengths and limitations from that base.
>
> *Becomes visible upon breakdown.* The normally invisible quality of working infrastructure becomes visible when it breaks.
>
> *Is fixed in modular increments, not all at once or globally.* Because infrastructure is big, layered, and complex, and because it means different things locally, it is never changed from the above.[15]

[15] Susan Leigh Star, "The Ethnography of Infrastructure," *American Behavioral Scientist* 43, no. 3 (1999): 381-82. https://doi.org/10.1177/00027649921955326.

The analytical chapters of this dissertation inspects how these nine components relate to the World Health Organization's Essential Medicines List (EML), the antibiotic research and development pipeline, and the antibiotic supply chain.

Latour's black box was not originally used to discuss infrastructure, but rather innovations on their own. His focus was on the user's perception of technology. However, this perception can still be applied to infrastructure itself. Philosopher of technology, Mark Thomas Young discusses Latour's blackboxing theory, and Star's nine elements of infrastructure, in his 2020 book chapter on how maintenance is a component of an invisible infrastructure.[16] For Young, it is the invisibility of infrastructure that is of particular importance. Latour's blackboxing indicates how "important aspects of scientific and technological processes are opaque and therefore must be rendered visible before they can be subjected to critical analysis," while Star's discussion on transparency highlights how for something to be an infrastructure it *must* withdraw from our attention.[17] Infrastructure must do this, because the *output* of infrastructure (in this case, access to effective antibiotics) is so much more spatially important to the human mind than the infrastructure which enables that output in the first place.[18]

Finally, this discussion cannot be had in full without recognizing that much of what is discussed trends towards the idealistic. As mentioned previously: the present-day reality is that many individuals *do not* have access to effective antibiotics, and thus are deprived of the antibiotic infrastructure that Chandler first discusses. Antibiotic access, defined by both the availability *and* affordability, is not a guarantee to these individuals. This dissertation's discussion of the infrastructure that allows for antibiotics to serve as a health care

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[16] Mark Thomas Young, "Now You See It (Now You Don't): Users, Maintainers and the Invisibility of Infrastructure," In *Technology and the City. Philosophy of Engineering and Technology*, edited by M Nagenborg, T. Stone, M. González Woge, and P.E. Vermaas, 36: 101–19, Religion and Philosophy, (Springer, Cham, 2021), https://doi.org/10.1007/978-3-030-52313-8_6.
[17] Young, "Now You See It (Now You Don't)," 102-3.
[18] Young, "Now You See It (Now You Don't)," 103-4.

infrastructure, is cognizant of these flaws. It tracks the history of how these infrastructures have been put in place, and where areas of neglect or areas that require improvement or *maintenance* exist.

B. Definitions, semantics, and linguistic discrepancies

Beyond "infrastructure" and "maintenance," this dissertation wrestles with several words with definitions that may change or evolve over time. "Pipeline" is perhaps the most variable, though "access" is equally convoluted. Chapter One will explore the historiography and evolution of the word pipeline in more detail, but suffice to say here: different actors utilize this word for their own means, with pharmaceutical companies using it primarily as an industry benchmark determining the steps of product development,[19] and outside agencies, NGOs, or governments occasionally extending or elongating the term to include accessibility or post-marketing surveillance that is absent in the pharmaceutical industry's original understanding of the phrase.[20] [21]

"Access," similarly, can change meaning depending on the actors who are deploying it. For the purposes of this dissertation, the word "access" is used in accordance with the definition developed by NGOs and health organizations since the 1990s to apply to the joint availability and affordability of medications.[22] This definition was the result of more than ten

[19] Roxanne Nelson, "Antibiotic development pipeline runs dry – New drugs to fight resistant organisms are not being developed, experts say," *Lancet* 362, no. 9397 (Nov 2003), https://doi.org/10.1016/S0140-6736(03)14885-4.

[20] George H. Talbot, John Bradley, John E. Edwards, David Gilbert, Michael Scheld, John G. Bartlett, and Antimicrobial Availability Task Force of the Infectious Diseases Society of America, "Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America," *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 42, no. 5 (March 1, 2006): 666, https://doi.org/10.1086/499819.

[21] Christine Årdal, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John H. Rex. "Revitalizing the Antibiotic Pipeline." Final Report 2018. (Geneva, Switzerland: DRIVE-AB, 2018), 5.

[22] Bernard Pécoul, Pierre Chirac, Patrice Trouiller, and Jacques Pinel, "Access to Essential Drugs in Poor Countries: A Lost Battle?" JAMA 281, no. 1 (1999): 361–67, http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.281.4.361
Veronique Menou, Allison Hornstein, and Elizabeth Lipton-McCombie, "Access to Medicines Index," (Amsterdam, Netherlands: Innovest Healthcare Team, June 2008),

years of work in global health, and is deeply politicized as a result. It contains layers beyond just supply chain commentary. In 2000, Médecins Sans Frontières specifically noted that access to effective medicines meant ensuring quality diagnosis, accurate prescription, appropriate selection, distribution of quality medicines, guaranteed strength of national health systems and budgets, improved research and development (R&D) for neglected diseases, and affordable pricing.[23] Each of these multi-tiered components are essential to ensure accessibility, which at its base root means only the ability to obtain or retrieve something (such as the ability to obtain or retrieve an antibiotic). This definition is used as opposed to more narrowed definitions, specifically because its multifaceted nature. As the purpose of the infrastructure discussed in this dissertation is to ensure antibiotics can continue to play a supportive role in global health care, a narrow definition of "access" would limit the efficacy of this infrastructure's presumed intentions.

To be perfectly clear, lack of affordability is not the only parameter that that prevents someone from purchasing an antibiotic. While discussions around the accessibility of drugs due to prohibitive pricing schemes did come into public discussion arise during the HIV/AIDS crisis of the 80s and 90s,[24] this dissertation expands that discussion to include the lack of *availability* of a product. If a pharmaceutical company creates a drug, but a regulatory authority refuses the sale of that drug (or the rarity of the active pharmaceutical ingredient means that it is frequently in short supply): that drug is both inaccessible and unavailable. It

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https://accesstomedicinefoundation.org/medialibrary/resources/5bc5edee6619d_2008-Access-to-Medicine-Index.pdf.
Erdem Erginel, "Access to Medicines at the Global Level," Presented at the Global Health Policy Forum, (Brussels, Belgium, March 20, 2014). https://health.ec.europa.eu/document/download/601134f8-e2a3-4057-8f3e-c38b78168b50_en?filename=ev_20140320_co4_en.pdf.

[23] MSF Access Campaign. "The Campaign: Frequently Asked Questions." Corporate. MSF is campaigning internationally for greater access to essential medicines. Accessed November 10, 2000. http://www.accessmed-msf.org/campaign/faq.shtm.

[24] James Love, Interview with Erin L. Paterson, 23 April 2024
James Love, Interview with Erin L. Paterson, 24 April 2024
James Love, Interview with Erin L. Paterson, 30 April 2024

does not matter if a patient or purchasing authority has unlimited funds to purchase the drug, it remains inaccessible *because* it is unavailable.

Access to antibiotics throughout this dissertation, and in relation to antibiotic infrastructure implies that once a drug successfully makes its way through product its research and development stages, the drug is well circulated as a result of appropriate marketing approvals and stable supply chains, as well as equitable pricing schemes, distribution systems, and retailers on the ground.

In shorthand, access equals available *and* affordable, and accessibility needs or stressors may vary due to differing income levels or physical circumstances. Both high income countries as well as low-income countries face these challenges. The United States has seen record numbers of antibiotic shortages since the 1990s as a result of availability concerns,[25] and despite charitable donations and pricing schemas put in place by organizations such as the Global Fund, medications for the treatment of multiple drug resistance tuberculosis, for example, are often both unavailable and unaffordable for low-income countries. These specific examples, and others, will be discussed in more detail throughout the dissertation, revealing the ways in which access is a complex and often ignored problem on a global scale. A continued discussion regarding the history and historiography of access to medicines, can be found in Chapter One, expanding on the current definitions discussed here and their impact overall.

"Resistance" is another word that needs clarification. In science, antimicrobial resistance can present in two key ways: intrinsic and acquired resistance. The former indicating that bacteria has and always will be insusceptible to a particular antibiotic, and the latter indicating that bacteria evolves to become resistant to an antibiotic.[26] Importantly,

[25] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.
[26] Denis K Byarugaba, "Mechanisms of Antimicrobial Resistance," In *Antimicrobial Resistance in Developing Countries,* edited by Anibal de J. Sosa, Denis K. Byarugaba, Carlos F. Amábile-Cuevas, Samuel Kariuki, Po-Ren Hsueh, and Iruka N. Okeke, (New York, United States: Springer, 2010), 19.

however, this does not necessarily mean the bacteria must evolve to resist an antibiotic, such as in the case with gram negative bacteria whose protective layer prevents many antibiotics that are efficacious against gram positive bacteria from being destroyed.

This dissertation primarily discusses cases of acquired antimicrobial resistance rather than intrinsic. Prior to the 1930s, intrinsic resistance was known and understood, but due to early research by Paul Ehrlich and later by the Liverpool School of Tropical Hygiene, acquired resistance slowly gained acceptance as a potential trait of bacteria.[27] While warnings of increased resistance were mentioned already in the early days of antibiotic development, it wasn't until the 1990s that the WHO and clinicians themselves began to show some concern over the impacts of acquired resistance.[28] [29] [30] Thus, it is the act of formerly treatable bacteria that have acquired resistance that have been the focus of most debates surrounding the rise of AMR in the periodization covered by this dissertation.

C. Actors: specific and non-specific

The actors that have had the most impact on antibiotic access and drug development are primarily large multinational organizations, governments, and private enterprises. Because of the impact of the United States and European (Union and regional) regulatory and oversight committees, these geographic territories and their respective governments are frequently discussed within this dissertation.[31] The World Health Organization, which began as an international health organization in the 40s, and evolved into a global and public health

[27] Christoph Gradmann, "Magic Bullets and Moving Targets: Antibiotic Resistance and Experimental Chemotherapy, 1900-1940," *Dynamis* 31, no. 2 (2011): 306, 316-320, https://doi.org/10.4321/S0211-95362011000200003.
[28] Podolsky, Scott H. "The Evolving Response to Antibiotic Resistance (1945–2018)." *Palgrave Communications* 4, no. 1 (October 23, 2018): 124. https://doi.org/10.1057/s41599-018-0181-x.
[29] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 796, Fourth Report of the WHO Expert Committee, Geneva: World Health Organization, 1990, 14.
[30] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 16-17.
[31] I have chosen to not include Japan specifically as a major point of discussion within this dissertation due to linguistic difficulties and a need to limit my scope. Japan is mentioned, particularly in the work of Japanese company Shionogi Pharmaceuticals in Chapter Three, however it will not be the full focus of this dissertation.

authority through the 1970s and 80s as a result of its push into public health debates, is also mentioned to great extent as they developed both calls to action and funding apparatuses in efforts to encourage both antibiotic development and distribution.[32] Non-government organizations such as Médecins sans Frontières (aka: MSF [founded in France in 1971]), and ReAct (founded in Sweden in 2005) both have made impactful attempts at addressing the access concerns; as have philanthropic organizations such as the Bill and Melinda Gates Foundation and the Wellcome Trust. Support and funding from all of these bodies, in conjunction with a massive investment by individual governments, has led to the development of individual Public Private Partnerships (such as TB Alliance [New York – 2002], IMI [Brussels – 2008], GARDP [Geneva – 2016], and CARB-X [Boston – 2016]) which have been dedicated in whole or in part to the production of new antibiotics.

Many of these entities are not wholly invested towards that goal, and some are wholly focused on innovation over access concerns. They are important, despite this, because of the impact that their actions have caused. As the most powerful actors in this space, their work and impact must be critiqued in full. This dissertation highlights the actions and inactions taken by these actors, the competition between them, as well as the differences that appear in their public statements versus physical effort. It assesses the efforts by individuals within organizations, as well as the impact on this overarching antibiotic infrastructure as it currently stands. This dissertation does not intend to hold these organizations or individuals to account for actions currently in progress, but to track their histories in conjunction with the overall history of the antibiotic infrastructure at the core of this work.

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[32] For more information on this transition, consult: Theodore M. Brown, Marcos Cueto, and Elizabeth Fee, "The World Health Organization and the Transition From 'International' to 'Global' Public Health," *American Journal of Public Health* 96, no. 1 (2006): 62–72, https://doi.org/10.2105/AJPH.2004.050831.
And: Jean-Paul Gaudillière, Claire Beaudevin, Christoph Gradmann, Anne M. Lovell, and Laurent Pordié. "Introduction," In *Global Health and the New World Order,* Historical and Anthropological Approaches to a Changing Regime of Governance, Manchester, United Kingdom: Manchester University Press, 2020, https://shs.hal.science/halshs-02976222/document.

Many of these actors have work beyond the sphere of antibiotics or antibiotic infrastructure. MSF and the WHO, for instance, quite obviously work in venues beyond the confines of antibiotics; the Innovative Medicines Initiative (IMI), in particular, is a Public Private Partnership that has dozens of research streams dedicated to other drug or medicine related fields. However, despite the diversity of their portfolios, these actors *did* conduct work within the scope of this project, and as such these target areas are analyzed, and interpreted, both in conjunction to their broader intentions and the specific focus of antibiotic infrastructure wherever possible.

II. Materials and Methods

Many researchers have tackled the hills and valleys of pharmaceutical company development, and even the rise of resistance in both human and animal health. What many of the works in this field have in common though, is that they are situated on events that take place largely before 1980. The contemporary nature of my research, in starting from 1977 onwards, is that there is a limit to what kind of information is materially available. Although, due to the digitization of records, and the utilization of the internet to transmit data there are many publicly available records online from government databases such as the FDA's Orange Book or the WHO's online archival database of available fonds, privacy concerns and date limitations prohibited access to many potentially valuable records. Even if a document existed, but was not scanned, these institutional restrictions limited the value of physically reviewing records in brick and mortar archives for in person review. The three archives that I was able to visit (The World Health Organization, United Nations, and New York Municipal Archives) had strict cut offs on end dates, with the latest being 1992 at time of visit. As a result, I needed to build a corpus that would support my research beyond the boundaries of traditional archival records.

In 2024 Mark Young and Mark Coeklebergh, highlighted how communication is one necessary component to addressing maintenance concerns.[33] Discussing and drawing out the options, as well as having multiple individuals or organizations capable of providing insight is key as addressing how breakdowns have occurred and what needs to be done is key. They also discuss maintenance as a potential for creative improvements and possibilities as new additions or considerations expand upon the original base infrastructure and make it grow.[34] This kind of communicative dialogue can be seen via a witness seminar that I helped organize and moderate on 29 January 2024, along with fellow Dry AP members, Mirza Alas Portillo, Claas Kirchhelle, and Frédéric Vagneron as well as Nadya Wells of the Geneva Graduate Institute. The comments and discussion of stakeholders regarding the development of Public Private Partnerships (PPPs) as a way to support antibiotic development (and the infrastructure as a whole) can be seen in greater detail within Chapters Three and Four.

Witness seminars, first developed by the History of Twentieth Century Medicine Group in the 1990s and originally funded by Wellcome Trust, are a form of oral history gathering exercise where individuals who share a community and cause are brought together to provide individual testimony in group settings, forming what can be considered a collective memory of events.[35] Our team replicated the form and style of these seminars, and invited representatives from the WHO, DNDi, GARDP, CARB-X, KEI, ReAct, MSF, and GlaxoSmithKline to discuss their experiences in choosing this funding model, their intentions for developing antibiotics, the fears and challenges faced with developing antibiotics, as well as their concerns for antibiotic access throughout. The full transcript has been published

[33] Young and Coeckelbergh, eds., *Maintenance and Philosophy of Technology: Keeping Things Going,* 10-11.
[34] Young and Coeckelbergh, eds., *Maintenance and Philosophy of Technology: Keeping Things Going,* 15-17.
[35] E.M. Tansey, "Witnessing the Witnesses: Pitfalls and Potentials of the Witness Seminar in Twentieth Century Medicine," In *Writing Recent Science: The Historiography of Contemporary Science, Technology and Medicine*, edited by Ron Doel and Thomas Soderqvist, 260, Routledge Studies in the History of Science, Technology and Medicine, (Oxon, United Kingdom: Routledge, 2006).

open-access and serves as an additional facet of the oral history methodology I applied to this dissertation.[36]

These participants included:

Participant Name	Representing:
James Anderson	IFPMA/GSK
Peter Beyer	GARDP/WHO
Otto Cars	ReAct
Stephan Harbarth	Hôpitaux Universitaires de Genève (HUG)
Marie-Paule Kieny	GARDP/DNDi and WHO
Joe Larsen	BARDA
James Love	Knowledge Ecology International (KEI)
Kevin Outterson	CARB-X/Boston University

Table 1 Witness Seminar Participants

Over the course of five hours, the participants were offered guiding questions to help steer their responses, but were mostly left to reminisce and provide testimony to how they felt about the development of public private partnerships in regards to antibiotic development.[37] Three key discussion sections were planned in advance: defining the problem, shaping/conceptualizing solutions, and fixing the pipeline. Participants were also invited to provide their thoughts on the current status of the antibiotic development pipeline in form of stock take at the close of the seminar. Follow up interviews were conducted with some participants after the fact to allow for more specific detail.

Oral history/testimony in general is a key support pillar of this research project. Lacking paper records, these personal perspectives provided not only insight but corroboration between individuals and groups that frequently appeared throughout my work. Between November 2022 and May 2024, I conducted a total of eighteen interviews with

[36] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)."
[37] The full transcript of the witness seminar can be consulted at: Mirza Alas Portillo, Erin Lindsey Paterson, Nadya Wells, Frédéric Vagneron, and Claas Kirchhelle, "Emerging Financial Models for Antibiotic Development (2000-2016). Witness Seminar Conducted by the DryAP Project and in Collaboration with the Global Health Centre, Geneva Graduate Institute," Université de Strasbourg, 2024. https://doi.org/10.34931/N7PK-3N88.

fifteen individuals (many not present in the witness seminar hosted in January 2024). The average length of each interview was roughly one hour. One interviewee, the director of Knowledge Ecology International and a key intellectual property rights expert (James Love), was particularly helpful in sharing the details of his experience in pharmaceutical development and policies involving drug development and access concerns. He participated in three interviews between 23 April and 30 April 2024. I also conducted two interviews in tandem with fellow Dry AP project member: Mirza Alas Portillo.[38] As our work covered many similar topics and themes, we worked together where possible and supported each other throughout this project. She has been a great help to me and the final version of this dissertation as a result. All interviews are listed in chronological order in Appendix 7.

Following each interview, I worked to track down any physical copy of evidence for the references I was given in whatever form those references took. I used corporate filings to understand the financing of companies, and publicly available government records to contextualize the impact of policy and regulation on antibiotic development and access. I listened to and read United States senate hearings and followed up with cited conference papers and publications made following such hearings. Finally, I generated databases based on the information I was able to find on these available government websites, identifying additional aspects of data not previously looked at in the initial data sets. This flexibility allowed me to identify sources that were relevant to my field of study, and to assess new information from old sources when possible. I also assessed published documentation not just for their historical discussion, but what the publication of that document at that particular time said about the history of events in that moment. This methodology provided me with a

[38] The first interview was with Otto Cars, an infectious disease specialist, founder of the NGO ReAct, and a former head of the Swedish strategic programme against antimicrobial resistance.
The second is with an individual who declined to be publicly identified as a part of this project.

substantive data set to analyze and discuss, and substantiated the lack that a physical archive represented in my current work.

Most of the data that I reviewed was publicly available, though I often utilized the Internet Archive to find digital records that had long since been deleted or removed from websites.[39] [40] This was an invaluable part of my research, and I have been sure to include the date of the saved webpage in any old websites that were resurrected in this fashion.

Jonathan Blaney, Sarah Milligan, Marty Steer and Jane Winters have said that data cleaning takes up 80% of the work devoted to doing digital history,[41] and this estimate proved very accurate. I made generous use of NVivo to organize the hundreds of journal articles, books, and primary source documents I was able to acquire, and coded key words throughout my readings for easy retrieval during the writing phase of this project. I created many charts and figures using Microsoft Excel to help organize data whenever possible. Most of these figures are printed either in the chapters directly, or in the Annexes of this dissertation.

It was not feasible to completely address the totality of every single antibiotic access and development concern. Two decisions were made in order to limit this scope. Although the use of antibiotics for animal health is very important, particularly in concerns to antimicrobial resistance and accessibility concerns, to combine the two fields in this dissertation would have been an exorbitant task.

First, this dissertation is focused solely on antibiotic use in humans. Chandler's article does discuss animal health, and the use of antibiotics in animal husbandry efforts.[42] The production of antibiotics for animal use is also a huge source of revenue for pharmaceutical

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[39] Internet Archive, "The Wayback Machine," Accessed 29 July 2024, https://web.archive.org/

[40] For more information on using this kind of methodology, please consult : Valérie Schafer, "De la Wayback Machine à la bibliothèque : les différentes saveurs des archives du Web," *La Gazette des archives* 253, no. 1 (2019): 95–107, https://doi.org/10.3406/gazar.2019.5689.

[41] Jonathan Blaney, Sarah Milligan, Marty Steer, and Jane Winters, *Doing Digital History,* (Manchester, United Kingdom: Manchester University Press, 2021), 108.

[42] Clare I. R. Chandler, "Current Accounts of Antimicrobial Resistance: Stabilisation, Individualisation and Antibiotics as Infrastructure," *Palgrave Communications* 5, no. 1 (May 21, 2019): 2, 6-7, 9. https://doi.org/10.1057/s41599-019-0263-4.

companies and manufacturers. Other historians of medicine, such as Claas Kirchhelle, have written excellent histories regarding the interplay between antibiotics and animals in agricultural settings. [43] However due to the differences in legislation, regulation, and individuals or corporate staff responsible for these spheres of antibiotic development, this dissertation cannot effectively cover both human and animal health at once. The decision to restrict this work to human health was thus made in the effort to ensure that one stable and coherent argument could be made. Future work on which components ensure a stable animal-focused antibiotic infrastructure should be conducted at another date.

The second choice made to limit the scope, was in relation to the vast quantity of antibiotics presently in existence. There are countless formulations of antibiotics circulating global markets at this time. Tracking each and their impact would be an exorbitant task. Therefore, only those antibiotics discussed on the WHO's Essential Medicines List will be given the most attention. The Essential Medicine List, to be discussed in greater detail in Chapter Two, provides a key insight as to those antibiotics deemed of highest priority to the global health community, and thus serves as a structural limitation for this research.

Antibiotic classes differentiate from another due to the precise mechanism of action they use against a bacterium.[44] [45] While some antibiotic classes are exceptionally limited and only have one drug within their scope of action (such as Mupirocin), others are far more expansive. Throughout this dissertation I have chosen to track and trace the access and

[43] Focus on animal use of antibiotics is outside of the confines of this dissertation, but for more information on this matter, consult: Claas Kirchhelle, *Pyrrhic Progress: The History of Antibiotics in Anglo-American Food Production,* (New Jersey: Rutgers University Press, 2020).
And: Claas Kirchhelle, "Pharming Animals: A Global History of Antibiotics in Food Production (1935–2017)," *Palgrave Communications* 4, no. 1 (August 7, 2018): 1-13, https://doi.org/10.1057/s41599-018-0152-2.
[44] MSD Manual Consumer Version, "Overview of Antibiotics - Overview of Antibiotics," Accessed July 29, 2024, https://www.msdmanuals.com/home/infections/antibiotics/overview-of-antibiotics.
[45] An outlier to the class structure is that of the β-lactams. β-lactam antibiotics include the penicillin class, cephalosporins, monobactams, carbapenems, and beta-lactamase inhibitors. However, each of these "sub-classes" differ from each other and have slightly different mechanisms of action and reaction when introduced to the body. For more information, consult: Neelanjana Pandey and Marco Cascella, "Beta-Lactam Antibiotics," In *StatPearls*. (Treasure Island, United States: StatPearls Publishing, 2024). http://www.ncbi.nlm.nih.gov/books/NBK545311/.

development challenges of antibiotic classes specifically as they are the root form of innovation and indicate specific alterations in mechanism of action against bacteria. Worldwide, there are countless iterations of each specific antibiotic class, and tracing each formulation is beyond the scope of this dissertation. However, by using the classes as a trigger point of unique innovative change, I am able to provide a concise overview of the way these drugs appear in the lab and on the market.

The United States FDA's Orange Book was of particular use as well. It lists all of the pharmaceutical companies which received regulatory approval to produce and market a drug, and were currently still active. I went through the listing of the antibiotics on the WHO's Essential Medicine List, and gathered all pertinent data from the Orange book in an excel spreadsheet. This revealed trends in antibiotic development, as well as identify impact of policies and regulations on companies after implementation. This dataset can be found in Appendix 2.

Finally, at the start of each chapter is collection of quotes. The vast majority of which emerge from the interviews I conducted with participants for this dissertation. These are intended to set the mood and theme for these chapters, and to provide brief personal insight into what is to come from the participants in ways that might not be able to be more thoroughly integrated into the overall work. These are largely grouped together to form perspectives, and commentaries only.

A. Chapter Five Methods

There is a distinct difference in methodology and materials in the final chapter of this dissertation due to a dataset received from Erin Fox of the University of Utah. Fox has been tracking drug shortages in the United States since the 1990s. Following an interview, I had with her in March 2023, Fox very generously provided to me her entire dataset of all

collected drug shortages, including their longevity and reason for stock rupture, since she began collecting her data. Having not originally anticipated this data, the form and function of this final chapter evolved to accommodate the information that I now had access to. Her data was extensive. I limited myself to only her statistics on antibiotics, and then proceeded to add additional coding and categories to more clearly understand the total impact of antibiotic supply frailty in the United States as a result. Appendix 4 and 5 detail the most relevant work that was done in modifying Fox' data for analytical use within this dissertation.

There is no corresponding database for any other country that I have been made aware of. To provide more global understanding as to the changes of antibiotic access and shortage concerns since the 1980s, I generated a specific corpus from the Web of Science database for all references and mentions to antibiotic access, availability, and shortages on a global scale and used this corpus as a comparator to the data Fox provided me. This additional compendium of data and statistics provided a more global context to the data received from Fox. With both the original data set, and my own assessment to analyze and assess the impact of shortages over time. I then created a Web of Science review in order to determine where I would be able to compare and contrast the data there. I chose Web of Science because of its unique tagging and coding system that allowed for articles of any language to be documented and listed, allowing for greater flexibility of related articles, as well as its overall global reach. It is not a perfect representation of documentation relating to antibiotic shortages, access, or availability concerns, but it provides a small sample of articles that could be compared to the far more specific data received from Fox. Appendix 3 provides a detailed explanation of how I gathered my data and what initial statistics can be determined from this data on its own.

Finally, chapter five largely revolves around the antibiotic supply chain as a component of antibiotic infrastructure. As such, Active Pharmaceutical Ingredient (API)

manufacturers, their ability to transport products, the additional final packing components included (at sometimes several points) in the supply chain, and the additional ways in which drugs reach patients beyond simply drug development are all necessary parts of this discussion are integral to this overall discussion. Within this chapter, I use both Fox and the Web of Science corpus to highlight the API structure whenever possible, creating a series of trends of events happening simultaneously to show how historically the supply chain API manufacturers are intrinsically a part of is struggling. I particularly draw focus to the "taken for granted" and purposefully invisible role of this particular infrastructure (à la Susan Leigh Star), and how additional obscurity of this infrastructure occurs due to the implementation of non-disclosure agreements that purposefully hide how the infrastructure is put together. Together, these choices help accentuate the issues within the antibiotic infrastructure, how accessibility has diminished over time, and how maintenance is continually delayed despite a burgeoning of reports highlighting new shortages year after year.

III. Announcement of the plan

Although my original time period was estimated to span between 1980-2010, I have since expanded that and included some measure of flexibility. I use, instead, the launching of the WHO's Essential Medicines List (EML) in 1977 as both a starting point for my research, and a nexus point for calls to action in both accessibility and developmental spheres. As a historical object, it equally serves as a triggering point for both the thoughts and consideration around access, as well as a marker in the historical timeline of events as an impact point seen only in retrospect. The EML served as a way for the WHO to identify drugs, not just antibiotics, that were of most importance in a hospital formulary.[46] Where initially it starts as a list that identifies only a few drugs that are most needed from a massive

[46] Chapter Two will discuss the EML and its impact on drug pricing, listings, and acquisitions in more detail.

list of available options, its use over the following decades increasingly highlights a lack of both new antibiotics entering the market and the increased need for appropriate access and availability worldwide. Therefore, this list and its history provides a comprehensive framework from which my research can build itself. Given the prescient nature of this work, current events have ensured that I follow through until 2023 in some aspects of my data gathering. For sake of impact and argument, most of this dissertation is therefore situated between 1977-2023, with key events transpiring around 2016 and beyond.

There have been many historians who have worked in the field of the history of antibiotic drug development and pharmaceutical action. Chapter One, *Historiography of Antibiotics, the Pipeline, Finances, and Access,* offers a detailed historiography of these works and how they relate specifically to the chapter topics that follow. However, despite the prolific publishing of these scholars, there has not yet been a dedicated study to the history of antibiotic development and access concerns specifically. This gap, as it is so timely and is still continually in flux, is one that most strongly reveals the concerns of where the access and development conundrum remains. Because the economic and financialization of drugs since in the 1980s has been so distinct,[47] the discussion around ensuring access is only heightened during this period. The ability to afford drugs, the ability to manage supply chains, and the oversight and control over the physical manufacturing of drugs becomes particularly distinct in this era. Thus, my work expands on the research provided by key historians who focused on the pre-1980s time frames and accentuates the key differences of this new era as a result.

This thesis is the result of intensive data collection and analysis, and the willingness to adapt my understanding as the data provided additional context I had not expected. Instead of focusing specifically on drug development and the state of the antibiotic pipeline, I look at the broader picture regarding antibiotics as an infrastructure and the feasibility of that

[47] Joan Busfield, "Documenting the Financialisation of the Pharmaceutical Industry," *Social Science & Medicine* 258 (August 2020). https://doi.org/10.1016/j.socscimed.2020.113096.

infrastructure in regards to antibiotic access needs. I measure the success of the antibiotic infrastructure described by Clare Chandler in terms of antibiotic accessibility, and ask how different parts of this infrastructure lead to successful access to effective antibiotics on a global scale. If access is poor, the infrastructure is also poor, and if the infrastructure is poor: how has it reached this state? In Braun & Clarke's 2006 publication on the utilization of thematic analysis, they stated that "a theme captures something important about the data in relation to the research question, and represents some level of patterned response or meaning within the data set."[48] In this way, I have broken this work into five unique thematic (rather than linear) chapters, each building on the last in terms of perspective and focus.

Chapter Two, *Essential Medicines as a Vehicle for Enabling Access to Antibiotics*, is dedicated to how the antibacterial section of the WHO's Essential Medicines List (EML) has evolved, and how this component of the larger antibiotic infrastructure has struggled to keep pace with AMR in recent years. It reveals how, prior to the 1980s there was a veritable time of plenty for the development and distribution of antibiotics, and the EML was initially created as a response to this excess by suggesting a limited selection of antibiotics that are of most therapeutic value. However, by the turn of the century the fears of antimicrobial resistance and a *lack* of new antibiotics becomes evident on the list. The list, therefore, highlights the global understanding of antibiotic need and the top-down reaction to the realization that new antibiotics were not developing at a satisfactory rate. This chapter lays the groundwork for the understanding that access to the right and best antibiotics has always been key, but a new fear surrounding access to new medications and the way those new medications are able to reach patients emerged in the late 90s as the narrative of the dry antibiotic development pipeline began to fully emerge.

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[48] Virginia Braun and Victoria Clarke, "Using Thematic Analysis in Psychology," *Qualitative Research in Psychology* 3, no. 2 (January 2006): 82. https://doi.org/10.1191/1478088706qp063oa.

Chapter Three, *Assessing access to new antibiotics through the implementation of Public Private Partnerships meant to correct a Dry Pipeline of antibiotic development*, analyzes how fear of AMR and a lack of effective treatments for it leads to increasing attention around a dry antibiotic pipeline, and how, in tandem with a desire to increase pharmaceutical company competitively, Public Private Partnerships as a method of addressing these concerns emerged throughout the 2000s. With the simultaneous publication of the 2004 Priority Medicines Report, as well as the increased attention towards priority pathogens, PPPs had a basis for targeting antimicrobial resistance and encouraging the development of new antibiotics. This chapter will use the transcript of the witness seminar discussed in the methodology section, drawing a narrative arc around the notions of priority medicines, the creation of PPPs such as the Innovative Medicines Initiative, Drugs for Neglected Diseases Initiative/Global Antibiotic Resistance Partnership, and the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. It traces the historical evolution and competition of these PPPs, highlights their distinct differences and pathways of financial support, as well as the efficacy and intentions of these funding models when it comes to developing antibiotics and addressing AMR. Throughout this chapter, the innovative development of these PPPs showcases a form of infrastructure maintenance being undertaken with the hopes that by utilizing this new financial pathway: new antibiotics can be eventually disseminated and be made accessible to those in need.

The fourth chapter of this dissertation, entitled *The Drug Trajectory of Bedaquiline,* continues the argument made in Chapter Three by exploring the history of the only first-in-class antibiotic to emerge from the PPP/PDP system: bedaquiline. As a treatment for multiple drug resistant tuberculosis, bedaquiline is an ideal case study on whether the current antibiotic infrastructure can support the kind of "maintenance" being applied. This chapter details the drug trajectory of bedaquiline, analyzing its corporate history and entanglements,

as well as the formation of alliance between its developer company, Johnson & Johnson and the PDP TB Alliance, that helped bring bedaquiline to market. This chapter assesses the notion that even if a drug makes it through the "Dry AP" its ability to actually assist and reach patients is put in conflict with the market factors determining its appropriate sale. It highlights the fragmenting relationship between the United States' neoliberal market, government policies and institutions, drug innovation and access. It also formulates the response to addressing the Dry AP as a maintenance concern, where a previously functioning pipeline required additional changes and innovative assistance in the form of the creation of PPP/PDPs.

Finally, the last chapter of my dissertation is dedicated to supply chains. Entitled, *Accessing that Which is Short: Antibiotics Old and New*, this chapter focuses on the increasing inaccessibility of antibiotics in general. It identifies key antibiotic shortages in the United States and highlights the growing concern for shortages and accessibility needs throughout the rest of the world. It indicates the differences between health systems and infrastructures that worsen access needs, and it makes the argument that the infrastructure that is meant to ensure global access to antibiotics occurs is broken. This chapter focuses on the part of the Dry AP that extends beyond the initial pharmaceutical industry perspective, by highlighting how failure for someone to be able to *access* an antibiotic inhibits that antibiotic's ability to act as a part of a health care infrastructure. It analyzes the progressive failings of the pipeline's continuity and efficacy as a potential response to AMR through this lens.

I conclude this work by reflecting on how the Essential Medicines List, the antibiotic pipeline, and the supply chain together work to ensure that Chandler's analytical framework of antibiotics as infrastructure can exist, and how a lack of access to antibiotics restricts how effective antibiotics can *be* as a health care infrastructure. Lack of attention to how

accessibility can be improved, could lead to catastrophic death tolls and economic strain due to lack of effective antibiotics on the market; it is a reality whose effects are already costing millions of people's lives each year.[49] [50] [51] [52] To limit the loss of life moving forward, the antibiotic infrastructure as a whole requires bottom-up maintenance and expansion – ensuring that those who had access previously can continue to have access, and those who never had it in the first place *will* receive access in the future.

[49] Jim O'Neill, "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations," Review on Antimicrobial Resistance. Wellcome Trust and Department of Health, 2016, 1.
[50] Christopher J.L. Murray, Kevin Shunji Ikuta, Fablina Sharara, Lucien Swetschinski, Gisela Robles Aguilar, Authia Gray, Chieh Han, et al, "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis," *The Lancet* 399, no. 10325 (February 2022): 629–30, https://doi.org/10.1016/S0140-6736(21)02724-0.
[51] Lee Howell, "Global Risks 2013 Eighth Edition." Insight Report. An Initiative of the Risk Response Network, Geneva, Switzerland: World Economic Forum, 2013, https://www3.weforum.org/docs/WEF_GlobalRisks_Report_2013.pdf.
[52] World Health Organization, *Global Action Plan on Antimicrobial Resistance*, (Geneva: World Health Organization, 2015), 1-7.

Chapter One: Historiography of Antibiotics, the Pipeline, Finances, and Access

"I spent the first 2 years in industry just sort of being agog at the number of place/times when I would realize it was something I was ignorant about and I didn't even know before there was a thing to be ignorant about." – John Rex.[53]

"The more progress you make, the harder it is to make even more progress. When a problem is big, usually it's easier to make progress than when the problem already has some relatively okay solutions." – Melvin Spigelman.[54]

The notion of an antibiotic infrastructure was discussed by Clare Chandler in 2019, however prior to 2019 the various factors and components that make up all the facets of that described infrastructure have been written about in great detail by different historians, economists, sociologists, and medical anthropologists alike. This dissertation explores these aspects together under Chandler's use of the concept infrastructure, but this chapter specifically provides a historiography of how these components have been discussed in the past, and where I have drawn both inspiration and edification for the writing of this work.

This chapter is split into four unique sections, each mirroring the four content chapters of this dissertation for clarity and future convenience. The first section focuses on the historiography of antibiotics in general, how antibiotics have been problematized by previous researchers, and the areas where researchers have primarily directed their focus. This includes focus on individual researchers and drugs, as well as the associated drug trajectories of unique drugs as they have been developed. The second section shifts gears from antibiotics on their own, to the conceptualization of an antibiotic pipeline. How has the development of drugs been discussed, and in which way these discussions have driven narratives surrounding drug development and financial consideration. This leads directly to the third historiography: that of an economic nature following the rise of the neoliberal market system and how it

[53] John Rex, Interview with Erin L. Paterson, 1 March 2024.
[54] Melvin Spigelman, Interview with Erin L. Paterson, 21 December 2023.

pertains to pharmaceutical development. I discuss the ways researchers have combined these two areas, and explore how their suggestions relate to the topic of antibiotic development specifically. Finally, the last area of exploration is the historiography of access to medicines and global medical supply chains. There is a vast difference between access needs and challenges between high income countries (HICs) and low-middle income countries (LMICs), and this section briefly elucidates how discussions regarding access and medical supply intersect and how previous researchers have addressed these areas.

Finally, much of the historiographies below are centered on the United States. As María Jesús Santesmases and Christoph Gradmann have pointed out in their own historiography on the circulation of antibiotics, the impact and influence of the United States within this domain (particularly during the post-war era) has been comprehensively studied and detailed in a way that is not necessarily the case for other countries around the world.[55] While these histories and their influences intersect and interweave with non-American sources and experiences, it would be difficult to fully avoid the way the United States maneuverer itself as a growing leader in pharmaceuticals post 1940s, taking over for Germany as a key developer and dominant presence in the market.[56]

I. Historiography of Antibiotics

In 2010, historians Viviane Quirke and Judy Slinn published a book entitled *Perspectives on Twentieth-Century Pharmaceuticals.* Their introduction describes "the growing dependence of the medical profession and the public on pharmaceutical products, and the resulting profits made by drug companies, which have been linked to the increasing

[55] María Jesús Santesmases and Christoph Gradmann, "Circulation of Antibiotics: An Introduction," *Dynamics* 31, no. 2 (2011): 293.
[56] Jesús Santesmases and Gradmann, "Circulation of Antibiotics: An Introduction," 293.

role of marketing in firms' activities."[57] This dependence is one that later supports to the understanding of antibiotics as an infrastructure that is to be relied upon. But to get there, antibiotics needed to become something to be relied on in the first place.

The history of antibiotics is one filled with due praise for the efficacy and efficiency of their use. Physicians and amateur scholars, historians proper, and researchers from across the academic spectrum have contributed to this history as personal experience and individual intrigue supports a perennial fascination with the so called "miracle drug."[58] That physicians might write histories of medicine is not surprising in itself, the American Association for the History of Medicine, for instance, was founded in 1925 specifically by physicians eager to record the histories of the work they conducted, perceived, and admired.[59] Many physicians have indeed gone on to study history as a field in conjunction to their medical training, although, obviously, not all. As a result of this variety of professionals reflecting historically on their fields and varying competencies, as well as internal biases that may arise from pride in the medical field as a whole, there is a range of emotional reactions and responses in many histories written. This does not mean that non-historian accounts should be entirely discounted.

Quirke as well as physicians Jonathan Miner and Adam Hoffhines have written about how the pre-antibiotic era was perceived with a good deal of skepticism revolving drugs or innovations meant to treat bacterial infections.[60] [61] However, their differences in presentation

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[57] Viviane Quirke and Judy Slinn, *Perspectives on Twentieth-Century Pharmaceuticals*, (Oxford: P. Lang, 2010), 4.

[58] More on Ehrlich and the concept of magic bullets or wonder drugs can be found in Bud, *Penicillin*, 14. as well as KJ Williams, "The Introduction of 'Chemotherapy' Using Arsphenamine – the First Magic Bullet," *Journal of the Royal Society of Medicine* 102, no. 8, August 1, 2009, 343–48, https://doi.org/10.1258/jrsm.2009.09k036.

[59] American Association for the History of Medicine, "History," Accessed February 2, 2025, https://histmed.org/history/.

[60] Jonathan Miner and Adam Hoffhines, "The Discovery of Aspirin's Antithrombotic Effects," *Texas Heart Institute Journal* 34, no. 2 (2007): 179, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1894700/.

[61] Viviane M. Quirke, "Penicillin (The History)," in *Van Nostrand's Scientific Encyclopedia*, edited by Glenn D. Considine, 1st ed. (Hoboken, United States: Wiley, 2007), 2, https://doi.org/10.1002/9780471743989.vse10080.

abound, with the physicians breaking into the biochemical make up of antibiotic structures and a continual progressivist perception on the transition from pre to post antibiotic eras, where Quirke makes no such additional references. Rather, she highlights how the use of fungi in medicine has gone back to ancient times, and credits these ancient medical practitioners for their use.[62] Other historians, such as Robert Bud, equally emphasize in their drug histories that even with clear effectiveness of a chemical cure such as an antibiotic against combating disease, the continued effectiveness of that cure is influenced by additional external factors such as infection prevention and control measures or living standards (housing, food, working conditions, etc.).[63]

Despite this, it must be noted that there is an undeniable a sense of wonder that still permeates the historical field when it comes to discussing the medical marvel of drugs. As the historian of science, Jean-Paul Gaudillière, makes clear in his 2005 article on drug trajectories, "Drugs are exceptional objects; if not literally magical, they are certainly wonderful."[64] Antibiotics are no such exception, and their histories are written about by both historians and medical men with that wonder. They are a historical object to be studied, and ones that have fascinated and intrigued both historians and non-historians alike primarily because of the broad scale of their use and the global health care benefits that they have allowed for.

The pre-antibiotic era is written about mainly with a good deal of skepticism revolving drugs or innovations meant to treat bacterial infections,[65] [66] with sanitary measures often cited as more efficacious and trustworthy during this period. However, these measures

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[62] Quirke, "Penicillin (The History)," in *Van Nostrand's Scientific Encyclopedia*, 2.
[63] Robert Bud, *Penicillin: Triumph and Tragedy*. (Oxford, United Kingdom: Oxford University Press, 2007), 5.
[64] Jean-Paul Gaudillière, "Introduction: Drug Trajectories," *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 603.
[65] Jonathan Miner and Adam Hoffhines, "The Discovery of Aspirin's Antithrombotic Effects," *Texas Heart Institute Journal* 34, no. 2 (2007): 179, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1894700/.
[66] Viviane M. Quirke, "Penicillin (The History)," in *Van Nostrand's Scientific Encyclopedia*, edited by Glenn D. Considine, 1st ed. (Hoboken, United States: Wiley, 2007), 2. https://doi.org/10.1002/9780471743989.vse10080.

required societal support and involvement, and were often difficult to implement wholesale. Although medical treatments took longer to develop, they were keenly sought after due to the strain of social reform.[67] [68] And so it is with little wonder that *wonder* is precisely what is attributed to these drugs and their histories.

Gaudillière's description of 'drug trajectories,' though, is one that should be noted in some detail. The term itself was coined in the early 2000s at a conference funded by the Max Planck Institute für Wissenschaftsgeschichte, and is used to describe "the four points of entry into the fate of pharmaceutical goods," i.e.: biological drugs, standardization of drugs, their legal appropriation, and lay expertise.[69] Any combination or reference to these, when focused on one drug in particular emphasizes its full trajectory and lifespan: where it originates from, where it currently rests, and its impact throughout. In Chapter Four, this methodology is applied in relation to the multiple-drug resistant tuberculosis medication, bedaquiline, as a part of this tradition of analysis.

An antibiotic specific drug trajectory that has been previously published can be found in Robert Bud's 2007 book *Penicillin: Triumph and Tragedy.* Bud's work explores the development of penicillin from initial conception through the rise of antimicrobial resistance (particularly that of Methicillin-resistant Staphylococcus aureus [MRSA]). He puts the drug in context with the external factors that exist beyond the drug's use, and highlights how deaths due to infectious diseases had already been steadily decreasing since 1900 due to

[67] Søren Brøgger Christensen, "Drugs That Changed Society: History and Current Status of the Early Antibiotics: Salvarsan, Sulfonamides, and β-Lactams," *Molecules* 26, no. 19 (October 7, 2021): 6057. https://doi.org/10.3390/molecules26196057.

[68] Although vaccines are not the topic of this dissertation, it should be noted that during this period vaccine development was considered a high priority, primarily due to their potential as prophylactics and ability to curb the need for societal interference. However, vaccines were slow to come and alternative interventions were implemented in their stead. For more information, consult: Christian Bonah, Guillaume Linte, Alexandre Wenger, *Maladies infectieuses sans fin. Le cas de la syphilis pour penser la mobilisation-démobilisation prophylactique (XXe-XXIe siècle),* (Geneva, Switzerland : Georg, 2022), 14-15.

[69] Gaudillière, "Introduction: Drug Trajectories," 609-10.

personal hygiene campaigns, an increase of sewage maintenance, ventilation, and overall health standards. In one section Bud specifically states that:

> By 1940, pneumonia and influenza were responsible for only one quarter of the deaths they had been causing there forty years earlier. Deaths from tuberculosis had fallen slightly faster. Typhoid and dysentery, once major causes of death, were now responsible for killing only 2 people in every 100,000. The success of the preventative measures that sustained these major health improvements would be a constant presence in both the prehistory and the history of penicillin. [70]

This part of his drug trajectory does not diminish the lives saved by these medicaments, but rather broadens the overall understanding of these drugs within the context of living in a global society. This is important, because as Susan Leigh Star stated in her discussion on what makes up an infrastructure: infrastructures are *built* upon pre-existing infrastructures.[71] The infrastructures that allow for antibiotics to be successful, are continually interwoven with other infrastructures that are serving alternate purposes.

Although not a drug trajectory, Kevin Brown's 2004 work *Penicillin Man* [72] also serves as a similar kind of history written about antibiotics, though in this sense: the story of who is responsible for the development of an antibiotic. Both Brown and Bud discuss Alexander Fleming, the Scottish physician credited with the discovery of the antimicrobial effects of the mold *Penicillium notatum* in 1928.[73] [74] Brown's account, however, has a tightly narrowed focus, exploring the life and educational pursuits of Flemming in the lead up to penicillin and to the many different thoughts and questions Flemming needed to confront in order to address it.[75] At their core, both Brown and Bud's work emphasize a similar style of writing history: great men and their great inventions. However, these books do provide insight to how the world has changed since Flemming's time.

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[70] Bud, *Penicillin*, 5.
[71] Susan Leigh Star, "The Ethnography of Infrastructure," *American Behavioral Scientist* 43, no. 3 (1999): 381-82, https://doi.org/10.1177/00027649921955326.
[72] Kevin Brown, *Penicillin Man: Alexander Fleming and the Antibiotic Revolution,* (Thrupp UK: Sutton Publishing 2004).
[73] Bud, *Penicillin*, 25-26.
[74] Kevin Brown, *Penicillin Man,* 107.
[75] Kevin Brown, *Penicillin Man*.

There is no infrastructure to support antibiotics in the 20s, and by the 40s, the development process is just beginning. Antibiotics *as* infrastructure certainly don't emerge in this time period. A miracle drug is not something that society is built upon, particularly when very few people globally had access to it in the first place. However, both books do indicate ways in which that infrastructure was capable of emerging. Flemming's various educational pursuits, questions, and negotiations all led to the development of the first wide-scale use of an antibiotic. All the components needed to spread that product: the manufacturing facilities, the development of regulatory oversight, etc. then were able to emerge. This slow development of processes are origins for the infrastructure that follows later. Education of scientists, and the understanding of how to bring a product from a laboratory setting to the market itself are essential to allow for the antibiotic pipeline to function and operate. This will be explored in more detail in Chapter Three.

One thing that should be noted, though, is that even as discussions surrounding miracle drugs proliferated during the early 20th century – not all countries were keen on immediately allowing any and all medication created to enter the market. Scandinavian countries, particularly Norway, hesitated to open the floodgates for countless antibiotics (and indeed drugs in general) from being marketed without cause. Bård Hobæk and Anne Kveim Lie's article on Norwegian drug regulation reveal that as early as the 1920s, Norway was skeptical of arbitrary medical contributions. Via the implementation of a "need clause" which specified that for a new drug to be sold, it needed to prove that alterations, updates, or iterations were all "medically justified," new classes and iterations of antibiotics were limited as they entered the country.[76] The clause pre-dated antibiotics, but even as penicillin began to gain in popularity and other antibiotics began to be developed: the Norwegian director of health, Karl Evang was not swayed to change the regulations. He questioned whether the

[76] Bård Hobæk, and Anne Kveim Lie, "Less Is More: Norwegian Drug Regulation, Antibiotic Policy, and the 'Need Clause,'" *The Milbank Quarterly* 97, no. 3 (2019): 765.

"miracle" of penicillin would be long lasting and if antibiotic resistance would wipe out that miracle's value. [77] Norway was reluctant to allow for any superfluous medication or combination to be disseminated, as maintaining the efficacy of the drugs when possible superseded offering additional variety or the potential for so-called "irrational use." [78] In this way, the potential drug trajectory of penicillin and other antibiotics met a regulatory slow down in Norway that was unlike anywhere else. At least on the global stage: antibiotics were not wholly without question, and even in the beginning of their proliferation – questions about their longevity and continued efficacy lingered.

Beyond the realm of unique drug trajectories and the famous scientists involved in their creation, exists a history of the global impact antibiotics have had as a collective group. As early as the 1950s, the medical miracle that was antibiotics and antibiotic innovation was being referred to as a "Golden Age" The term was coined originally by Maurice L. Tainter, the retiring president of the New York Academy of Sciences, and the then director or the Sterling-Winthrop Research Institute in Rensselaer, N. Y. as he was giving an address on the triumph of the experimental method prior to his departure from the Academy of Sciences, and over the course of an hour extolled upon the great virtues of antibiotic development and the great value and benefit it served to mankind.[79] Tainter may not have realized it at the time, but the era that historians have largely termed the "Golden Age of Antibiotics" (specifically referring to the discovery and development of new antimicrobial compounds) ended not long after he gave his address, with the consensus being that it lasted only between the 1940s and 1960s, with one estimate suggesting that half of all the drugs currently used

[77] Hobæk and Kveim Lie, "Less Is More," 770.768.
[78] Hobæk and Kveim Lie, "Less Is More," 770.
[79] Maurice L. Tainter, "Medicine's Golden Age: The Triumph of the Experimental Method," *Transactions of the New York Academy of Sciences*, II, 18, no. 3 (January 1956): 206–27.

today were developed within that time frame.[80] [81] Matthey I. Hutchings et al published a chart in 2019 detailing detailing each class, its origin, year of discovery, year of introduction, and that has been discovered, along with an example of what specific drug emerged from that class and its molecular target.[82] When expanded graphically, the dates of discovery show a very distinct pattern, with 65% of all antibiotic classes developed between 1940-1969.[83] These antibiotics have remained the first- line defense medical practitioners use against bacterial infections.

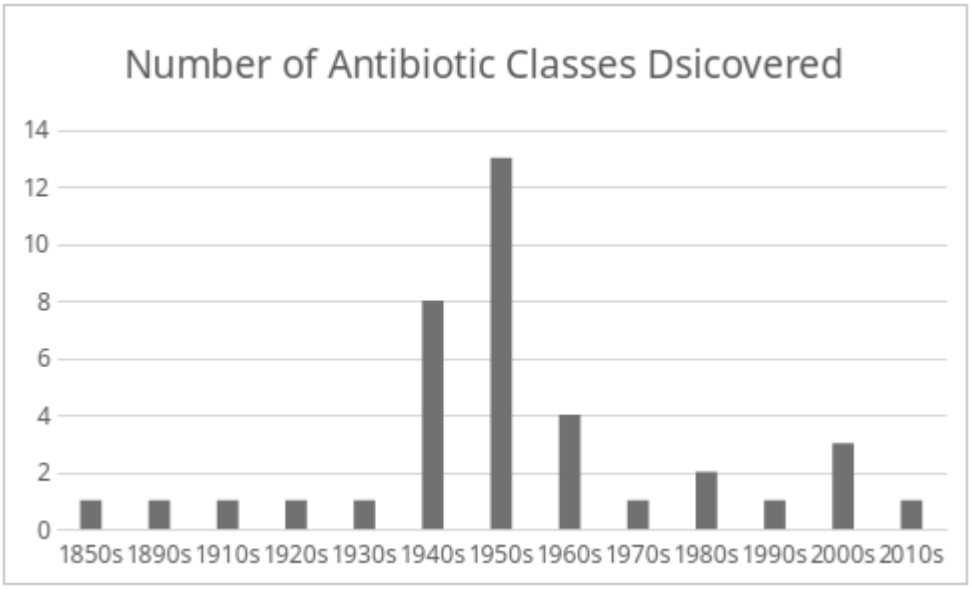

Figure 2 Number of Antibiotic Classes Discovered 1850s-2010s[84]

This period, though, was not simply a period of antibiotic innovation and discovery. In her work on the evolution of policies and politics within pharmaceutical companies, historian and sociologist of science, Dominique Tobbell, described the drug and medical

[80] Christensen, "Drugs That Changed Society," 3.
[81] Julian Davies, "Where Have All the Antibiotics Gone?" *The Canadian Journal of Infectious Diseases & Medical Microbiology* 17, no. 5 (2006): 287, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2095086/.
[82] Matthew I. Hutchings, Andrew W Truman, and Barrie Wilkinson, "Antibiotics: Past, Present and Future," *Current Opinion in Microbiology* 51 (October 2019): 75-76, https://doi.org/10.1016/j.mib.2019.10.008.
[83] For many of these dates, generalized estimates have been used as it depends on public announcement of laboratory discoveries which may vary greatly from the actual moment when a compound was first "discovered" properly. For more information on how these figures were specifically selected for this appendix and this dissertation, please consult: Hutchings, Truman, and Wilkinson, "Antibiotics: Past, Present and Future."
[84] Hutchings, Truman, and Wilkinson, "Antibiotics: Past, Present and Future," 75-76.

research that emerged from the 1950s as "the foundation of innovation."[85] Her choice of words is particularly interesting as a *foundation* is something upon which other things are built. Innovation, is what Tobbell describes growing from this foundation, but with it – infrastructure. The infrastructure capable of supporting that innovation and allowing it to advance. Though that infrastructure was not in place yet, slow but sure – it was on its way.

What Tainter called a "Golden Age," however, historian Scott Podolsky calls the *Antibiotic Era* in his 2015 book on the subject.[86] Within Podolsky's text, this era is a time where antibiotics were fast becoming a key fixture in the medical world – i.e., the infrastructure was forming. Although Podolsky's text is focused on the United States as a center of antibiotic development as well as regulatory innovation, he references events in Europe periodically to provide a general understanding of what is happening in the world beyond American boarders.[87] He builds a strong case on how pharmaceutical companies began building up and promoting these antibiotics as incredible cures capable of handling the terrifying diseases of the past, and with simultaneously reviewing the sprawling scope of these marketing campaigns and their influence on eventual governmental regulations in the United States from the 1950s through to the 1980s.[88] These campaigns included messaging that practitioners should not wait for a culture to come back to identify which antibiotic would be best suited for treatment, testimonials from physicians (later revealed to not exist in the first place) who all claimed a certain antibiotic was the best one to transition to, and "continuing education" campaigns run by pharmaceutical companies that specifically instructed practitioners on their drugs alone.[89] [90]

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[85] Dominique Tobbell, *Pills, Power, and Policy: The Struggle for Drug Reform in Cold War America and Its Consequences,* (Berkeley, United States: University of California Press, 2012), 23.
[86] Scott Podolsky*, The Antibiotic Era: Reform, Resistance, and the Pursuit of Rational Therapeutics, (*Baltimore: John Hopkins University, 2015).
[87] Podolsky*, The Antibiotic Era*; 172.
[88] Podolsky*, The Antibiotic Era*.
[89] Podolsky*, The Antibiotic Era*, 70, 99, 137.
[90]For information on specifically how these salesmen conducted themselves and their intentions within their meetings, consult: Jeremy A. Greene, "Attention to 'Details': Etiquette and the Pharmaceutical Salesman in

These efforts, again, point to a *lack* of infrastructure rather than an established one. Pharmaceutical companies during this era were racing to find ways to ensure their product was getting noticed and that physicians would prescribe their formulation above others. If an infrastructure already existed and was established, most of these efforts would not be necessary as the physician would already be aware of and capable of prescribing effectively without such machinations.

These efforts, of course, were not solely limited to the United States. Quirke has also noted how marketing and pharmaceutical influence began to intersect with European physicians as well. In the 1960s, the Sainsbury Committee was set up by the British Government "to investigate the relationship between the pharmaceutical industry and the National Health Service," and found that "research and sales promotion were "closely entwined" and had a "profound influence" over each other."[91] Both British and French companies would, in the following decades, also begin to replicate and participate in the process of marketing to American audiences specifically,[92] emphasizing the international spectrum of "the industry" as a whole. Rarely was the industry or its influence wholly confined to one country's territorial boarders.

What is clear, though, is that with all of this attention towards marketing, there was a stock surplus of goods to be sold. The many pharmaceutical companies that were involved in these aggressive marketing campaigns did so with the belief that demand would be able to keep up with production, and that production was good. Indeed, the numbers of new antibiotics entering the market as well as the number of antibiotics that were shifting from patent protection to off-patent protection rose at an exponential rate during the golden

Postwar American," *Social Studies of Science* 34, no. 2 (April 2004): 271–92, https://doi.org/10.1177/0306312704043029.

[91] Viviane Quirke, "Targeting the American Market for Medicines, ca. 1950s–1970s: ICI and Rhône-Poulenc Compared," *Bulletin of the History of Medicine* 88, no. 4 (2014): 657, https://doi.org/10.1353/bhm.2014.0075.

[92] Quirke, "Targeting the American Market for Medicines;" 655–6.

age/antibiotic era. While unique classes of antibiotics seemed relatively low by comparison, differing formulations numbered within those classes were quickly releasing year after year. By one calculation, some six-thousand formulations had been identified and marketed by 1990,[93] more than 150x the number of classes. As these antibiotics shifted off patent and into the generic sphere, attempts to keep brand name loyalty was essential and marketers insisted on the quality and effectivity of originator compounds as a result.

Generic drugs, and drugs that were close enough to originator compounds to pass regulatory approval but not necessarily trigger patent infringement (i.e.: biosimilars), are a key part of antibiotic history and consideration. Jeremy A. Greene writes about both in his book *Generic: The Unbranding of Modern Medicine.* To be considered a biosimilar, the molecular modifications to an existing antibiotic had to be "*not* significantly different" or similar drugs sold at different prices (higher, in the case of drugs attempting to be passed along as newly innovative, and lower if they were purely an off patent generic version of a pre-existing drug) but, even if they were, competitor companies frequently complained about anything that was *too* similar to their own product as being "false innovations, or 'me-too' drugs."[94]

The term "me-too" was first used in relation to drug development in the 1950s, but medical theorists and practitioners began using it more frequently in the 1960s.[95] By 1994, a professor of pharmacology, Desmond Laurence, defined the phrase as "Slang for a drug developed to allow a pharmaceutical company to gain a share of the existing market. Any gain to therapeutics is purely incidental. Where a company introduces a drug very similar to

[93] Milton Wainwright, *Miracle Cure: The Story of Penicillin and the Golden Age of Antibiotics*, Oxford, United Kingdom: Basil Blackwell Ltd, 1990 185.
[94] Greene, *Generic*, 211.
[95] Jeffrey K. Aronson, and A. Richard Green, "Me-too Pharmaceutical Products: History, Definitions, Examples, and Relevance to Drug Shortages and Essential Medicines Lists," *British Journal of Clinical Pharmacology* 86, no. 11 (November 2020): 2114-2115, https://doi.org/10.1111/bcp.14327.

one of its own existing drugs, this has been called a me-again drug."[96] [97] Pharmaceutical companies only achieve profits if their patents are active, and so if a me-too drug is released onto the market and can start chipping away at the profit (and worse: when a generic drug is released at a substantially lower price than the originator) then the company loses value as a result. Discrediting me-too, biosimilars, and generics, therefore was essential.

And yet, both Greene and Podolsky (writing together) have called attention to the fact that pharmaceutical companies on a whole produced both originating drugs *and* me-toos, and the very companies complaining about generic versions of *their own products* also created generic versions of *other companies' products.* Nowhere is this more clear than during the 1959-1962 Kefauver hearings on drug efficacy and price assessments. During the drafting stage of the Amendments that would emerge from the hearings, these companies cried foul at the idea that me-too drugs be eliminated from the market, *and* at the notion that only drugs with a "significantly greater" therapeutic value be permitted for sale.[98] "Efficacy was hard enough to prove, [the pharmaceutical companies suggested]; proving comparative efficacy would be 'completely impracticable.'"[99] Complaining about other companies inferiority in the public was one thing, but actually putting it into practice and law was something else entirely different, as the companies themselves don't seem to actually want regulation that would inhibit the practice of product generation should they decide to do it themselves.

[96] Desmond Roger Laurence, *A Dictionary of Pharmacology and Clinical Drug Evaluation*. London: UCL Press, 1994, 138.
[97] While there was no discussion of an antibiotic pipeline during this period, retrospectively, the support of an off-patent ecosystem of drugs that were easily able to be circulated fits in well with Drive-AB's 2019 pipeline that extended into the concept of a generic market. More on this interpretation can be found in: DRIVE-AB Antibiotic Pipeline. Christine Årdal, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John H. Rex. "Revitalizing the Antibiotic Pipeline." Final Report 2018. (Geneva, Switzerland: DRIVE-AB, 2018), 5.
[98] Jeremy A. Greene and Scott H. Podolsky, "Reform, Regulation, and Pharmaceuticals — The Kefauver–Harris Amendments at 50," *New England Journal of Medicine* 367, no. 16 (October 18, 2012): 1482, https://doi.org/10.1056/NEJMp1210007.
[99] Greene and Podolsky, "Reform, Regulation, and Pharmaceuticals," 1482.

Generics, me-toos, and biosimilars are all a part of the economic system that supported the industry, one way or another.

The debate around generics, off-patent, biosimilars, and originator products, however, reveals that what was once considered a miracle drug had now in fact been turned into a common place commodity. Penicillin wasn't the only antibiotic on the market, countless formulations were developed and distributed each year, and with increasing global access. Tracking the extent of that global access, and in what areas it was improving is challenging.

In 2022, Palanco Lopez et al., published *Antibiotic arrivals in Africa* to help elucidate on this transition. They note that there is an "impressive body of historical research on antibiotics, particularly in the global north," but how such a corpus is lacking for the global south.[100] Their article (specifically focused on Africa) goes on to describe how antibiotics were used as a form of biomedical humanitarianism on one hand, and as a justification for empire on the other.[101] It would take until the 60s before anti-colonial sentiment allowed for a non-empirical influx of humanitarian (and antibiotic) assistance to take place. [102] In the interim, they found that antibiotic use was primarily found via East African public health campaigns that catered to colonial paradigms and presumptions were led largely around venereal disease as what could be seen as a way to relieve suffering equally was a method of stabilising colonial rule. [103]

Dialogue surrounding the use of antibiotics took on a strongly paternalistic role, particularly as the effective quality of antibiotics meant that those being treated for venereal disease didn't need to change their "bad behaviours" in order to be heathy. [104] Concern over

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[100] Paula Palanco Lopez, Salome Manyau, Justin Dixon, Eleanor MacPherson, Susan Nayiga, John Manton, Claas Kirchhelle, and Clare I. R. Chandler, "Antibiotic Arrivals in Africa: A Case Study of Yaws and Syphilis in Malawi, Zimbabwe and Uganda," *Medicine Anthropology Theory* 9, no. 3 (September 23, 2022): 2. https://doi.org/10.17157/mat.9.3.5633.
[101] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 4-5.
[102] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 5.
[103] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 7-10.
[104] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 18.

misuse of antibiotics equally was on the rise, as Africans were accused of "discontinuing treatments and not committing to medical science." [105] This paternalistic language and demeaning oversight, was compounded by the fact that the treatment plans for Europeans differed than that of Africans. Where Europeans received a combination therapy for the treatment of syphilis, Africans received only one shot of procaine penicillin with repeated doses only administered of supplies were "plentiful." [106] Palanco Lopez et al., put the situation particularly bluntly by stating that "This example shows how explicitly treatment of Africans with antibiotics depended on the resources available—and how accepted this fact was at that time." [107]

While antibiotics did exist and were entering communities, the variety and the availability of those drugs was in question. Knowledge of the antibiotics was there, and treatments could be provided, but in specific circumstances and depending on external factors. Palanco Lopez et al., identify this particular usage of antibiotics as a component of the colonial government infrastructure set on maintaining control and power over populations. [108] While this is certainly the case, they also identify how those infrastructures can be put in place to allow for antibiotics to function in the way that they do. Government purchasing and down-stream distribution methods provide drugs and make them available, and while not *every area* did have access to these drugs – the density of populations with increasing access to them was clearly growing.

In a 1979 New York Times article, Marietta Whittlesey listed countries from one side of the world to the other that not only had ample access to antibiotics, but also: antibiotic resistance.[109] Her, at times, judgemental and paternalist view of lower income countries such

[105] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 18.
[106] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 18.
[107] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 18.
[108] Palanco Lopez, et al., "Antibiotic Arrivals in Africa," 20.
[109] Marietta Whittlesey, "The Runaway Use of Antibiotics," (*The New York Times*, May 6, 1979), sec. Health, https://www.nytimes.com/1979/05/06/archives/health-the-runaway-use-of-antibiotics.html.

as Brazil, Guatemala, and Mexico were tempered by concern for American servicemen serving in places such as the Philippines or Guam who were also susceptible to acquiring a resistant strain.[110] Whittlesey identified overuse as one major problem, but to overuse a drug: it cannot have been difficult to acquire in the first place. More to the point, it becomes evident that antibiotics by the end of the 1970s, those in the global north at least took antibiotics for granted. They were easy to use, and seemingly accessible, and the idea that others were potentially not using them appropriately was of more concern than anything else. This perception of how simple antibiotics were to take, and acquire, indicates that they were no longer a miracle meant to be treasured. They had saturated the market, and an infrastructure capable of ensuring they did so: was in place.

This does not mean that antibiotics were globally accessible to all people in all places. Palanco Lopez et al., have already made that clear. However, there was a *perception* in the north that they were perfectly accessible, and as such they had begun to be taken for granted by some populations around the world. The infrastructure meant to ensure that antibiotics could be capable of supporting healthcare: had been established for these individuals, and all the intersecting components that had been developed in order to ensure that it could succeed: were a part of a Latourian black box, and invisible from sight.

There are no discussions on how this process was put into place. Rather, conversations in this time period and about this time period tend to focus on patent law and changes in financial structures and institutions. Both of these areas contribute to the infrastructure that enable antibiotics to succeed, but they are not identified as such. Innovation, and unique discoveries continued to capture the attention of those working in this space. One off discoveries and how they're managed, rather than how each of these discoveries take shape in a larger ecosystem.

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[110] Marietta Whittlesey, "The Runaway Use of Antibiotics," sec. Health.

It was this spirit of innovation and a desire to more quickly and accurately discover new antibiotics that how pharmaceutical companies searched for new compounds began to change. Prior to the 1970s, pharmaceutical companies relied on mass-screening of natural samples in a hit-or-miss method of seeing if a molecule could have antimicrobial potentials. Many of antibiotics were discovered in this way, however calls for new innovation led to discussions revolving round *rational* drug design.[111] [112] Rational drug design is a methodology where researchers specifically target "molecular structures already known to have antimicrobial effects… [in hopes of minimizing] risks in developing new drugs and avoid[ing] wasting resources on ineffective compounds."[113] Quirke has suggested that the rise of rational drug design came as a result of the increased presence of marketers within pharmaceutical development spaces.[114] Because companies already know that there is a more-than likely chance an effect will take place when certain chemical components are put together, research focus and investment is thus more funneled in these "proven" directions. Chances of dire consequences are equally mitigated by this strategy. [115] Marketers were able to generate funding and increase interest in drugs within developmental pipelines by assuring prospective shareholders of their lead's scientific potential. In the case of cancer research, these leads were largely successful, but for antibiotics: this was not the case.

In 2013, molecular microbiologist Kim Lewis published a scathing condemnation of the use of rational drug design when it came to antibiotic development. If rational drug design could be condensed into a series of rules delineating likelihood of success (e.g.: Lipinski's

[111] L. Silver and K. Bostian, "Screening of Natural Products for Antimicrobial Agents," *European Journal of Clinical Microbiology and Infectious Diseases* 9 (July 1990): 455, 459.
[112] Kim Lewis, "Platforms for Antibiotic Discovery," *Nature Reviews Drug Discovery* 12, no. 5 (May 2013): 371, https://doi.org/10.1038/nrd3975.
[113] Mirza Alas Portillo, Isabel M. Gomez Rodríguez, Christoph Gradmann, Claas Kirchhelle, Jørgen J. Leisner, Laura Martinenghi, Erin L. Paterson, Maria Jesús Santesmases, Belma Skender, and Frédéric Vagneron, "Paradoxes of the Antibiotic Pipeline," *Humanities and Social Sciences Communications* 11, no. 678 (May 27, 2024), 2, https://doi.org/https://doi.org/10.1057/s41599-024-03211-1.
[114] Quirke, "Targeting the American Market for Medicines," 659.
[115] Quirke, "Targeting the American Market for Medicines," 659.

Rules), then in Lewis's own terms: "antimicrobials do not obey the rules." [116] Where other molecular compounds were showing increased promise,[117] making it through the developmental pipeline and out into the world of market authorization and accessibility: antibiotics floundered.

One reason for this, could be that rational drug design by its very nature targets that which is already in existence. If an effect or a molecular composition is already known, then developing a drug that mimics such a thing is naturally a more straight forward process. Chapter One has already discussed the ways in which subtle molecular changes for antibiotics do not necessarily indicate class or efficacy changes. A truly *new* molecular entity is a rare output using this methodology. And indeed, since the 1990s, brand new and uniquely innovative medicinal developments have been rare across all sectors of pharmaceutical innovation, with attrition rates only ever on the rise.[118]

The infrastructure that allowed for antibiotics to be depended on was already in place, and the pillar here that was most affect was that of the antibiotic research and development pipeline. To put it in stark terms: the pipeline had been working more or less as it always had been with researchers going into the field, finding samples, then returning to the lab to conduct tests and eventually produce a new product. Flaws, such as the lead time or the amount of staff or man power needed to conduct these tests and experiments, were identified by the pharmaceutical industry who were interested in cutting costs to improve the pipeline's efficiency. Maintenance, here meaning a correction applied to the pipeline, was conducted. This maintenance came in the form of rational drug design, altering the way in which that

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[116] Lewis, "Platforms for Antibiotic Discovery," 374.
[117] Matthias Adam, "Integrating Research and Development: The Emergence of Rational Drug Design in the Pharmaceutical Industry," *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 36, no. 3 (September 2005): 514, https://doi.org/10.1016/j.shpsc.2005.07.003.
[118] Fabio Pammolli, Laura Magazzini, and Massimo Riccaboni, "The Productivity Crisis in Pharmaceutical R&D," *Nature Reviews Drug Discovery* 10, no. 6 (June 2011): 429, https://doi.org/10.1038/nrd3405.

pipeline was operating.[119] This maintenance, regrettably, did not produce the results expected, and the pipeline as a result slowed to a crawl. The equivalent of someone attempting to adjust a leaking faucet and snapping the whole pipe in half in the process. Maintenance is not always preventative or restorative. Sometimes, it can make matters worse.

The choice to transfer to rational drug design, however, was perfectly – in a word – rational, and throughout this dissertation it has been important to understand the context of how and why changes to already established components of infrastructure were put into place. Rational drug design promised that there would be a higher likelihood of success if the proven outcome is known, pharmaceutical companies were convinced that these targets would be a safe (if not certain) financial bet. However, when it proved that there were limited outcomes to using this methodology, they were still left with the same issue that inspired them to make this "maintenance" adjustment in the first place – a need to lower the overall costs of producing a new antibiotic without accruing the excess expenses that emerged from high rates of attrition.

Enter, the 1980 Bayh-Dole Act.

The act, designed by democratic senator Birch Bayh and republican senator Bob Dole, restructured United States patent laws so that any academic institution that developed a product using government money would be able to patent that technology and sell the product or license for royalties.[120] Prior to its passing, government funded research remained in the public domain or was retained by government ownership.[121] After its passing, sales from academia to pharmaceutical companies paved the way for a veritable market boom as

[119] This type of maintenance, where in an effort to "repair [something, the] technology is 'fixed' by altering the manner in which users perceive or engage with it," is discussed in greater detail in: Mark Thomas Young and Mark Coecklebergh, *Maintenance and Philosophy of Technology: Keeping Things Going*, (Routledge Studies in Contemporary Philosophy. New York, United States: Taylor & Francis Group, 2024) 11.
[120] Aaron S. Kesselheim, "Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation," *The New England Journal of Medicine, Health Law, Ethics, and Human Rights, 363*, no. 19 (2010): 1856.
[121] Michael S. Mireles, "Adoption of the Bayh-Dolye Act in Developed Countries: Added Pressure for a Broad Research Exemption in the United States?" *Maine Law Review,* Trends in Intellectual Property & Scientific Research, 59, no. 2 (June 2007): 261.

publicly research could now earn profits beyond the government's oversight. Universities and small biotech companies quickly flourished in this new environment. In the United States, this opened the door for pharmaceutical companies to monitor and observe, and in some cases financially support, educational facilities that were conducting research using government funds. If a failure occurred at a university – then it would be no great loss to the pharmaceutical company. But if a success happened, rather than conduct their own in-house research and development, they could instead monitor promising drug development processes taking place in universities or biotechs and simply buy the license once it became available.[122]

European interaction between university, industry, and government had once been a standard state of affairs.[123] Prior to antibiotics, medical research was largely conducted in university or other research institute settings. [124] When antibiotics quickly began to gain popularity in the new post-war world, though, pharmaceutical companies brought much of that research in-house. [125] Quirke highlights the ways some of these differences manifested in her book, *Collaboration in the Pharmaceutical Industry: Changing Relationships in Britain and France.* However, similar changes were occurring across the ocean as well. Lines of ownership, delineation of departments, and conflicting political motivations, led to the formation of distinct research bodies.[126]

After the United States' breaking the barriers between their public and private sectors via the passing of the Bayh-Dole act, other countries in Europe followed suit.[127] New

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[122] Such as in the case of sofosbuvir and Emory University: Victor Roy, *Capitalizing a Cure: How Finance Controls the Price and Value of Medicines,* (Oakland, United States: University of California Press, 2023), 30.
[123] For more information on how these evolving collaborations took place in two European nations, consult: Viviane Quirke, *Collaboration in the Pharmaceutical Industry: Changing Relationships in Britain and France 1935-1965,* (New York: Routledge, 2008).
[124] Quirke, *Collaboration in the Pharmaceutical Industry,* 247.
[125] Quirke, *Collaboration in the Pharmaceutical Industry,* 170.
[126] Quirke, *Collaboration in the Pharmaceutical Industry,* 170.
[127] Thorsten Gores and Albert N. Link, "The Globalization of the Bayh–Dole Act." *Annals of Science and Technology Policy* 5, no. 1 (2021), 9-11, https://doi.org/10.1561/110.00000018.

businesses, such as technology transfer businesses aimed at helping to move the rights over innovative technology from the originating inventor to another entity more capable of marketing and producing that technology, equally began to emerge in the fall out. One such enterprise, AUTM (the Association of University Technology Managers) proudly declares that over 200 drugs and vaccines have been developed through public-private partnerships since Bayh-Dole Act was put in place.[128] This growth, and the tradition of utilising these partnerships, as well as how these partnerships have influenced the infrastructure of antibiotic development in particular, are a core piece of the analytical discussion relating to the antibiotic pipeline in Chapters Three and Four.

It should be noted, though, that pharmaceutical companies have not completely abandoned research responsibilities to universities with the sole expectation that public funds will support drug discovery. By 2002, it was estimated the amount invested into university research by pharmaceutical industries had reached upwards of $1 billion, with the number of research institutes growing from "twenty-five in 1980 to two hundred in 1990."[129] However, this investment is still a fraction of what in-house drug development would have cost the industry had they continued to devote themselves fully to in-house research. Their investments, though, do carry with them their own biases. For academic institutions: enticing a company to provide research money is only as effective as the promise of a potential compound. Biases on which kinds of products could be of most value or interest to the industry naturally would feed their way into these new research centers.[130]

[128] For more information consult: AUTM, "Driving the Innovation Economy: Academic Technology Transfer In Numbers," Infographic, AUTM, 2021, https://autm.net/AUTM/media/Surveys-Tools/Documents/AUTM-Infographic-2021.pdf.
[129] Aaron S. Kesselheim, "An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences: Review of Legislation Affecting Drug Development," *Milbank Quarterly* 89, no. 3 (September 2011): 460. https://doi.org/10.1111/j.1468-0009.2011.00636.x.
[130] For a comprehensive breakdown on the ethical and research bias concerns, consult: Ajai Singh and Shakuntala Singh, "The Connection between Academia and Industry," *Mens Sana Monographs* 3, no. 1 (2005): 5-35, https://doi.org/10.4103/0973-1229.27876.

Aaron S. Kesslheim, Professor of Medicine at Harvard Medical School, has indicated in his own research that the direct relationship between Bayh-Dole and pharmaceutical development may not be a perfect link of uncontested trajectory. And that while research has shown that "between 1998 and 2005 … [United States] government funding played a role in almost half of the 478 products [produced during that time period], including almost two-thirds of the most important or innovative ones," (such as 157 FDA approved drugs, vaccines, or new indications) it is not clear if the Bayh-Dole Act was the progenitor of such action or changing in licensing process.[131] I would argue that this is an unnecessarily splitting of the question at hand. As Kesslheim himself states in that same article, the act "gave U.S. small businesses and nonprofit organizations the authority to retain control of the patent rights in inventions arising from government sponsored research and to offer exclusive licenses to private firms…" and that it "enhanced patenting and licensing at research universities."[132] To delineate between the impact of Bayh-Dole or the impact of licensing changes and quibble over if one or the other had the greater impact on public spending in universities leading to private ownership of patents and investment is to create an artificial separation between two intrinsically aligned transitions.

Throughout all of this: the infrastructure that allows for antibiotics to thrive continues to take shape. Education is needed to generate new scientists capable of creating new antibiotics. Those antibiotics then need to be developed, and some form of financial influx is put into the development process in order to ensure the drug makes it through those phases, and eventually out into the world. Regulations, tightening the control on when and where antibiotics can be used and in which circumstances, as well as quality control and clinical trial testing requirements, are put in place to make sure the efficacy of the drug is there, and

[131] Kesselheim, "An Empirical Review of Major Legislation Affecting Drug Development," 462.
[132] Kesselheim, "An Empirical Review of Major Legislation Affecting Drug Development," 453-454.

then the drug moves along.[133] Even as this myriad of researchers are discussing drug histories and antibiotic potentials: they are also describing how the infrastructure that eventually holds up antibiotics as a key facet of health care take shape.

This infrastructure however, is one that was also operating under changing regulatory measures that specifically targeted the production, testing, and dissemination of antibiotics. Two forms of regulatory measures that affected antibiotics include those dedicated specifically to concerns of antibiotic resistance and those that were concerned with drug safety/efficacy.

Christoph Gradmann and Class Kirchhelle recently wrote a book chapter in *Steering Against Superbugs* highlighting regulatory efforts specifically targeting resistance. They discuss how the notion of resistance, or drug fastness as it was originally called, was not unique or unheard of. The concept had been circulating since the 1910s and with particular attention regarding antibiotic resistance rising in the 1950s.[134] However, it should be noted that there was no true concern for antimicrobial resistance at this time. The general conception of the problem of resistance was that even should bacteria gain resistance, a new antibiotic could be developed to replace the old. (The black box of not worrying about a problem until it arises, continuing to take effect). Intermittent outbreaks of MRSA were cause for alarm, but they were localized hospital-specific outbreaks that could be addressed with improved hygiene and not nearly pandemic worthy in occurrence. [135] Agricultural usage of antibiotics *were* the target of regulatory efforts, however, and throughout the 60s this use was

[133] Regulations are extremely expansive and can cover a broad spectrum of changes and influences, some of this history can be explored here: Scott H. Podolsky, Robert Bud, Christoph Gradmann, Bård Hobaek, Claas Kirchhelle, Tore Mitvedt, María Jesús Santesmases, Ulrike Thoms, Dag Berild, and Anne Kveim Lie, "History Teaches Us That Confronting Antibiotic Resistance Requires Stronger Global Collective Action," *Journal of Law, Medicine & Ethics* 43, no. S3 (2015): 27–32. https://doi.org/10.1111/jlme.12271.

[134] Christoph Gradmann and Claas Kirchhelle, "Pills and Politics: A Historical Analysis of International Antibiotic Regulation since 1945," In *Steering Against Superbugs*, edited by Olivier Rubin, Erik Baekkeskov, and Louise Munkholm, 1st ed., 19–30, (Oxford University Press: Oxford, 2023), 20, https://doi.org/10.1093/oso/9780192899477.003.0002.

[135] Gradmann and Kirchhelle, "Pills and Politics: A Historical Analysis of International Antibiotic Regulation since 1945," 20-21.

eventually restricted so as to delineate antibiotics that would be used for humans from those in the agricultural sector in efforts to ensure overuse in one area would not promote resistance in the other.[136] [137]

More attention towards antimicrobial resistance (AMR) specifically began to emerge in the 1990s, and the heightened attention of these regulatory efforts reinforce that at this point: antibiotics were broadly used enough, and depended on enough, that they truly had become an infrastructure by this point. Gradmann and Kirchhelle identify, "the structural factors driving increasing antibiotic use— and growing infrastructural antibiotic dependency," [138] as matters that had not fully been addressed by this point. Rather, the ball had continually been kicked down the road. Without a problem large enough to deal with, the regulatory efforts being put in place to maintain this infrastructure were seen as sufficient. The succeeding chapters of this dissertation will address these points in more detail.

The second branch of regulatory involvement when it came to antibiotics, though, was slightly different. The 1950s-60s saw a series of health scares where multiple medications were registered and marketed around the world without proper testing. [139] [140] [141] The worst of these scares was known as the thalidomide catastrophe, where more than 10,000 children were born with serious birth defects across 46 countries (4,000 in West Germany alone).[142] [143] The result of these events, by and large, led to regulatory agencies becoming "major

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[136] Gradmann and Kirchhelle, "Pills and Politics: A Historical Analysis of International Antibiotic Regulation since 1945," 22.
[137] Additional information regarding this transition can be found in: Claas Kirchhelle, *Pyrrhic Progress: The History of Antibiotics in Anglo-American Food Production,* (New Jersey: Rutgers University Press, 2020).
[138] Gradmann and Kirchhelle, "Pills and Politics: A Historical Analysis of International Antibiotic Regulation since 1945," 22.
[139] Christian Bonah and Jean-Paul Gaudillière, "Faute, Accident Ou Risque Iatrogène ? : La Régulation Des Événements Indésirables Du Médicament à l'aune Des Affaires Stalinon et Distilbène," *Revue Française Des Affaires Sociales*, no. 3 (September 1, 2007): 123–51. https://doi.org/10.3917/rfas.073.0123.
[140] Jean-Paul Gaudillière and Volker Hess, eds, *Ways of Regulating Drugs in the 19th and 20th Centuries*, (London, United Kingdom: Palgrave Macmillan, 2013), 5.
[141] Neil Vargesson, "Thalidomide-induced Teratogenesis: History and Mechanisms," *Birth Defects Research Part C: Embryo Today: Reviews* 105, no. 2 (2015): 140. https://doi.org/10.1002/bdrc.21096.
[142] Gaudillière and Hess, *Ways of Regulating Drugs in the 19th and 20th Centuries*, 5.
[143] Vargesson, "Thalidomide-induced Teratogenesis: History and Mechanisms," 140.

gatekeepers" when it came to the medicines market.[144] In West Germany, the manufacturer of thalidomide had only been required to register the drug, and it had been "up to the company when and how (if at all) it would test its new product." [145] However, as Jean-Paul Gaudillière and Volker Hess have pointed out: in countries where regulatory requirements were more stringent, fewer individuals were affected by the drug. [146]

For the United States: they intended to keep it that way. Fear of a thalidomide style disaster happening in the United States, despite their already present testing requirements, led to then Senator Estes Kefauver to initiate a series of inquiries into not only drug efficacy, but also drug pricing, between 1959-1962. The final result was what has been called the Kefauver-Harris Amendments. These Amendments granted the FDA "the power to restrict advertisements and establish standards for clinical trials," and "required drug manufacturers to provide proof of efficacy for all drugs approved since 1938."[147]

Greene and Podolsky both wrote on how these regulations were put into practice, and the overall impact on drug development. For instance: the implementation of clinical trial regimes, or the restriction of combination therapies that used more than one drug at once. Their work found that by the end of the 60s, these regulations required pharmaceutical companies to clinically prove that the drugs taken in concert with one another were superior that merely taking the individual components separately. [148] All fixed dose combinations that had been previously available were banned, and by 1980 only one such combination (trimethoprim–sulfamethoxazole [Bactrim]) had managed to prove its improved efficacy. [149] The use of fixed dose combinations is something that appear throughout this dissertation as

[144] Quirke, "Targeting the American Market for Medicines," 659.
[145] Gaudillière and Hess, *Ways of Regulating Drugs in the 19th and 20th Centuries*, 5.
[146] Gaudillière and Hess, *Ways of Regulating Drugs in the 19th and 20th Centuries*, 5.
[147] Edward Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," *Sage Publications, Ltd.* 44, no. 4 (August 2014): 491, https://www.jstor.oerg/stable/43284157.
[148] Podolsky and Greene, "Combination Drugs — Hype, Harm, and Hope,"490.
[149] Podolsky and Greene, "Combination Drugs — Hype, Harm, and Hope,"490.

some researchers have found that these therapies (when applied correctly) may help reduce rates of AMR and improve health outcomes.[150]

Understanding how regulations have potentially created a "breakdown" in the infrastructure allowing these combinations to go through, and seeing where the concern originated from helps give perspective onto cost benefit analysis of whether the rewards outweigh the dangers of their use. In all these cases though, the antibiotic development pipeline is slowly yet surely coming to the fore, and it is the pipeline's historiography which must be understood next.

II. Historiography and Analysis of the Use of the (Dry) Antibiotic Pipeline

While undertaking my doctoral research, I worked frequently with my fellow Dry AP team member: Mirza Alas Portillo of University College of Dublin. Our two work packages were very closely aligned, particularly in regards to how we were problematizing the antibiotic pipeline, though her work was specifically dedicated to tracing the historiography of the Dry AP phenomenon and its specific uses and connotations in the modern era. The antibiotic pipeline as it has been problematized by different actors and governments, is a fairly nascent concept. Alas Portillo's thesis is one of the first major bodies of work that analyses the historiography of the pipeline and its trajectory. However, this section offers a primer to her greater work, and highlights the ways that different actors have used the pipeline to further their own particular motivations. Throughout this section, though, I reflect on how these narratives relate to the concept and notion of antibiotic infrastructure.

In her 2024 doctoral dissertation, Alas Portillo indicates that rising concern for lack of antibiotics in development experienced a particular spike in the early 2000s, rising to a fever pitch around 2016.[151] Together, our research uncovered that prior to this time period,

[150] Richard Laing, Interview with Erin L. Paterson, 11 November 2022.
[151] Mirza Alas Portillo, "How the pipeline ran dry: towards a critical historiography of the antibiotic pipeline 1980-2020," Unpublished doctoral dissertation, University College of Dublin. 2024.

concerns about antibiotics were primarily focused on "secondary to other issues,[152] such as antibiotic stewardship," (i.e.: the careful management/conservation of antibiotics).[153] In the United States, the wake of the 9/11 terror attacks raised fears of bioterrorism and lack of effective antibiotics as a national security risk. Project Bioshield and the Biomedical Advanced Research and Development Authority (BARDA) were developed as government responses to the concern,[154] and national attention on antibiotics and the necessity of new and old formulations rose as a result.

As Alas Portillo's research mentions, only a short time after the United States began ramping up its concerns around antibiotic productivity and supply chain surety, the first uses of the words "dry pipeline" appeared in two separate articles published first in *Nature*[155] by an academic specializing in infectious disease research, and later in the *Lancet*[156] by an active-duty nurse. The *Lancet* article links the United States' concern of lack of effective treatments against "superbugs" (aka: resistant bacterial infections) to a need to develop new antibiotics immediately, and highlights how few companies are actually still invested in antibiotic research.[157] Both articles, however, immediately link the problem of the dry pipeline not to the scientific discoveries inherent in product creation, but to financial sources. Due to the rising costs of drug development, increased regulation, and soaring profits in other

[152]K. Overton, N. Fortané, A. Broom, S. Raymond, C. Gradmann, E. S. F. Orubu, Scott H. Podolsky, S. R. Van Katwyk, Muhammad H. Zaman, and Claas Kirchhelle, "Waves of Attention: Patterns and Themes of International Antimicrobial Resistance Reports, 1945– 2020," BMJ Global Health 6 (2021): 4, https://doi.org/doi:10.1136/bmjgh-2021-006909.
[153]Mirza Alas Portillo, Erin L. Paterson, Nadya Wells, Frédéric Vagneron, and Claas Kirchhelle, "Emerging Financial Models for Antibiotic Development (2000-2016). Witness Seminar Conducted by the DryAP Project and in Collaboration with the Global Health Centre, Geneva Graduate Institute," Université de Strasbourg, 2024, 30, https://doi.org/10.34931/N7PK-3N88.
[154]Jackson Landers, "The Anthrax Letters That Terrorized a Nation Are Now Decontaminated and on Public View," *The Smithsonian Magazine,* September 12, 2016, https://www.smithsonianmag.com/smithsonian-institution/anthrax-letters-terrorized-nation-now-decontaminated-public-view-180960407/.
[155]T. Clarke, "Drug Companies snub antibiotics as pipeline threatens to run dry," *Nature* 425, no. 6955 (Sep 2003), https://doi.org/10.1038/425225a.
[156]Roxanne Nelson, "Antibiotic development pipeline runs dry – New drugs to fight resistant organisms are not being developed, experts say," *Lancet* 362, no. 9397 (Nov 2003), https://doi.org/10.1016/S0140-6736(03)14885-4.
[157]Nelson, "Antibiotic development pipeline runs dry."

sectors: antibiotics were simply too unprofitable to develop for the expected return on that investment.[158]

Continued discourse around the dry pipeline emerged in 2006 when the Infectious Diseases Society of America published its report: "Bad Bugs Need Drugs: An Update on the Development Pipeline"[159] It too discusses how development is key to treat a "medical need," but when it discusses the pipeline, it does so by distinctly linking the development pipeline to eventual production and dissemination of the product.[160] There are two factors at play here: the pipeline of scientific inquiry and innovation, and the ability for a newly invented antibiotic to actually emerge onto the market. Indeed, "the pipeline reflects active decisions by these companies about where they are investing research dollars on behalf of their shareholders," [161] and therefore while the pipeline in its own originating state may purely be a matter of product development, its efficacy is judged by the financial return that the pharmaceutical company can make on its investment *and* by the ways in which their product can successfully treat a disease.

For the infrastructure that enables antibiotics to *be* an infrastructure, this understanding of financial interaction is key. The research and development pipeline is not one that is solely science focused, there is a financial component that allows it to be able to process and function. Science may feed into the pipeline and ensure that a product can physically be developed, but without a financial base supporting it, it fails. This serves as an additional example of Star's theory of embeddedness – one mechanism enabling another to

[158]More on this will be discussed later within this chapter, and in more specific analytical detail in chapters Three and Four.
[159]George H. Talbot, John Bradley, John E. Edwards, David Gilbert, Michael Scheld, John G. Bartlett, and Antimicrobial Availability Task Force of the Infectious Diseases Society of America, "Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America," *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 42, no. 5 (March 1, 2006): 657–68, https://doi.org/10.1086/499819.
[160]Talbot, et al., "Bad Bugs Need Drugs," 657, 666.
[161] Talbot, et al., "Bad Bugs Need Drugs," 666.

succeed. Tracking how these financial influences effect the pipeline and the overall infrastructure described within this thesis will be the focus of Chapters Three and Four.

Only a few years after the Bad Bug Needs Drugs report was published, two pharmaceutical company researchers (SJ Projan from Wyeth Research and DM Shales from Idenix Pharmaceuticals Inc.), published their own take on the situation directly relating the lack of scientific discovery within the "dry pipeline" to the increase of cases of resistance.[162] Their concern was put in blunt words, stating that "despite the fact that some companies have remained engaged, the view here is that the current level of industrial effort is insufficient to sustain a healthy flow of new and better agents that are needed to counter the imminent threat of bacterial drug resistance."[163] While still incorporating metaphorical language of the *flow* of something through a *pipe*(line), Projan and Shales emphasize that there is an intentionality behind the pipeline that specifically links the production of a product to the treatment of a disease, and that ensuring that product reaches an at-need patient is a priority that needs to be addressed.

Visual representations of the pipeline continue to stress the diversity of its usage and intentions throughout the 2000s. In 2006, the United States Government Accountability Office, using data from the Pharmaceutical Manufacturers of America, published this view of the research and development pipeline, as well as the prospects of potential compounds making their way through the end.[164] Its four stages, from drug discovery to FDA review specifically refer to drug development alone. There is no attention or focus to what happens to the drug once it reaches the market. Furthermore, while this image is representative of the

[162]S.J. Projan and D.M. Shales, "Antibacterial Drug Discovery: Is It All Downhill from Here?" *Clinical Microbiology and Infection* 10, no. Supp 4 (2014): 18, 22.
[163] Projan and Shales, "Antibacterial Drug Discovery," 18.
[164] United States Government Accountability Office, "New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts," Report to Congressional Requesters, (Washington D.C., United States: United States Government Accountability Office, November 2006), 8.

overall drug pipeline, it provides a general understanding of the domain in which antibiotics naturally reside. Their development process takes place in the same structure as other drugs, and so its experience (at least in theory) should replicate the same pathway as other drugs in this space.

What is key about this perception of the pipeline, is not only what it does show, but what it does not show. The diagram is specifically focused on development only, and thus the image stops at "FDA approved drug." However, there are additional steps to that drug's trajectory beyond development. This is not a fault of the diagram itself, but it does beg the question of what comes next. What is the point of the drug once it makes it through the approval process? This image, in its traditional form, shows only the scientists' involvement with the drug, rather than the company's use of the drug, or as Projan and Shales indicated – the company's financial investment/interest into the basic approval stage in the first place, and it is due to this lack of representation or continuation in an area where there is clearly more to be done post approval – that other pipeline images have emerged.

From an antibiotic infrastructure perspective, the antibiotic pipeline is a key component particularly because of its role in adding new products to the pool of potentially available drugs to draw from. Without this pipeline, there would be no new candidates, and as rates of AMR rise: the number of effective antibiotics would fall, and the infrastructure meant to uphold public health would fail. Thus the pipeline in essence reflects how the corporations responsible for the production of these new drugs perceived their involvement in that part of the overall antibiotic ecosystem.

However, this image is not static. In 2009, the European Centre for Disease Prevention and Control (ECDP) and the European Medicines Agency (EMA) published a technical report entitled *The Bacterial Challenge: Time to React*.[165] It's Annex B2 contained

[165] ECDC and EMA, "The Bacteria Challenge: Time to React," Technical Report, Stockholm: ECDC and EMA, 2009, 37-39.

one chart that indicated the various steps that two separate research and development databases/trackers used to define pipeline phases. One included research, the other did not. One included a phase 0 (for first in human trials) the other did not.[166] Both included launches, but neither included any kind of post-launch surveillance indications. Despite this, the launch phase clearly indicated that the drug pipeline needed to extend beyond the laboratory and into a marketing phase where a consumer would be able to purchase the drug.

There is an inconsistency, therefore, on what *the* pipeline is meant to be. Even in the same document, the pipeline reveals itself in different ways, and when compared to the United States Government Accountability Office (GAO)'s use of the pipeline, those differences only continue to grow. There is a launch phase and expected sales/marketing step included in the ECDC/EMA document that differs from the GAO's. Considering that it is the *sales* that tie back to the financial return expected by the company, this prolongation of this prolongation of the pipeline and inclusion within the infrastructure is a clear and logical step. The goal of the pipeline is not simply to develop a drug, but to sell it. Though certainly for scientists working through the drug development process, their priorities may only be in the development stages, for the *company* that is more long winded. Thus, it depends on who is using the pipeline and what it means for their individual needs that additional or extra "steps" are required.

Three years later, in 2012, an international research group headed by Anthony So[167] and Otto Cars[168] offered their own perspectives of a pipeline in the graphic.[169] In their interpretation, their pipeline highlights the connection between product development to

[166] First in human trials is usually considered phase 1, but in this instance was categorized as phase 0. ECDC and EMA, "The Bacteria Challenge: Time to React," 38.
[167]Funded at the time by the Rockefeller Foundation and later served as a member of the World Health Organization's Antibiotic Resistance Working Group and would eventually serve as an advisor to the United States President's Council of Advisors Organization's Science and Technology
[168]Founder of ReAct, an NGO dedicated to "advocating and stimulating…global engagement on antibiotic resistance." ReAct, "About Us," ReAct, Accessed September 10, 2024, https://www.reactgroup.org/about-us/.
[169] Anthony D. So, Quentin Ruiz-Esparza, Neha Gupta, and Otto Cars, "3Rs for Innovating Novel Antibiotics: Sharing Resources, Risks, and Rewards," *BMJ* 344 (April 3, 2012): e1782, https://doi.org/10.1136/bmj.e1782.

disease management (thus strengthening its ties to the antibiotic infrastructure as it is actively seen supporting the health crises the infrastructure is meant to address). Their chart shows the drug pipeline from discovery through a post-marketing phase, with tabs and indicators highlighting were stressors or "breaking points" could be in pipeline success.

This framing presents the pipeline as something that needs assistance from many people in order to be fixed. This would reflect Susan Leigh Star's belief that if an infrastructure is to be corrected, it must receive maintenance from bottom up support.[170] So and Cars' hopes in identifying research, risks, and rewards are to make it so that if enough people work on antibiotic development together then there is a greater chance for an overall positive result.

One final example of the pipeline and its use comes from 2018, when European Union funded project, DRIVE-AB, include not only a generic market, but particularly make a note for the need for continuity within space. The members of the Drive-AB group came from all different walks of life, with some holding positions in government, some as academic researchers, and some affiliated with pharmaceutical companies.[171] Despite this diversity, their pipeline suggestion is perhaps the most clear example of how the pipeline can

[170]Star, "The Ethnography of Infrastructure," 381-82.

[171]Christine Årdal: MA and PhD and current Senior Scientist, Norwegian Institute of Public Health previously the co-lead of the research and innovation work package for the European Union's Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) and currently co-leads the access work package of EU-JAMRAI-2, aiming to strengthen access to important antibiotics with vulnerable supply chains.
David Findlay: current co-founder and CEO of Rosta Therapeutics, former managing director of GlaxoSmithKline
Miloje Savic: is a senior advisor on global health and antimicrobial resistance for the Norwegian Institute of Public Health (NIPH).
Yehuda Carmeli: Head Division of Epidemiology at Tel Aviv Medical center
Inge Gyssens: professor of Infectious Diseases at Hasselt University, Belgium and has an appointment for research and teaching at the Department of Medicine, Radboud University Medical Center, Nijmegen, the Netherlands.
Ramanan Laxminarayan: economist and epidemiologist and founder/director of One Health Trust.
Kevin Outterson: law professor at Boston University and current co-founder and Executive Director of PPP: CARB-X.
John H. Rex: Physician and drug developer, current chief medical officer of F2G, former consultant and operating partner of Advent Life Sciences, former Adjunct Professor of Medicine at University of Texas.

be conceived as a part of a continued and long-lasting infrastructure.[172] The use of "continuity" indicates a need for the drugs to be continually available. Though there is no specific mention of affordability, and therefore no specific reference to *accessibility,* the nature of a continuous supply of generic formulations presupposes a need for availability of that supply.

What this review of the different ways the pipeline has been depicted and conceived shows, that the usage of the term "antibiotic pipeline" as a metaphor mutates in different contexts. Different actors are highlighting different aspects of the pipeline, with some focusing solely on scientific innovation, others emphasizing the financial relationship between drug and corporation, and others using the pipeline to refer to potential disease impact. What is evident across the board, however, is that increased discussion of *an* "antibiotic pipeline" began to truly emerge in the 2000s and that these discussions were being held in tandem with talk of AMR.

These discussions of the antibiotic pipeline are wholly surrounded by the clear and unavoidable thought that there needs to be new antibiotics developed. If that goal was not important, than neither would fixing the pipeline be important. The fear of not having effective antibiotics (and entering a post antibiotic era), draws attention to the invisible infrastructure for those antibiotics of which the pipeline is a part of. This pipeline becomes visible *because* of AMR, and the need for something to be done to fix it. Maintenance, the act of repairing that which is broken, is thus sought as a result. So and Cars' work highlight where financial breaks in the pipeline occur, as do the other articles in this space, which equally emphasize concern over what would happen should antibiotics fail en masse. The failure of these antibiotics as a functioning healthcare infrastructure wouldn't just be a result

[172] Christine Årdal, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John H. Rex, "Revitalizing the Antibiotic Pipeline," Final Report 2018, (Geneva, Switzerland: DRIVE-AB), 5.

of resistance, but of the infrastructure supporting those antibiotics that no longer functions effectively.

Each of the early 2000s articles that first mentioned the dry pipeline, from the *Lancet* publication through to Projan and Shales indicated their concern about the relationship between financial interest and pipeline development. Lack of finances (or more specifically: lack of perceived return on the economic investment of new antibiotics in comparison to other medicaments) was the known and commonly discussed cause of "pipeline failure," where the new antibiotics are not successfully making it through to the end. As no distinct action was taken to address the financial circumstances, no true action transpired from the early 2000s until 2016.

By 2016, though, a new report published by British economist Jim O'Neill helped encourage action to take place.[173] Entitled, *Review on Antimicrobial Resistance*, O'Neill's work concluded that as of 2016, 700,000 people died annually of resistant infections, and that number would likely grow to 10 million people dead each year, with a financial loss of 100 trillion USD by 2050.[174] Critiques, from the National Office of Animal Health and independent researchers have both questioned the totality and impact of O'Neill's estimates.[175] [176] And additional critiques have been noted by those questioning why the UK government decided to present O'Neill's findings in the manner they did.[177] However, the

[173] Political posturing in an attempt to be 'the voice' or the forefront of AMR may have delayed the efforts of others within this space, as jockeying for being center stage removed some voices from key votes. For more information on this controversy, please review: Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 52-55.
[174] O'Neill, "Tackling Drug-Resistant Infections Globally," 1.
[175] National Office of Animal Health, "NOAH Response to Final O Neill AMR Review Report July 2016," Response, Middlesex, England: NOAH, July 2016, https://www.noah.co.uk/wp-content/uploads/2016/07/FINAL-NOAH-response-to-final-O-Neill-review-25-07-16-cle.pdf.
[176] Marlieke E. A. de Kraker, Andrew Stewardson, and Stephan Harbarth, "Will 10 Million People Die a Year Due to Antimicrobial Resistance by 2050?" *PLoS Med* 13, no. 11 (2016): e1002184, https://doi.org/doi:10.1371/journal.pmed.1002184.
[177] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 54.

report did garner the political attention required to begin raising large quantities of money in efforts to address AMR.

Early on, he states that the global cost to address AMR and to "overhaul the antibiotics and TB R&D *pipeline* using new market incentives," (emphasis mine) would be around $16 billion.[178] He neglects to include estimates for infection prevention and control methods as these and other methods designed for improved global health "are part of normal investment to achieve good healthcare."[179] But as global health historian Randall Packard has criticized in the past, these kinds of measures are usually nebulous in nature, and despite frequently being brought up as things that should be done, rarely receive the full funding required.[180]

Funding the pipeline, and the finances that play a role in pipeline management make up the next section of this historiographical chapter as understanding how those finances play a role in the pipeline provides clarity on how the overall infrastructure is financed as well.

III. Historiography of the Neoliberal Market Affecting Drug Development

Jeremy A. Greene opens his book, *Prescribing by the Numbers: Drugs and the Definition of Disease,* with an anecdote from the head of Pfizer in 1957 discussing how despite the fact that "antibiotics had effectively reduced the frequency and severity of infectious disease…they had also effectively reduced their own potential market…[And] drugs needed to *grow* their markets, not shrink them."[181] Because the key feature of antibiotics is the fact that they cure bacterial illnesses, the better and healthier a society is, the less antibiotics are needed. Infrastructures are not necessarily ever-growing systems. The

[178] O'Neill, "Tackling Drug-Resistant Infections Globally," 7.
[179] O'Neill, "Tackling Drug-Resistant Infections Globally," 47-50.
[180] Randall M. Packard, *A History of Global Health* (Baltimore, United States: John Hopkins University Press, 2016), 305-328.
[181] Jeremy A. Greene, *Prescribing by Numbers: Drugs and the Definition of Disease*, (Baltimore, United States: The Johns Hopkins University Press, 2007), 1-2.

infrastructure in this dissertation supports the access to antibiotics which enables antibiotics *themselves* to serve as an infrastructure for global health care. Infrastructures on their own are meant to provide stability and an invisible presence that support the average day to day goings-on without question or comment. There when needed, but otherwise ignored. Because antibiotics support society when people are sick, and then are set to the side when people are not sick, at a certain point: there is no additional *growth* to be had. Financially, though, this is not ideal for a company looking to make year after year profits for the creation, and sale, of their antibiotic product.

Histories of how economic financial structures specifically relate to pharmaceutical (let alone antibiotic) industries are vanishingly few. However, economics, and neoliberal capitalism specifically, trickle in through various accounts. Physician and professor of public health, Richard J. Coker, suggests that for the United States at least, Reagan inspired legislation helped encourage a shift away from 'social-engineering' infrastructures of welfare and social support in favor of individualism and individual economic freedoms.[182] Edward Nik-Khah, a historian of economics with a specialization in pharmaceutical interests at Roanoke College, also credits this era as a profound shift, and highlights the interconnection between the Chicago School of Economics and the way pharmaceutical companies have begun to prioritize shareholder value first and foremost in their own business architectures.[183]

For Nik-Khah, the start of the pharmaceutical industry's transition, was a result of deep discontent with Kefauver-Harris Amendments (mentioned earlier). Panic over reformations and the potential for the FDA to continue to develop new regulations led to the formation of industry lobbyists dedicated to arguing, disrupting, and dismantling the Amendments in any way possible.[184] The Chicago School became a hotbed for this level of

[182] Coker, *From Chaos to Coercion,* 78-79.
[183] Edward Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," *Sage Publications, Ltd.* 44, no. 4 (August 2014): 489–517. https://www.jstor.oerg/stable/43284157.
[184] Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," 492.

discontent, with the economist, Sam Peltzman leading the charge against the reformations as they arose.[185] Peltzman, though, according to Nik-Khah, was focused solely on the economic impact of the Amendments and not the "scientific and medical considerations" as to why the Amendments were put in place to begin with.[186] His work was funded by the Walgreens Foundation, a massive fund initially given to the Chicago School by Charles R. Walgreen (head of the Walgreens drug store chain) in 1937 for the specific purpose of supporting student research.[187] By taking this funding, Peltzman displayed a great conflict of interest as the economic determinations he was making directly impacted the source of the funds he was receiving.[188]

Although the initial response to Peltzman by the larger health-associated community was middling, the Chicago School continued its rounds. Nik-Khah found that the university hosted several drug conferences over the next few years, published several books all dedicated to the financial concerns of drugs, and routinely hosted respected drug researchers such as Louis Lasagna (a man once dubbed "the father of modern pharmacology" due to his work on calculating the actual availability of patients during a clinical trial) in efforts to convince them of the School's economic positioning. [189]

Lasagna was a powerful figure in the medical field at the time. He worked with several governmental departments, and delivered testimony during the Kefauver hearings. He was one of the staunchest supporters when it came to requiring clinical trials to prove drug efficacy. His recruitment, therefore, was paramount. Nik-Khah highlights how, over time, Lasagna's language began to adopt the perspective of the neoliberal economists from the

[185] Sam Peltzman, "The Benefits and Costs of New Drug Regulation," In *Regulating New Drugs*, edited by RL Landau, 113–211. Chicago, United States: University of Chicago Center for Policy Studies, 1973.
[186] Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," 495.
[187] Walgreens, "Our Past," Accessed February 3, 2025, https://www.walgreens.com/topic/about/history/hist5.jsp.
[188] Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," 492.
[189] Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," 496-497.

Chicago School, particularly in his 1974 publication, "Unholy Grail." There, Lasagna listed the myriad of ways that medical doctors disagreed over data, efficacy, relevance, and necessity. He compared drugs and perspectives on those drugs, and concluded that

> since it is more often true than not that doctors and patients will disagree on what is 'best' or 'proper' and since individual judgments are both necessary and desirable in most of medicine, the appropriate goal should be a clear exposition of the facts (such as they may be, including what is not known) to doctors and patients, with the probabilities (where they exist and updated as necessary) of benefit and harm for the various options available. Then the individual can make his own judgment.[190]

For antibiotics specifically, Lasagna's words get to the heart of rational vs irrational prescribing. Antibiotics are a unique class of drug because their inappropriate use (using them in scenarios where there is no bacterial infection present, not using them for the time period suggested, or not following appropriate dosing) leads to AMR and diminishing health outcomes. Irrational prescribing, or prescribing antibiotics when there is no clinical need, can have serious long-term effects as the efficacy of the drug is diminished. If individual desire to have a drug, and individual judgment, overcomes *rational* prescribing metrics: while the freedom of the patient to make their own choice might be secured, community health, the antibiotic infrastructure as a whole, and access to effective antibiotics could be at risk.

Podolsky's *Antibiotic Era* also discusses Lasagna's transition and the ways rational therapeutics were a hot-button issue in the 60s.[191] He even notes that Lasagna's own research group found that antibiotics were the most commonly over prescribed medications, and that Lasgana was certainly aware of the desire for antibiotic treatment that could outweigh the need for such treatment.[192] Lasgana, however, stayed fast to his newly formed beliefs, as influenced by the focus on individual personal and economic freedom suggested by the Chicago School. And meanwhile, the School itself was gaining ground among those who

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[190] Louis Lasagna, "Consensus among Experts: The Unholy Grail," *Perspectives in Biology and Medicine* 19, no. 4 (1976): 547.
[191] Podolsky*, The Antibiotic Era,* 110-120.
[192] Podolsky*, The Antibiotic Era,* 118.

were watching the pricing of drugs begin to rise due to the extended clinical trial and evaluation times that were put in place as a result of the Kefauver-Harris Amendments. [193]

From an accessibility standpoint, this was striking at both branches: availability and affordability. New drugs were no longer available because they were trapped at the regulatory and clinical trial phases, and once those drugs did come onto the market: the prices now needed to cover all of the excess time in the pipeline. Nik-Khah does not mention the words pipeline or infrastructure in his article, but the shape of both seems to start to emerge within these discussions. Financial despair, a keen interest on a return on the investment, and the phases of clinical trial "valley of death" lurk within the history he traces.[194]

In the early 2000s, Merck published a study stating that it costs over $800 million to bring a drug to market, and the Chicago School quickly circulated that figure, compounding on it and insisting once again that regulations and clinical trial expenses were the reasons why drugs were becoming so prohibitively expensive.[195] By placing the blame outside of the pharmaceutical industry, they take their stance in assuming no fault. [196] Merck seems to have implied that the pipeline was working perfectly fine *prior* to such interventions, but now that there are increased regulations: it is simply too expensive to make drugs.

The infrastructure here, once more, begins to show its cracks. If the drug and development pipeline was now prohibitively expensive, then the pipeline itself was unmanageable. Maintenance – in this case, directly addressing the source of the financial troubles, would need to be applied in order to return the pipeline to effective operating

[193] Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," 501-502.
[194] The valley of death, can be explored more in: Tove C. Bolken and Dennis E. Hruby, "Discovery and Development of Antiviral Drugs for Biodefense: Experience of a Small Biotechnology Company," *Antiviral Research* 77, no. 1 (2008): 1, https://doi.org/10.1016/j.antiviral.2007.07.003.
[195] Joseph A DiMasi, Ronald W Hansen, and Henry G Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (March 2003): 329, https://doi.org/10.1016/S0167-6296(02)00126-1.
[196] Nik-Khah, "Neoliberal Pharmaceutical Science and the Chicago School of Economics," 502.

conditions. Those conditions, though, are variable. How much would Merck, and other pharmaceutical companies need in order to be satisfied with the financial return on investment within their pipeline? That figure has never been revealed. Chapters Three and Four will discuss how specific financial maintenance in this place have been applied, and what it looks like to be put in practice.

Nik-Khah's original 2014 article, detailing the rise of the Chicago School's influence on pharmaceutical thought and the transition of key speakers such as Louis Lasagna to a more neoliberal mindset in an attempt to change and challenge regulations, was in fact challenged not long after it was published by David Healy (a psychologist from Bangor University), Derelie Mangin (a physician and primary care academic form McMaster University), and Kalman Applbaum (an anthropologist from the University of Wisconsin-Milwaukee). Entitled *Shipwreck of the Singular,* Nik-Khah's assertion that Lasagna's position as evolving face of neoliberalism for the pharmaceutical industry is challenged due to Lasagna's previous far more conservative stances displayed during the Kefauver trials.[197] Healy et al., lean into the notion that Lasagna's fluctuating beliefs were complex. And while he did champion the thought of individual freedom and choice, this was largely due to the fact that he distrusted the ways in which federal oversight of clinical trials was being applied. Rather than allow the government to insist upon trials, and for corporate marketers to profiteer over the high prices that emerged from these trials, Lasagna preferred to throw the baby out with the bathwater (so to speak), and simply allow the patient to be the one to decide their own fates.[198]

In his seven-page response to Healy et al. published in the same issue of the same journal as their initial rebuttal, Nik-Khah bluntly states that the group does not "challenge the

[197] David Healy, Derelie Mangin, and Kalman Applbaum, "The Shipwreck of the Singular," *Social Studies of Science* 44, no. 4 (August 2014): 519, https://www.jstor.org/stable/43284158.
[198] Healy, Mangin, and Applbaum, "The Shipwreck of the Singular," 520.

central thesis of [his] article, that the Chicago School of Economics sought to forge an alliance with the pharmaceutical industry to influence pharmaceutical policy and science. Nor [did they] challenge [his] argument that Chicago scholars attempted to influence scientists to accomplish the same," but rather that their focus was wholly on whether "Louis Lasagna's views and activities [could] be attributed in part to his interactions with members of the Chicago School of Economics."[199] To this, Nik-Khah provides ample evidence. He details Lasagna's exploits, his interactions, and his publication history, while also connecting Lasagna to other actors, particularly that of Milton Friedman (the father of neoliberalism).[200]

Friedman's own ideals which he published in his famous work *Capitalism and Freedom,* extolled the successes in the rise of government income due to strict Keynesian economics methodologies, capitalism had proven itself to be a global success,[201] and argued that "competitive capitalism - the organization of the bulk of economic activity through private enterprise operating in a free market – [is] a system of economic freedom and [is] a necessary condition for political freedom."[202] The market economy, to Friedman, was one that depended on individual liberty and a cessation of any thought that was deemed for a collective was impermissible. Except, as Friedman would later concede, should the social good be merely performative. From the start, Friedman and the Chicago School of Economics were pitching neoliberalism as a way to increase corporate strength and financial wealth for shareholders first and foremost. All of these notions were ideas that Nik-Khah drew continual attention to in Lasagna's work regarding the pharmaceutical industry and medical regulation within the United States.[203]

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[199] Edward Nik-Khah, "'Power to the People': A Reply to Healy, Mangin, and Applbaum," *Social Studies of Science* 44, no. 4 (August 2014): 524, https://www.jstor.org/stable/43284159.
[200] Nik-Khah, "'Power to the People,'" 524-258.
[201] Milton Friedman, *Capitalism and Freedom*, Fortieth Anniversary, (Chicago, United States: The University of Chicago Press, 2002), viii-ix.
[202] Friedman, *Capitalism and Freedom*, 4.
[203] Nik-Khah, "'Power to the People,'" 524-259.

In his rebuttal against Healy et al., Nik-Khah points out that

> They conjecture that Lasagna forged relations with the pharmaceutical industry not because he was entranced by its pursuit of profit but instead because he wanted to use its muscle to countervail a scientific community and government bureaucracy, and ultimately to put his vision of the ideal medical marketplace into practice; Although they appear to believe et his distinguished Lasagna from the Chicago School, this attitude was actually characteristic of neoliberals. Milton Friedman gave voice to the associated imperative when he argued 'For advocacy of capitalism to mean anything, the proponents must be able to finance their cause.' The crucial point is that for neoliberals, alignment with corporation was one of the primary points of departure from classical liberals, who were wary of the danger of corporate power...The big picture here is not of 'conspiracy' but rather a certain kind of collective effort, composed of economists, lawyers, corporations, think-tankers, and a handful of scientists.[204]

In short: Nik-Khah utterly rejects the response given by Healy et al.

Although Nik-Khah does provide, in both his arguments, a brief understanding of the history and evolution of the conjunction between neoliberalism and the pharmaceutical industry, deeper understanding into how these two areas intersect is found elsewhere. Mariana Mazzucato, professor in the Economics of Innovation and Public Value at University College London where she is the founding director of the UCL Institute for Innovation and Public Purpose, described the history and evolution of the neoliberal movement in her 2018 book: *The Value of Everything.* There, like Nik-Khah, she observes and comments on how capitalist Milton Friedman and his followers argued that the prior managerialist market system had led to executives mismanaging their companies due to a lack of attention paid to profit or success.[205] Mazzucato makes it explicit that for the burgeoning neoliberal movement that was evolving in the late 60s through the 80s, shareholders were the true owners of companies, and managers were simply employees– a distinction that clashed with legal definitions of corporate law and continues to do so to this day.[206]

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[204] Nik-Khah, "'Power to the People,'" 527.
[205] Mariana Mazzucato, *The Value of Everything: Making and Taking in the Global Economy* (Northwood, United Kingdom: Penguin Allen Lane, 2018).
[206] Lynn A. Stout, "The Toxic Side Effects of Shareholder Primacy," *The University of Pennsylvania Law Review* 161, no. 7 (June 2013): 2006.

From an infrastructure perspective, this dependency on shareholder value seems to run counter to the eventual development of a product meant to support health care needs, as the shareholder is an absent party to the actual innovation and eventual dissemination of antibiotics. Understanding where this complexity comes into place, and seeing how this works in practice is a large component of Chapter Four of this dissertation.

The concern with a need for increasing shareholder value particularly in a health care setting however, and how an infrastructure may (or may not) be able to support such a thing, has been studied by other scholars previously. (Though the word infrastructure is not used, the general implication and description of such a thing can be understood throughout the text as a subtle concept just waiting to be given its name). Most recently, in 2021, Jean-Paul Gaudillière and Kaushik Sunder Rajan published an article in *BioSocieties* discussing the intersection of capitalism and public health. Building on a wealth of scholars before them including Michel Foucault, Nikolas Rose, Joe Dumit, and Michel Aglietta among others, Gaudillière and Sunder Rajan argue that *health* has become an abstract concept from which value could potentially "be grown."[207] In essence, that instances of poor health are so deeply correlated to notions of "access to and consumption of drugs," that there is little meaning to the concept of healthcare without medication any longer.[208] Infection prevention and control measures, once put into practice as a sign of good citizenship with in a society in the 1800s,[209] in fact limit the potential corporate value that could be extracted from an ill population as a healthy society spends less money on medications. Gaudillière and Sunder Rajan highlight the need for value maximization by utilizing the pharmaceutical company, Gilead, and its drug sofosbuvir as an example of profit maximization at the expense of those

[207] Jean-Paul Gaudillière and Kaushik Sunder Rajan, "Making Valuable Health: Pharmaceuticals, Global Capital and Alternative Political Economies," *BioSocieties* 16, no. 3 (September 2021): 313. https://doi.org/10.1057/s41292-021-00247-3.
[208] Gaudillière and Sunder Rajan, "Making Valuable Health: Pharmaceuticals, Global Capital and Alternative Political Economies," 313.
[209] Robert Bud, *Penicillin: Triumph and Tragedy*. (Oxford, United Kingdom: Oxford University Press, 2007), 5.

suffering from Hepatitis-C,[210] and I grow off this argument within Chapter Four of this dissertation by comparing sofosbuvir to the MDR-TB drug: bedaquiline. Gaudillière and Sunder Rajan, though, make it clear from their article that: wealth must be extracted from the ill population by setting a price to a particularly high point, but once that patient is ill: they will no longer purchase the product. Managing that value differential, without losing its patient pool to death prematurely, is key to keeping the company alive.

Their analysis is supported by two separate researchers, Victor Roy and his book *Capitalizing a Cure*[211] and Brett Christophers' book *Rentier Capitalism.*[212] By thoroughly investigating Gilead and Sofosbuvir, Roy introduces the concept of a pricing escalator, where pharmaceutical companies are so dependent on increasing shareholder value year after year that the price of drugs must continue to be higher than what comes before. [213] Meanwhile, the need to ensure that companies can depend on steady purchasing by consumers, transforms the practice of buying drugs for chronic diseases, or other such diseases that take time to treat, into a renting relationship between the pharmaceutical company and its consumer. The consumer must pay its *rent* (i.e.: pay for their drugs) in order to survive on a daily basis, and it behooves the company to either maintain the ability to control that rent (i.e.: the price of those drugs) by maintaining patent monopolies on their drugs for as long as possible, or to increase the price of that rent year after year in an attempt to improve its shareholder value. [214]

Gaudillière and Sunder Rajan identified Sofosbuvir as standing "at the apex of the hegemonic rent-based global economy of drugs," particularly because Gilead's actions were

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[210] Gaudillière and Sunder Rajan, "Making Valuable Health: Pharmaceuticals, Global Capital and Alternative Political Economies," 317-318.
[211] Roy's work will be discussed in more detail within Chapter Four of this dissertation. Victor Roy, *Capitalizing a Cure: How Finance Controls the Price and Value of Medicines*, (Oakland, United States: University of California Press, 2023).
[212] Brett Christophers, *Rentier Capitalism: Who Owns the Economy and Who Pays for it?* London: Verso Books, 2020.
[213] Roy, *Capitalizing a Cure*, 46-47.
[214] Christophers, *Rentier Capitalism,* 174-178.

so egregious in terms of trying to extract value out of patients in a life or death situation.[215] However, the combination of neoliberalism and its progressive evolution into rentier capitalism within the pharmaceutical industry is not limited to one sector (or one company) alone. Rather it can be chiefly associated with a collective transition towards the development of drugs that can be sold to treat chronic illnesses, and drugs whose unique life-or-death properties justify ever increasing prices points. Value is considered key first and foremost, and the more imperiled an individual consumer is: the higher the value of that product.

In Maurice Cassier's 2020 critique on the sofosbuvir issue, he directly addresses how the concept of value in itself is one that is largely based on the perceived justifications of whomever has decided on a purchasing price for their product. He describes how sofosbuvir's prices "were directly related to the capital advanced and invested in the invention, appropriation, production, and commercialization of this medicine," and how not only did sofosbuvir go through two capital increases throughout its development cycle.[216] Cassier calls focus onto the notion of morality in the face of such valuations. If value is determined not only by the need and desire of a purchaser (i.e.: someone dying of a disease), but also in the costs associated with the production of the good being exchanged, while equally taking into consideration the overall *saved* costs that the purchaser *could* have spent elsewhere (i.e.: additional hospital visits, long term care, by utilizing an alternative medication), then from a corporate perspective: a high drug price is entirely logical.

The historiography of the neoliberal market and how it intersects and affects drug development, is of particular importance to this dissertation due to how frequently "market

[215] Gaudillière and Rajan, "Making Valuable Health: Pharmaceuticals, Global Capital and Alternative Political Economies," 318.
[216] Maurice Cassier, "Value Regimes and Pricing in the Pharmaceutical Industry: Financial Capital Inflation (Hepatitis C) versus Innovation and Production Capital Savings for Malaria Medicines," *BioSocieties* 16, no. 3 (2021): 33, https://doi.org/10.1057/s41292-020-00214-4.

failure" is brought up as a reason for the lack of antibiotics currently in development. If the infrastructure that supports antibiotics requires a pipeline to ensure the development of new and effective antibiotics, and that pipeline is beholden to a financial market system that is incompatible, then restoring that crumbling infrastructure may maintenance that specifically *addresses* how that financial relationship interacts with the pipeline itself. In the next and final section of this historiographical overview, access takes center stage. After antibiotics, its pipeline, and its funding concerns are considered, how then has access been defined and problematized by previous historians, and what is the status of supply chains and accessibility networks worldwide?

IV. Historiography of Access to Medicines and Global Supply Chains

Access to medicines as a notion and a concept is relatively new field. Action and activity within this space emerged largely between the 1950s-1970s, particularly with the creation of essential medicines list, first in Sri Lanka under Senaka Bibile,[217] and later at the World Health Organization (to be discussed in more detail in Chapter Two). This time period, was particularly noteworthy for the developing notions of public and global health. Randall M. Packard's book *A History of Global Health* elucidates the financial prerogative of the World Bank (founded in 1946) to invest fully in top down methods of health care reform and adjustment, where monies were spent not on supporting stable economies or healthy living spaces, but one-stop-shop fixes based on technological prowess and innovation. In 1979 the World Bank, in consortium with UNICEF and the Rockefeller Foundation decided to focus not on Primary Health Care (characterized by a whole of society approach to health, where disease prevention, treatment, and rehabilitation are considered as necessary and total components of any health care structure), but in *Selective* Primary Health Care (SPHC),

[217] Joëlle M. Hoebert, Liset Van Dijk, Aukje K Mantel-Teeuwisse, Hubert Gm Leufkens, and Richard O Laing, "National Medicines Policies – a Review of the Evolution and Development Processes," *Journal of Pharmaceutical Policy and Practice* 6, no. 1 (2013): 6, https://doi.org/10.1186/2052-3211-6-5.

where the most prevalent diseases would be targeted first and foremost leaving out comprehensive healthcare reform in favor of a targeted approach.[218]

At the same time these groups were deciding on how health care was to be implemented and by whom, hospital infrastructures were also being built and established in an ever-greater number of communities. Fanny Chabrol and Jean-Paul Gaudillière write about these growing infrastructures in their *Introduction à la santé globale,* published in 2023.[219] As Palanco Lopez et al. mentioned earlier, the investment in these hospital settings (particularly in colonial territories) was managed by empires and religious missions, and initially targeted towards those of European descent first before outwardly extending to indigenous populations.[220] These hospitals, though, would be of great importance to those populations when they did require care, as some *on their own* accounted for as much as 20% of the total national health budget each year. [221] Without these hospitals or the care they provided: many individuals simply wouldn't *receive* care.

As we look at the development of an antibiotic infrastructure, therefore, it must be done in the understanding of this larger health care infrastructure at the same time. The overlapping of different health groups, funds, and initiatives, as well as the hospitals that are established and the managers assigned to oversee their upkeep and indeed their "maintenance." [222] The interaction between these physical infrastructures as well as how primary or SPHC measures are entangled, once more raises questions regarding their financing and funding. In his book *Global Health for All,* Gaudillière writes that "Neoliberalism is folded into the tools and systems that guide global health,"[223] and the

[218] Packard, *A History of Global Health*, 254-259.
[219] Fanny Chabrol and Jean-Paul Gaudillière, *Introduction à la santé globale,* (Repères 817, Paris: la Découverte, 2023), 75-88.
[220] Chabrol and Gaudillière, *Introduction à la santé globale,* 76.
[221] Chabrol and Gaudillière, *Introduction à la santé globale,* 76-77.
[222] Chabrol and Gaudillière, *Introduction à la santé globale,* 76-77.
[223] Jean-Paul Gaudillière, Andrew McDowell, Claudia Lang, and Claire Beaudevin, eds, *Global Health for All: Knowledge, Politics, and Practices*, (New Brunswick, United States: Rutgers University Press, 2022) 20.

World Bank's managerial nature regarding the implementation of SPHC and roll out of health care initiatives throughout this time was made entirely with the understanding of neoliberal economics in mind.

This global health era is one defined by its departure from previous ways of handling health care. No longer are individual nations or groups of people managing local illnesses, but world-wide efforts are being done simultaneously to shape and control the ideas and notions of health. New actors, new finance, new directives, and with it, new changes in the way the infrastructures supporting drug development and dissemination (let alone drug access) are emerging. With all of these changes, though, there is a distinct lack of global agreement on which steps are the best to take.

Although WHO director Halfden Mahler and his team vehemently opposed the Selective Primary Health Care methodology, they were overruled by those at the World Bank as SPHC promised immediate results at a comparatively low cost.[224] The long-term impact of this decision came in the form of technological dependence. Rather than investing in the socio-economic support structures of infection prevention and control and poverty improvement, SPHC offered medications to resolve health issues and depended on vaccine, rehydration, and malarial treatment programs, to ameliorate illnesses within LMICs.

In its own way, the SPHC thus encouraged the dependency on an antibiotic infrastructure, to whatever extent those diseases are covered. If diseases, such as tuberculosis, were a part of SPHC programs, then those antibiotics were made available and thus communities could come to depend on their existence when ill. For an infrastructure to exist, it must depend on another infrastructure first as its base: and here, the SPHC takes this shape.

Randall Packard's work in global health, highlights the way that LMICs were often trapped economically when it came to the kind of support and aid SPHCs were receiving, as

[224] Packard, *A History of Global Health*, 259.

countries in financial crisis were forced to accept Structural Adjustment Policies from the International Monetary Fund (IMF) and World Bank.[225] [226] According to Packard, these policies were meant to transform LMIC economies "in ways that would support free-market economies that were beneficial to the economic interests of *donor countries,"* (emphasis mine) with advancing the economic development of the debtors as a secondary result.[227]

As Jeremy A. Greene would point out in his chapter, "Pharmaceutical Geographies: Mapping the Boundaries of the Therapeutic Revolution," between the 60s and 70s, those involved in health care circles readily acknowledged that there had never been a better opportunity to bridge the gap between the healthy and unhealthy, and that the technology to improve health outcomes certainly existed, but no one in "industry, government, profession, or academia—appeared to have any clear idea about how to *capitalize* on these opportunities"[228] (emphasis mine). By the 1990s, the seventh managing director of the IMF, Michel Camdessus said it bluntly:

> The important element from our point of view is that in most cases funds were expended on infrastructural projects that indeed facilitated the process of economic and social development. They did not, however, yield returns directly usable for the servicing of the debts incurred for their realization.[229]

The SAPs' insistence that health was a *commodity* rather than a right,[230] thus ensured that a widespread infrastructure meant to fully and completely sustain and manage a healthy population was never fully built or established in many LMICs. The infrastructure that

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[225] Packard, *A History of Global Health*, 260.
[226] For more information on how the World Bank was operating during this time, please consult: Béatrice Hibou, "The Political Economy of the World Bank's Discourse : From Economic Catechism to Missionary Deeds," *Les Études CERIN* 39 (January 2000), https://www.sciencespo.fr/ceri/sites/sciencespo.fr.ceri/files/etude39a.pdf.
[227] Packard, *A History of Global Health*, 261.
[228] Jeremy A. Greene, "Pharmaceutical Geographies: Mapping the Boundaries of the Therapeutic Revolution," In *Therapeutic Revolutions: Pharmacueticals and Social Change in the Twentieth Century*, edited by Jeremy A. Greene, Flurin Condrau, and Elizabeth Siegel Watkins, 151, (Chicago, United States: The University of Chicago Press, 2016).
[229] Michel Camdessus, "Opening Remarks," In *Policies for African Development From the 1980s to the 1990s*, (Washington DC, United States: International Monetary Fund, 1992), 18, https://www.elibrary.imf.org/downloadpdf/book/9781557752321/front-1.xml.
[230] Packard, *A History of Global Health*, 262.

supports antibiotics, similarly, could not have been broad reaching or expansive, however because of the increased dependency on antibiotics in order to serve as a stop gap function: its presence was still vital even in a diminished capacity. Overarching all of this, though, was the understanding that investments, loans, and national economic structures limited the kind of spending that would improve access to healthcare and effective medications. And the infrastructures that had already been in place began to deteriorate. Access, in the limited capacity that it had already started out in: was a struggle.

In Carine Baxerres and Maurice Cassier's edited collection *Understanding Drug Markets: An Analysis of Medicines, Regulations and Pharmaceutical Systems in the Global South*, the differences between health systems inherited from differing colonial legacies are examined. They explore how health care infrastructures in Ghana, Benin, Côte d'Ivoire and Cambodia, differ depending on if they were colonized by either the British or the French. This work helps elucidate the ways in which former colonies were able to build up national health systems and gain access to drug markets – either internal markets based on national product development and dissemination, or external markets that imported into the countries proper. This focus on the ways in which drug infrastructure, and supply chains: from development to distribution, can be deeply unique from one country to another, and face different regulatory and practical hurdles is an essential component to understanding the broader antibiotic supply chain in Chapter Five.

Cassier and Baxerres begin by drawing attention to Ghana's industrial and pharmaceutical production and distribution capabilities that were created initially with support from United States and European investors.[231] This external support lead to the development of local production and regulatory frameworks, and the establishment of a

[231] Jessica Pourraz, Claudie Haxaire, and Daniel Kojo Arhinful, "Strengthening National Pharmaceutical Regulation Through Local Production," In *Understanding Drug Markets: An Analysis of Medicines, Regulations and Pharmaceutical Systems in the Global South*, edited by Carine Baxerres and Maurice Cassier, 31. Oxon: Routledge, 2022.

home-grown pharmaceutical industry. However, during the 1980s financial crisis, investment failed and the industries Ghana had been creating, collapsed. Many health professionals began to leave to find employment elsewhere compounding an already delicate situation.[232] The whole health care infrastructure faltered, not just antibiotics, but access to antibiotics would have been a natural consequence of this circumstance.

Comparatively: former French colonies Benin and Côte d'Ivoire had chosen not to focus on building their own internal pharmaceutical infrastructure, but instead chose to strengthen their ties with France to ensure strong and dependable supply chains that could import all necessary medicaments.[233] When they too began to struggle during the 1980s financial crisis, their lack of internal infrastructure meant that importing high cost drugs became a greater challenge, and they had no alternative to replace it with. Financial constraints, deep wells of debt, and overcoming the hurdles of decolonization, however, continued to create barriers that they would need to overcome.

Although antibiotics and antibiotic infrastructure is not the focal point of the case studies within *Understanding Drug Markets*, it can be inferred from the book that such an infrastructure cannot be supported by a single branch alone. Internal, national, production of antibiotics is just as essential as trade. Maintaining healthy lines of support ensures that if there is a financial crisis there could be alternative pathways of accessing needed medication. Of course, depending on the depth of the crisis even those alternatives may not be effective, but having a backup plan or additional support structure would potentially elongate the effective nature of the supply chain infrastructure as a whole.

Cori Hayden discusses another aspect to access to medicine and supply chain effectivity in her book *The Spectacular Generic: Pharmaceuticals and the Simipolitical in*

[232] Pourraz, et al., "Strengthening National Pharmaceutical Regulation Through Local Production," 33-34.
[233] Pourraz, et al., "Strengthening National Pharmaceutical Regulation Through Local Production," 31-32.

Mexico.[234] There, she describes how health coverage in Mexico was largely supplied by either the Instituto Mexicano del Seguro Social (Mexican Institute of Social Security) or the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (Institute for Social Security and Ser vices for State Workers) to all those who had proof of *formal* employment Many people were not covered by these institutions as qualifying for formal employment was difficult and increasingly exclusive. Most, therefore, were required to pay out of pocket for health coverage. During the latter half of the 20th century, two streams of purchase might be available for those seeking medications: generic drugs purchased at a public pharmacy or, should they be of a higher economic class, branded medications available only at private pharmacies.[235]

This attention to health coverage is an important part of the infrastructure story as it addresses affordability. If there is no insurance, or there is no way for someone to afford for the drugs that come out as a result of deep income disparity: the drug will remain inaccessible. In both HICs (particularly the United States context) and LMICs, health coverage, donation schemes, and other forms of insurance are the only way that patients can afford medical care, and lacking such assistance could lead to patients failing to go to the doctor or receiving care as needed. Thus, understanding both how health coverage is applied, and how those who are not covered access medications is key.

Hayden's book targets how, in response to their own financial crisis during the 1990s; the cost of patented drugs in Mexico rose to 141% above its original fee: a price too high for local markets to bear.[236] The Mexican Ministry of Health responded by strongly promoting the use of generic and off-patent drugs, with González Torreso leading the charge and

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[234] Cori Hayden, *The Spectacular Generic: Pharmaceuticals and the Simipolitical in Mexico,* Edited by Vincanne Adams and João Biehl. Critical Global Health: Evidence, Efficacy, Ethnography, (Durham, United States: Duke University Press, 2003), 6.
[235] Hayden, *The Spectacular Generic,* 35-36.
[236] Hayden, Cori. "A Generic Solution?: Pharmaceuticals and the Politics of the Similar in Mexico." *Current Anthropology* 48, no. 4 (August 2007): 478.

establishing the pharmacy chain Farmacias Similares which only sold off-brand medicines. United States based pharmaceutical corporations responded by calling for legal action to be taken against Farmacias Similares and their slogan (translated as) "the same but cheaper!"[237] Their fight continued through to 2002 as Torreso joined forces with HIV/AIDS activists, cancer activists, and legislators in an effort to decrease the patent term on branded medications from 20 years to 10 years on essential medicines.[238] However, it was a move that was met by extreme push back from United States pharmaceutical manufacturers, who pressured the United States to cease all investments in Mexico if they legislature went through with such a move; naturally, in 2003, the attempt failed and the patent terms for branded medications stayed in place.[239]

Hayden's book draws particular attention to the ways in which an LMIC country, suffering from a financial crisis and hoping to ensure continued access to necessary medications, can struggle with international legislation that is put upon them. For the antibiotic infrastructure that was in place: political machinations beyond the Mexican border limited or strained the successful flow of access to effective medications. Supply chains, as a result, were affected.

When taken together, the historiographies within this section show a trend of political, financial, and international conflict that all impact how the access and supply chain components of an antibiotic infrastructure can be assessed. I used these historiographies as inspiration to help guide my more dedicated research pathways, and understand the deeper meaning of where and how antibiotic infrastructure can be traced and detected. They also provided clarity as to which areas of interest should be judged, in essence: marks on a

[237] Hayden, "A Generic Solution?" 480.
[238] Doha Declaration: Ministerial Declaration of 14 November 2001, WT/MIN (01)/DEC/1, 41 ILM 746 (2002).
[239] Hayden, "A Generic Solution?" 480.

template for how best to assess the health of the antibiotic infrastructure as a whole he infrastructure that holds up

Conclusion

This chapter summarizes and analyzes a select corpus of key works in the histories of antibiotics, the antibiotic pipeline, neoliberalism as it relates to health care, and access to medicines/supply chains. Throughout all of these historiographies, it made connections to the overall premise of this dissertation: that of an antibiotic infrastructure and access to antibiotics. Each of the subsections are components of this infrastructure, and each shed light on how the case studies and analyses in the remainder of this dissertation will be conducted.

Clare Chandler's framing of the notion of antibiotics as an infrastructure[240] is perhaps a new concept by title alone, but there is a clear and marked history of how the infrastructure that enables antibiotics to have such a great impact was developed. This framing of infrastructure as an analytical tool to understand how antibiotics are capable of being effective works because it is multifaceted. It equally spawns deep and pervasive questions on how it can be mended appropriately. Beyond simply looking at the "dry antibiotic pipeline" as the sole cause of trauma in addressing AMR, these historiographies have shown that there are multiple components to the infrastructure that must be addressed. Through it all, access remains paramount, and as the infrastructure is assessed and analyzed throughout, this

[240] Clare I. R. Chandler, "Current Accounts of Antimicrobial Resistance: Stabilisation, Individualisation and Antibiotics as Infrastructure," *Palgrave Communications* 5, no. 1 (May 21, 2019): 1-13. https://doi.org/10.1057/s41599-019-0263-4.
Sheila Rose, Varadan, Clare Isobel Rosina Chandler, Kym Weed, Syed Masud Ahmed, Caesar Atuire, Deepshikha Batheja, Susan Jane Bull, et al, "A Just Transition for Antimicrobial Resistance: Planning for an Equitable and Sustainable Future with Antimicrobial Resistance," *The Lancet* 403, no. 10446 (June 2024): 2766–67. https://doi.org/10.1016/S0140-6736(23)01687-2.
Miriam Kayendeke, Laurie Denyer-Willis, Susan Nayiga, Christine Nabirye, Nicolas Fortané, Sarah G Staedke, and Clare IR Chandler, "Pharmaceuticalised Livelihoods: Antibiotics and the Rise of 'Quick Farming' in Peri-Urban Uganda," *Journal of Biosocial Science* 55, no. 6 (November 2023): 995–1014. https://doi.org/10.1017/S0021932023000019.

dissertation asks overall: If the antibiotic infrastructure is crumbling, how did it get like that and where does maintenance need to be applied in order to help ensure it works once more?

Chapter Two: Essential Medicines as a Vehicle for Enabling Access to Medicines

"The key thing is that complex problems rarely have simple solutions." – Jonathan Quick.[241]

"Making the essential drug concept really evidence based made it very strong." – Hans Hogerzeil.[242]

Of the forty classes of unique antibiotics developed and approved since the nineteenth century, approximately three hundred unique drugs within those classes were identified by 1980. From there, an unknown number of proprietary names have been issued and used interchangeably across the globe to indicate more specific indications, me-toos, or generic formulations of the drugs in question. In 1983, this wealth of options and possibilities was investigated by the Pan American Sanitary Bureau. They issued a report on the status of all drugs in the United States (not simply antibiotics), determining that:

> The brand-name system produces a bewildering array of different names for the same drug. For the 700 active ingredients available in the United States, there exist an estimated 20,000 names--an average of 30 names for each drug product. The situation is similar in other nations. The number of pharmaceutical brand names registered in various countries in 1974 is as follows: Argentina, 17,000; Belgium, 9,000; Brazil, 14,000; Canada, 17,000; Colombia, 15,000; the Federal Republic of Germany, 24,000; France, 8,500; India, 15,000; Iran, 4,200; Italy, 21,000; Japan, 17,400; and the United Kingdom, 9,000. This proliferation of product presentations has greatly increased the utility of familiar brand names to the physician.[243]

In order to appropriately treat patients, physicians were placed in a position of wading through a vast amount of excess. Globally, effects of this could be seen in physicians working directly with individual pharmaceutical representatives capable of recommending the products of one company in specific to the exclusion of any others that may provide benefit simply because it was far more clear to do so in that capacity. In high income country

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[241] Jonathan Quick, Interview by Erin L. Paterson, 11 November 2022.
[242] Hans Hogerzeil, Interview by Erin L. Paterson, 2 February 2023.
[243] "Policies for the Production and Marketing of Essential Drugs." Washington DC, United States: Pan American Sanitary Bureau, April 18, 1983, 14-15. https://iris.paho.org/bitstream/handle/10665.2/6594/25835.pdf?sequence=1&isAllowed=y

settings, this type of marketing, and excess was not necessarily a problem as the financial ability to purchase effective medications was clear. However, in low-middle income countries (LMICs), understanding which drug, company, or intervention to purchase in order to most appropriately manage limited resources for the best overall health outcomes could be challenging. It is not merely a matter of purchasing the best drug, but purchasing the best drug that can treat the most people in a patient population.

In the late 1970s, before the Pan-American Sanitation Bureau's report but with full understanding of the rising complexity of drug purchasing around the world, the WHO developed what would eventually be known as the Essential Medicines List (EML). This list, which highlighted the generic names of the drugs capable of treating the most common ailments that affect a patient population, was intended to assist countries when it came to how best to invest their funds into appropriate medications. It was, therefore, a method of influencing accessibility of *the right* drugs, something which many pharmaceutical companies took cumbrance to after the list's initial population.[244]

Although the EML was not wholly dedicated to antibiotics, antibiotics are (of course) a part of the EML. This chapter analyzes the antibacterial section of the EML, as well as the history and context of the EML as a whole, by regarding the EML as a component of the infrastructure that allows for greater access of antibiotics. Antibiotics are able to serve as a major stabilizing base to global health care needs because of their accessibility, lacking accessibility – they would lack the ability to be of use. Therefore, with this understanding at the forefront, this chapter asks how arguments regarding accessibility influence the development of the EML? How were accessible and essential medicines co-related? And finally, how effective has the infrastructure that was developed by the implementation of the EML been since the list first went into practice?

[244] Egli, J., Letter, "Untitled," Letter, April 13, 1978. File A408 Folder E19/81/1. World Health Organization. Geneva, Switzerland.

I. Creation of a list as a method of ensuring antibiotic access to LMICs

The 1970s was a time of transition for the World Health Organization. The eradication campaigns that began in the 1940s with malaria and later smallpox, were once seen as the pinnacle of public health achievements.[245] If a disease no longer existed, it could no longer be seen as a threat. Although smallpox would eventually be eradicated in the 1970s, at the same time: the malaria campaign was not nearly as successful, particularly in low to middle income countries, particularly those in Africa who were excluded from many campaign efforts due to logistical issues. [246] [247] These increased funding deficits and shortages eventually led the new director general of the WHO, Halfden Mahler, to ask the WHO Executive Board if focusing on eradication specifically had been a mistake.[248] Smallpox's eradication seemed to be an outlier rather than a certainty, and the WHO was keen to replace the notion of eradication with something different.

In 1975, just before smallpox was declared officially eradicated, the WHO began looking into alternative methods of securing better global health. They started with their executive board collaborating with UNICEF on a report entitled "Organizational Study on Methods of Promoting the Development of Basic Health Services."[249] The report itself garnered a lively discussion at the World Health Assembly (WHA), particularly in regards to whether preventative or curative medicine was most "essential in the long term."[250] Two

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[245] For a more substantive review of various eradication campaigns, see: Donald A. Henderson, "A History of Eradication—Successes, Failures, and Controversies," *The Lancet* 379, no. 9819 (2012): 884–85. https://doi.org/10.1016/S0140-6736(12)60381-X.
[246] Marcos Cueto, Theodore M. Brown, and Elizabeth Fee, *The World Health Organization: A History,* (Cambridge: Cambridge University Press, 2019), 109.
[247] Katy Migiro, "Timeline: The Long Road to Malaria Eradication," *Reuters*, 8 June 2016, https://www.reuters.com/article/business/healthcare-pharmaceuticals/timeline-the-long-road-to-malaria-eradication-idUSKCN0YU0ER/.
[248] Cueto, *The World Health Organization,* 112.
[249] Cueto, *The World Health Organization*, 174.
[250] Report of WHO Executive Board. "Organizational Study on Methods of Promoting the Development of Basic Health Services." WHA A26/20. Provisional Agenda Item 3.12.1. (Geneva, Switzerland: World Health Organization, 1973), 13.

years later, Mahler echoed this exact argument by presenting to the WHA his thoughts regarding "Lists of essential medicines." As UNICEF doubled down in 1976 on "meeting the essential needs of children and mothers in rural communities and urban slums,"[251] Mahler directed the WHO towards the publication of the inaugural Selection of Essential Drugs published in 1977.[252] This list is a form of nascent infrastructure meant to ensure that the best and most efficacious drugs found their ways into hospitals as opposed and those in need, and as the list received a series of revisions roughly every two years this infrastructure experienced continued and routine maintenance in order to ensure it was operating at a functional level.

The maintenance that the EML received did lead to a great deal of change over the years. Not all of these maintenance efforts, however, have gone smoothly. While each new iteration of the EML systematically works to improve previously noted issues in form and function, there are occasionally mishaps or confusing sections (to be discussed later in more detail). However generally speaking the clarity and intention of the list's composition improves upon each edition. Bolded sections leading to more detailed subsections were added in the 1988 EML to help group together changes that are made for ease of reading and disseminating information.[253] The depth of detail regarding each new addition and change also increased over time. When the 1977 EML was first published it contained only a few pages of description prior to the printing of the list itself. The 2021 EML is over eight hundred pages in length and includes the Essential Medicines List for Adults, the Essential Medicines List for Children (originally conceived in 2007 and providing for indications suitable for young people), an alphabetical listing of all essential medicines for ease of

[251] Cueto, *The World Health Organization*, 174.
[252] World Health Organization. "Twenty-Eighth World Health Assembly Geneva, 13-30 May 1975." Official Records of the World Health Organization. No. 226. (Geneva, Switzerland: 1975).
[253] Report of WHO Expert Committee. "The Use of Essential Drugs." Technical Report Series 770. Third Report of the WHO Expert Committee. (Geneva, Switzerland: World Health Organization, 1988), 50-57.

location, applications and detailed discussion on recommended doses, publications of related interest, summaries of recommendation, citations of referenced material, and a detailed introduction and general discussion.

As these changes to the structure evolved, so too did its content and purpose. Originally defined and explained in the 1977 EML[254] as drugs that are of "the utmost importance, and are basic, indispensable and necessary for the health needs of the population," the concept of 'essential medicines' quickly became a polarizing topic.[255] Only a few months after the WHO published its first Selection of Essential Drugs, the International Pharmaceutical Manufacturers Association (IFPMA) addressed a letter to Mahler decrying the list and its purpose, and stating it had "serious reservations" about allowing the proposed list to go forward.[256] While ostensibly the arguments presented were against the phrasing and usage of the word 'essential' (implying those not included on the list were therefore *inessential*), and that the WHO had specified only generic drugs to be included on the list, the IFPMA also suggested that the list might in fact limit the commercialization and use of drugs in the public health sector.[257] To combat such fears, the WHO responded with a rather acerbic declaration: that the list is designed to provide a template in order "to ensure the availability of raw materials and of the most appropriate and economical pharmaceutical forms to meet the health needs of developing countries."[258] It was designed to create a support system, and if a country was not *in need* of such a system, then they didn't *need* to take part in that system. But that did not mean the system itself was without value.

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[254] Hereafter, each WHO Essential Medicines List will be described as the year of its publication and EML, regardless of if it was published as 'Essential Drugs List'.
[255] Report of WHO Expert Committee, "The Selection of Essential Drugs," Technical Report Series 615, The Selection Essential Drugs. (Geneva, Switzerland: World Health Organization, 1977), 9.
[256] Egli, J., Letter, "Untitled," Letter, April 13, 1978. File A408 Folder E19/81/1. World Health Organization. Geneva, Switzerland.
[257] Egli, "Untitled."
[258] Report of WHO Expert Committee, "The Selection of Essential Drugs," Technical Report Series 641, The Selection of Essential Drugs. (Geneva, Switzerland: World Health Organization, 1979), 44.

Where the 1977 EML had nine sections of various description and analysis for how and why the list was made and its purpose, the 1979 EML decreased this content to only three sections: an introduction, general considerations, and guidelines for the selection of pharmaceutical forms.[259] Even in this reduced capacity, the term "developing countries" is used four times throughout the report to further illustrate the intent behind the document. This isn't altogether surprising considering the backlash the WHO had received in its initial publication of the 1977 EML. [260] By limiting the amount of material that could be used against them, the 1979 EML kept the attention on the list and its intended use by low to middle income countries in specific. Simultaneously, actions were transpiring in the greater WHO arena to help refocus the narrative and goal behind the list and its purpose.

Nine months prior to the 1979 EML's publication, UNICEF and WHO had convened a conference in the former Kazakh Soviet Socialist Republic city of Alma Ata dedicated to ensuring Health for All.[261] As all member countries signed the declaration, they also affirmed that "the existing gross inequality in the health status of the people particularly between developed and developing countries as well as within countries is politically, socially and economically unacceptable and is, therefore, of common concern to all countries."[262] The global focus and commitment was, temporarily, in the WHO's favor here. With little outside support and with the global efforts seemingly dedicated to the Health for All initiative, the IFPMA withdrew its disapproval, grudgingly accepting the 1979 revision. However, as a

[259] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 685, Report of a WHO Expert Committee. (Geneva, Switzerland: World Health Organization, 1983), 3.
[260] Egli, J., Letter, "Untitled," Letter, April 13, 1978. File A408 Folder E19/81/1. World Health Organization. Geneva, Switzerland.
[261] It was this conference referenced by Chandler in 2019 when she stated that "antimicrobials [are] seen [as] essential to human life with access to these medicines enshrined as primary health care in the declaration signed by 134 countries from around the world at Alma Ata in 1978." Clare I. R. Chandler, "Current Accounts of Antimicrobial Resistance: Stabilisation, Individualisation and Antibiotics as Infrastructure," *Palgrave Communications* 5, no. 1 (May 21, 2019): 9. https://doi.org/10.1057/s41599-019-0263-4.
[262] World Health Organization, "Declaration of Alma-Ata," (Copenhagen, Denmark: Regional Office for Europe, 1978).

result: the concept of *essential drugs* became associated with developing nations rather than a humanistic need for medicines that transcended national incomes or borders.

II. The EML as an advocate of stewardship while promoting cost-conscious health care worldwide

There have twenty-two Essential Medicine Lists between 1977 and 2021.[263] These lists, as mentioned previously, were continually updated and maintained to reflect the most recent health recommendations. For the purposes of infrastructure and maintenance discussions, these updates were of great importance. Health needs do change over time, and the 1977 list does not reflect the needs or the requirements of those living in 2021. New information regarding drugs and their usages have also changed over time. Upgrades are a part of maintenance systems as they maintain the purpose of the system: to give the deliverable required.[264] For the EML, these updates or upgrades consistently allowed for improved access and awareness of the most essential medicines a hospital formulary could acquire, thus keeping that infrastructure continuously useful.

In 1977, the EML started with only seventeen antibiotics on its first list. There were forty by 2021. The indications and the uses of these antibiotics changed, as did the advice given for their use. Where the 1977 EML did not have any specific instructions on prioritization of one drug over the other, such suggestions were inescapable in 2021. For antibiotics, this was a clear reaction to the existence of antimicrobial resistance and the need to address it as a rising health concern.

[263] This chapter was written prior to the publication of the 2023 EML and as such that EML has not been included for analysis within this work.
[264] More on how upgrades and maintenance are related can be found in: Mark Thomas Young and Mark Coeckelbergh, eds., *Maintenance and Philosophy of Technology: Keeping Things Going,* Routledge Studies in Contemporary Philosophy, (New York, United States: Taylor & Francis Group, 2024), 69-70.

Drug resistance was first mentioned on the1983 EML, but only in the context of malaria.[265] However, that same year, the WHO Scientific Working Group published a report regarding Antimicrobial Resistance which highlighted inappropriate use, quality of antibiotics being created, and the use of antibiotics in veterinary/animal husbandry as three key factors in leading to resistance.[266] It would take until 1990 before antimicrobial resistance (AMR) was discussed in depth, mirroring global trends in rising AMR awareness that continued throughout the eighties, nineties, and noughts.[267]

Mark Thomas Young and Mark Coeckelbergh have written about how there is a difference between preventative maintenance and corrective maintenance, where "preventative maintenance encompasses activities performed in advance of the failure of a system, artefact or component" and "Corrective maintenance…addresses failures that have already occurred that threaten the overall functionality or longevity of an artefact or system."[268] The EML at its core is a list meant to help inform purchasing decisions relating to health care needs. Its lack of mention of AMR during the 1980s reflected the broader health care sentiment which did not herald the notion of drugs as the answer to resistance. No preventative maintenance was required at that time. However, as resistance rates began to rise, the WHO responded with calls for increased surveillance and stewardship. Neither of these measures *stopped* resistance, and were therefore not corrective forms of maintenance, but both could be seen as a form of initial preventative maintenance set in place to help reduce rates of AMR through management and oversight.

The WHO's efforts in both surveillance and stewardship can be seen particularly via their collaboration with various groups such as the Alliance for the Prudent Use of

[265] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 685, Report of a WHO Expert Committee. (Geneva, Switzerland: World Health Organization, 1983), 44.
[266] WHO Scientific Working Group, "Antimicrobial Resistance," *Bulletin of the World Health Organization* 61, no. 3 (1983): 383.
[267] Overton, et al., "Waves of Attention," 4.
[268] Young and Coeckelbergh, *Maintenance and Philosophy of Technology*, 19-20.

Antibiotics (APUA). APUA was originally developed by Stewart Levy, a Tufts University researcher and physician who prioritized work on antimicrobial resistance and effect of the overuse and misuse of antibiotics both in human and animal health. Levy, and APUA, argued for adjustments on how antibiotics were to be used, and specifically called for antibiotic stewardship measures which were intended to monitor and observe antibiotic prescription and encourage the reduction of such prescriptions should there be no clear medical need for their existence. Seven key problems were recorded in APUA's 1982 statement: *Misuse of Antibiotics.* These included prescribing antibiotics for non-bacterial infections, failure of patient to follow appropriate instructions (or completion of their course), using human antibiotics to promote growth or health in animals or plants, "advertising of newer antibiotics as replacements for older, still effective ones," acquiring antibiotics without prescriptions, inappropriate doses, or the packing and selling of drugs in combinations unnecessary for the treatment of the bacterial infection in question.[269]

Not long after APUA's statement was published, the Drs. O'Brien and Stelling of the World Health Organization Collaborating Centre for Surveillance of Antimicrobial Resistance developed a free desktop Window's application entitled "WHONET" with Brigham & Women's Hospital and Harvard Medical School. WHONET's purpose was to promote "standardization and comparison of local resistance data."[270] It became a form of resource infrastructure capable of assisting those hoping to implement surveillance and stewardship efforts effectively. Anyone who downloaded the application would be able to use various "modules for laboratory configuration, data entry, data analysis, public health reporting, and data encryption among others,"[271] all with the express purpose of ensuring that

[269] Alliance for the Prudent Use of Antibiotics and Stuart B. Levy, *Misuse of Antibiotics*, https://iris.paho.org/bitstream/handle/10665.2/38351/13086.pdf.
[270] Podolsky, *The Antibiotic Era*, 163.
[271] WHONET, *WHONET Microbiology Laboratory Database Software*, https://whonet.org/index.html. Accessed 8 Jan. 2025.

anyone using WHONET can keep track of resistance trends globally. As of 2024, WHONET is still active and it proclaims that it is available in "44 languages, supports local, national, regional, and global surveillance efforts in over 2,300 hospital, public health, animal health, and food laboratories in over 130 countries worldwide."[272]

Both APUA and WHONET highlight surveillance and encourage the limited use of medications. On their surface, that is incongruent to the notion of the EML which encourages the purchase of antibiotics. Of course, the purchasing of a drug for a hospital formulary does not imply that the purchase should be done imprudently, nor that the drug should be used inappropriately, but there is a subtle separation between the two concepts. As such, the EML does not discuss AMR. During the 1980s, despite the WHO's involvement in other ventures dedicated to AMR.

It would take until 1990 before the first reference to AMR appears, and it does so by specifically calling out nine bacterial strains (gonorrhea, chancroid, *Hemophilus influenza* type b meningitis, *Hemophilus ducreyi*, *Salmonella*, *Shigella, Escheria coli, Klebsiella, Pseudomonas aeruginosa,* and *Staphylococcus aureus*) and the high financial cost associated with recommending the "unrestricted use" of antibiotics capable of treating these bacteria.[273] This emphasizes the EML's initial focus and intention: the suggestion of appropriate medications for developing nations that are facing financial burden when it comes to supplying their formularies, but it is now doing so in association with an awareness of the rising health concern AMR brings with it.

From an access perspective, antibiotic surveillance/stewardship and the EML are at a complicated crossroads. Levy and APUA argued that there were too many antibiotics being used inappropriately, and WHONET helped to provide data on exactly how many antibiotics

[272] WHONET, *WHONET Microbiology Laboratory Database Software*.
[273] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 796, Fourth Report of the WHO Expert Committee, (Geneva, Switzerland: World Health Organization, 1990), 14.

were being used and how that related to resistance mechanisms. Overuse of antibiotics implies that there are physically too many antibiotics in circulation to begin with. For low to middle income countries, the EML was developed to help them access the best antibiotics – to know what should fill their formularies in times of need. Now, though, it was not merely a matter of *what* those countries needed, but what those countries did with them once they had them. From the start the EML was designed to limit excess, and as stewardship concerns began to rise: how the EML went about recommending additional limitations became important. Rather than simply recommend that an antibiotic be purchased, now, purchasing came with restrictions. The infrastructure itself needed to be modified because the end goal of access to *what* and how *much* was changing.

The 1990 EML, therefore, served as a kind of whistle blower for all parties involved as to the changes taking place regarding antibiotic care and practice. It notes that resistance had been noted in all of the antibiotics on its list, and that "reserve antibiotics" (where use is limited to specific instances only) should be considered. The section starts with a call of alarm, stating that:

> The increasing prevalence of strains of common pathogenic bacteria resistant to widely available, relatively cheap antimicrobials included in the model list is dangerously eroding their effectiveness. The need for more systematic and coordinated international approaches to laboratory monitoring of antimicrobial sensitivity is important and urgent.[274]

What is perhaps most concerning about this verbiage, is the focus on the excessive use of *cheap* antimicrobials: i.e. the very same antimicrobials that the EMLs have been suggesting for use to developing nations. While the WHO's self-awareness on the relationship between the rise of AMR and the increased use of drugs on their own list does not extend beyond that initial statement, their call to action remains focused on a need for surveillance measures to be implemented in order to understand the gravity of the situation in its entirety. They revert

[274] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 796, Fourth Report of the WHO Expert Committee, (Geneva, Switzerland: World Health Organization, 1990), 13.

to their already preexisting partnerships with stewardship focused groups, rather than suggest infection prevention or control measures or even go so far as to suggest a new drug to replace the older less effective products. This decision puts them in somewhat familiar territory with APUA whose 1981 statement suggested that the use of *new* antibiotics in place of old and effective antibiotics may have been a stressor on increasing rates of resistance, [275] however it also leaves them open to critique as it was the older drugs on their own list that they admit have experienced resistance. The 1990 EML thus threads the line between highlighting the fact there is a growing health need and suggesting appropriate action for that need.

Two years later, the 1992 EML continued the call to action takes the form of increased surveillance once again. "Knowledge of prevailing sensitivity patterns," the 1992 EML argues, "is vital to the proper selection and use of antimicrobials and to the development of appropriate prescribing policies."[276] Various recommendations on reporting possibilities and options are provided, and the notion of "reserve antimicrobials" is brought up once more in the case of second- and third-generation cephalosporins, the fluoroquinolones and vancomycin. [277] Of these three drugs, only the fluoroquinolone ciprofloxacin was added to the list proper.

From an accessibility standpoint, the WHO's decision to not include the others was a matter of *affordability* rather than availability, as the EML states: "because of the need to reduce the risk of development of resistance and because of its *relatively high cost*, it would be inappropriate to recommend [a reserve antimicrobial] unrestricted use" (emphasis mine).[278] Cost was once more a determining factor in what made a medication essential or

[275] Alliance for the Prudent Use of Antibiotics and Stuart B. Levy, *Misuse of Antibiotics*, https://iris.paho.org/bitstream/handle/10665.2/38351/13086.pdf.
[276] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 825, Model List of Essential Drugs, (Geneva, Switzerland: World Health Organization, 1992), 7.
[277] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 825, Model List of Essential Drugs, (Geneva, Switzerland: World Health Organization, 1992), 7.
[278] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 825, Model List of Essential Drugs, (Geneva, Switzerland: World Health Organization, 1992), 8.

not. Although the 1992 EML does provide instruction on potential uses for these reserve antibiotics, and it does state that these antibiotics should be used in strictly appropriate settings where the bacteria and antibiotic are proven efficacious, the lack of formal recommendation implies that the problem of antimicrobial resistance is not quite at a point where the health need supersedes the financial constraints. Surveillance and stewardship to drop the rates of resistance, rather than potentially risking the new forms of resistance in their reserved antibiotics remained their priority.

In the case of vancomycin resistance, these concerns were well founded. In 1993, Denmark became the third country in the world to note the existence of vancomycin resistant enterococci (VRE) in pig and poultry farms as a result of the animal-version of the drug avoparcin.[279] Growing concern over potential crossover from animal to human health, and the risk of this reserve antibiotic no longer being efficacious for humans, led to Denmark eventually phasing out the use of avoparcin, but the fear remained. It would take until 1997 before vancomycin and two cephalosporins were added to the list, all under a "restricted indication."[280]

As for ciprofloxacin, the fluoroquinolone that was added to the 1992 EML, it was included in what was initially called a "complementary list." Although such drugs are listed side by side with other drugs on the EML, those listed under the complementary "heading are not essential. They are added as examples of drugs that provide (a) alternatives when infectious organisms develop resistance to essential drugs, (b) treatment in rare disorders, and (c) special pharmacokinetic properties, etc.; they should be available as funds permit."[281] Ciprofloxacin moved off the complementary list and on to the officially *essential* component

[279] Claas Kirchhelle, "Pharming Animals: A Global History of Antibiotics in Food Production (1935–2017)," *Palgrave Communications* 4, no. 1 (August 7, 2018): 8, https://doi.org/10.1057/s41599-018-0152-2.
[280] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 867, Model List of Essential Drugs, (Geneva, Switzerland: World Health Organization, 1998), 31.
[281] Report of WHO Expert Committee, "The Selection of Essential Drugs," Technical Report Series 615, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 1977), 20.

of the EML in 1997 after briefly being removed entirely in 1995. It has remained a part of the EML ever since, gaining a square symbol ("□") by its name in 1997 to denote that it serves only as an example of a "therapeutic group" and that pricing should dictate if it or another drug of the same class/mechanism should be used in its place.

As with vancomycin and the cephalosporins, the health *need* for ciprofloxacin when it came to addressing antimicrobial resistance was noted by the WHO. However, its cost was a prohibitive factor. Those concerns appeared to be alleviated after 1997 as the drug was now seen as a "first-line antimicrobial agent in many infections."[282] Perhaps most intriguingly, once it found its place on the main list, discussions of its use as a "reserve agent" for AMR becomes far more tentative. The 1997 EML instead generalizes the class itself and shifts focus to second- and third- generation cephalosporins as the next potential reserve class (with vancomycin listed specifically due to its capacity to respond to MRSA).[283] Although the general diction from the 1990 EML regarding how ciprofloxacin and other forms of quinolones should be utilized in regards to treating resistant strains repeated itself in every list from 1992-1998, ciprofloxacin *specifically* slipped from any kind of targeted mentioning by 2000.

The EML during the 1990s was, therefore, a strong supporter of antibiotic stewardship measures, while equally conscious of the rise of AMR. It applied preventative maintenance to the infrastructure in hopes of reducing the potential risk to AMR, but offered no direct corrective maintenance yet. It equally hesitated to recommend "reserve antibiotics" that could specifically treat resistance, as it feared doing so would make the drugs more widely used. It also showed consistent concern for the cost of the drugs, and the cost was often used as an excuse to not include these drugs on the list in the first place. This reveals a strained priority regarding the drug's recommendations. In the face of public health needs,

[282] Report of WHO Expert Committee, "The Selection of Essential Drugs." Technical Report Series 615, 55.
[283] Report of WHO Expert Committee, "The Selection of Essential Drugs." Technical Report Series 615, 11.

would cost alone be a determining factor on whether a drug could be considered essential? Furthermore, does restricting the availability of a drug that may be able to treat specific or unique bacteria lead to greater health outcomes? As the EML began to approach the new millennium, these concerns only became more evident.

III. Rising costs of medication and the conflict between patents and accessibility

In 1999, the executive director of the France division of Médecins sans Frontières (MSF), Bernard Pécoul, and his colleagues published a scathing assessment of the cost of medicines in regards to the WHO's essential drugs program. The article, "Access to Essential Drugs in Poor Countries: A Lost Battle?" detailed the numerous deficiencies of cost related care when it came to Low- Middle-Income Countries.[284] Ideal treatment for two bacterial infections, *Shigella dysenteriae* and *Streptococcus pneumoniae* include the use of fluoroquinolones (e.g., ciprofloxacin and norfloxacin) and ceftriaxone sodium respectively, however both treatments were ten times more expensive than the standard treatments previously given for these diseases.[285] Indeed, while ciprofloxacin was added to the WHO EML in 1992, norfloxacin never made the list. Ceftriaxone was added in 1997, but only for use in cases of meningitis caused by *Streptococcus pneumoniae, Hemophilus influenzae* and *Neisseria meningitidis.*[286] Cost again was the key concern in each case, highlighting that even in cases when drugs do make it onto the EML, the pricing may still be too prohibitive for a Low- Middle Income Country (LMIC) to take advantage of. That drugs such as vancomycin took so long to get on the list, in these circumstances, is not a surprise. But circumventing cost or providing alternatives became the epicenter of the EML debate in the succeeding years.

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[284] Bernard Pécoul, Pierre Chirac, Patrice Trouiller, and Jacques Pinel, "Access to Essential Drugs in Poor Countries: A Lost Battle?" *JAMA* 281, no. 1 (1999): 361–67.
[285] Pécoul, "Access to Essential Drugs in Poor Countries: A Lost Battle?" 363.
[286] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 867, Model List of Essential Drugs. (Geneva, Switzerland: World Health Organization, 1997), 11.

As early as 1970, prior to the first iteration of the EML, developing countries were working to try to limit patent protections that they saw as prohibitive to productive trade. Their goal had been initially to prioritize local working requirements, and allow for compulsory licensing rather than enable a system that forced them to pay foreign entities for essential goods or materials.[287] Their attempts to establish such trade agreements failed as the United States government made intellectual property protection a "precondition for access to the US market under the Generalized System of Preferences (GSP) for developing countries."[288] Without accepting the neoliberal policies set forth by the United States, LMICs could not receive United States goods or services.

On 15 April 1994, two massive global trade initiatives took place in Marrakesh, Morocco. The first, was the transformation of the post-war international trade agreement, General Agreement on Tariffs and Trade into the World Trade Organization (WTO) in what would be called the Marrakesh Agreement.[289] With this transformation came the implementation of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) whose key measure allowed for twenty-year global patent protections. Criticism of the WTO and TRIPS were immediate, with one Tribhuvan University professor of economics saying that it was about "fair trade, and, in particular, about gaining access to the markets of the developing countries. [But] all it gave to developing countries is damageable limitations."[290] Two of these limitations included the fact that "global minimum requirements for the creation and protection of IP were [now] enforceable through the WTO" and that patent protection on "*essential* goods such as medicines and foods" (emphasis mine), which

[287] Carlos M. Correa and Abdulqawi A. Yusuf, eds., *Intellectual Property and International Trade: The Trips Agreement,* Third, (The Netherlands: Wolters Kluwer, 2016), 5.
[288] Correa and Yusuf, *Intellectual Property and International Trade*, 9.
[289] Vishnu Prasad Sharma, "Marrakesh Endorsement of GATT's Eighth Round and Its Impact on Developing Countries," *The Economic Journal of Nepal* 17 No. 2, no. 66 (1994): 109-110.
[290] Vishnu Prasad Sharma, "Marrakesh Endorsement," 111.

were "for a long time considered an act against the public interest" were now permissible and encouraged.[291]

The developing nations within the GATT (and later WTO) who were responsible for offering their input to the development of TRIPS attempted to isolate the WTO's patent provisioning to non-essential products, and India (who had up until then been building a steady pharmaceutical business that largely relied on the reverse engineering of patented medication developed elsewhere) submitted their concerns regarding the potential problems patent monopolies would have on pharmaceutical innovations.[292] A schism between "western" interests and "developing countries" abounded where the former wanted diverse IP interests with strong patent monopoly protections, while the latter felt these monopolies denied competition and limited their potential economic development.[293] As lawyer, international medical activist, and policy and advocacy director of the Médecins sans Frontières' Access Campaign, Ellen 't Hoen has pointed out:

> Access to medicines is by no means a recent problem for the developing world. For decades countries have suffered from dependency on Western companies for the supply of medicines. The TRIPS Agreement's extended requirements for pharmaceutical patents are likely to further increase developing countries' dependency on multinational pharmaceutical companies…[Furthermore] Patents have a major impact on product prices because they prevent competition…Before TRIPS, many developing countries did not grant pharmaceutical product patents and/or they limited patent terms, which allowed a generic industry and competition to flourish.[294]

The TRIPS agreement then was a massive concern for potential access to medicines, and as the essential medicines department at the WHO became more aware of the potential impact of the agreement and what it could mean to the drugs they were trying to ensure made it into the hands of those in need, the subject of cost of medicines now and in the future could not be ignored. If cost was already a prohibitive factor prior to TRIPS, it would certainly be one

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[291] 't Hoen, Ellen F.M., *The Global Politics of Pharmaceutical Monopoly Power: Drug Patents, Access, Innovation and the Application of the WTO Doha Declaration on TRIPS and Public Health*, Netherlands: AMB Publishers, 2009, 9.
[292] 't Hoen, *The Global Politics of Pharmaceutical Monopoly Power*, 10.
[293] 't Hoen, *The Global Politics of Pharmaceutical Monopoly Power*, 11.
[294] 't Hoen, *The Global Politics of Pharmaceutical Monopoly Power*, 2, 5.

afterwards when the patent terms and pricing of drugs were both extended and increased in equal measure.

IV. Assessing the Impact of HIV/AIDS on Access to Essential Antibiotics

Even while the TRIPS agreement was being drafted, the world was experiencing a massive health crisis in the form of the HIV/AIDS epidemic. Tens of thousands of people were dying globally each year as a result of HIV/AIDS complications, and there were few treatments that could successfully mitigate symptoms. The first antiretroviral to be developed was put into the market in 1987, and when TRIPS came into fruition: its patent was well covered by the regulations. For those unable to afford the drug, and with no access to a generic version that had been reverse engineered from the patented copy: there was a potential for millions of individuals suffering from HIV/AIDS to die before they could afford access to the medication.

Although the focus of this dissertation is on the history of access to antibiotics new and old and the crumbling infrastructure that supports appropriate access to these medicaments, the HIV/AIDS epidemic had a distinct and profound impact not only on the way antibiotics were used. Similarly, it had a vivid and evident impact on the EML and how it began to recommend antibiotics in the fight against AMR in the years that followed. The infrastructure that the whole concept of essential medicines and the Essential Medicines List in general was a part of was effected by HIV/AIDS and as a result – so too was the antibacterial section. Though a virus, patients with HIV/AIDS are known for often contracting opportunistic infections (or co-infections), such as tuberculosis (TB) that lead to increased suffering and, often, death, one of the most lethal being that of tuberculosis (TB). Therefore, there are three pathways the HIV/AIDS epidemic effected the EML's handling of antibiotics. First, politically via the development of the Doha Declaration which adjusted the TRIPS agreement in regards to patent regulations and generic medications. Second,

medically via the rise of resistant pathogens that were impacting HIV/AIDS patients and the need to address these pathogens effectively. And third, structurally via the changes made to the EML in an attempt to address the growing health needs of populations in need of essential medications but facing economic frustration when it comes to accessing that medication.

A. Political Ramifications of HIV/AIDS on the EML: TRIPS and the Doha Declaration

Only a few years after the TRIPS agreement went into effect, its prohibitive impact on the pharmaceutical industry was already being felt. James Love of Knowledge Ecology International (KEI), an NGO dedicated to addressing matters of intellectual property and public health, discussed the evolution of the TRIPS agreement and the eventual Doha declaration during a series of interviews in April 2024.[295] Love played a hugely influential role in the development of the declaration, and he began his recollection by stating it all went back to HIV/AIDS and the realization around 1996/1997 that a triple combination therapy of antiretrovirals worked and could actually make a difference on the course of the epidemic.[296]

Only a year later, in 1998, arguments were taking place on the World Health Assembly floor as differing delegates failed to agree on compromises on what kind of action should be taken place to address the accessibility crisis HIV/AIDS, antiretrovirals, and TRIPS was causing. The acting director of Essential Drugs and Medicines Policy at the WHO at that time, Dr. Jonathan Quick, he recalled those meetings as the greatest professional challenge of his career:

> it was a 20-hr negotiation led by the North by the US and the South by South Africa which blew up on a Friday afternoon at the Assembly in Committee A. The assembly works in two groups and so, you got 140 countries all in this big UN room and the six languages translation. And it ends with a 20 min shouting match between the South African Ambassador and the US political attaché because the north had sort of worked out a procedural thing that bumped the resolution out. It was just a mess Friday afternoon at 4 o'clock.[297]

[295] Doha Declaration: Ministerial Declaration of 14 November 2001, WT/MIN(01)/DEC/1, 41 ILM 746 (2002).
[296] James Love, Interview by Erin L. Paterson 23 April 2024.
[297] Jonathan Quick, Interview by Erin L. Paterson, 11 November 2022.

What followed, was "a year of tough discussions and it happened at a time when WHO had new leadership coming in," [298] and a complex series of negotiations between various stakeholders with different levels of "vested interest" in various medicines policy, legal, and intellectual property issues.

For Love, his vested interest was purely in the humanitarian aspect of access to medicines. Patented medications were always more expensive than their generic counterparts, and following a May 1998 Workshop on Intellectual Property, Health Care and International Trade Agreements that took place in Washington DC, he began to try to find if it would be possible to make an antiretroviral drug for cheap – and just how cheap it could go. [299] Eventually, he found a knowledgeable and trustworthy pharmaceutical company, CIPLA, an Indian company under the direction of Dr. Yusuf Hamied, who offered a price tag of $350/year. [300] After a series of meetings and discussions with both Hamied and MSF, Love reached out to Donald McNeil at the NYT who reported on the CIPLA offer as well as the current cost of antiretrovirals: $10,000-15,000/year. [301] [302]

The timing could not have been more auspicious. Although Love remembers the WTO immediately stating that they would be open to negotiating potential patent relief for essential medicines within a week of McNeil's article, less than a month later 39 pharmaceutical companies sued Nelson Mandala's South Africa for changes to their Medical Act. The act, originally published in 1997 called for:

- [The use of] 'parallel importing' to obtain patented life-saving medicines from countries where they [were] sold more cheaply;

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[298] Richard Laing, "Talking Essential Medicines," *Essential Drugs Monitor*, 2003, 4.
[299] James Love, Interview by Erin L. Paterson 23 April 2024.
During the course of our interview on this matter, Love provided the following document relating to the meeting in Washington: https://web.archive.org/web/19980523133145/http://www.cptech.org/may7-8/agenda.html
[300] James Love, Interview by Erin L. Paterson 23 April 2024.
[301] James Love, Interview by Erin L. Paterson 23 April 2024.
[302] Donald G. McNeil Jr, "Indian Company Offers to Supply AIDS Drugs at Low Cost in Africa," *New York Times*, February 7, 2001, https://www.nytimes.com/2001/02/07/world/indian-company-offers-to-supply-aids-drugs-at-low-cost-in-africa.html.

- [The authorization of] imports of generic versions of patented medicines for non-commercial government use, through compulsory licenses
- [The adoption of] measures to ensure that pharmacists dispense cheaper generic copies where doctors have prescribed more expensive brand-name drugs;
- [And the establishment of] a pricing committee to introduce a transparent pricing system for all medicines.[303]

The Pharmaceutical Research and Manufacturers of America and the basis for the coalition that brought suit against South Africa, lobbied extensively in the United States until the government threatened issued legal sanctions against South Africa unless the Act was repealed.[304] James Love wrote to Vice President Al Gore, lambasting that even quotes from the South African representatives to the World Health Organization arguing that there should be fewer patent protections in the TRIPS agreement had been cited by the lobby and US government as cause for alarm, complaining that "the exercise of free speech in international forums is an astonishing basis for trade sanctions."[305]

Public condemnation of the case was fierce. Where the pharmaceutical lobby may have been strong, the organization of public actors and civilians arguing against the parameters of the case was even stronger. The United States was the first to bow to pressure, dropping its threat of sanctions in 1999,[306] but the pharmaceutical lobby persisted through the start of the trial in March 2001. However, an international media campaign with hundreds of new consultants reporting on the trial increased public support for South Africa and public condemnation to levels too impossible to ignore.[307] By April, the outcry had become so loud, that in the midst of the trial: they conceded and agreed to allow the law to be upheld while simultaneously paying for South Africa's legal costs in the process.[308]

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[303] Oxfam, "South Africa vs. the Drug Giants A Challenge to Affordable Medicines: Oxfam Background Briefing," Oxfam, February 2001, https://oxfamilibrary.openrepository.com/bitstream/handle/10546/620381/bn-access-to-medicines-south-africa-010201-en.pdf;jsessionid=E4F60D5F3610FB0C2D51F9F5B065CED9?sequence=1.
[304] Oxfam, "South Africa vs. the Drug Giants."
[305] Oxfam, "South Africa vs. the Drug Giants."
[306] Oxfam, "South Africa vs. the Drug Giants."
[307] James Love, Interview by Erin L. Paterson 23 April 2024.
[308] Rachel Swarns, "DRUG MAKERS DROP SOUTH AFRICA SUIT OVER AIDS MEDICINE," *The New York Times*, April 20, 2001, Online edition, sec. A, 1, https://www.nytimes.com/2001/04/20/world/drug-makers-drop-south-africa-suit-over-aids-medicine.html.

Eyes now turned to the WTO and if it would honor its promise to offer patent flexibility for essential medicines – ostensibly for HIV/AIDS medications that started the fight, but practically for all other potential drugs that could fall under this umbrella. By the end of 2001, it had done so at Doha, Qatar, via a declaration that "affirmed nearly all the points WHO tried to make in 1998."[309] The declaration itself made clear that TRIPS

> does not and should not prevent Members from taking measures to protect public health…[affirming] that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and in particular to promote access to medicines for all… [and reaffirming] the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement which provide flexibility for this purpose.[310]

The impact was one that was not limited to HIV/AIDS and its ramifications are still felt on the EML today.

The EML had always been a list comprised of generic names and with a focus on low cost measures and treatments. The initial TRIPS agreement made the influx of new generics impossible for twenty years, but Doha offered a pathway for generic or low-cost formulations, tiered pricing, or potential negotiations regarding pricing to ensure access to essential medicines even if those medicines were on patent. During the fierce debates between TRIPS and Doha regarding licensing and parallel imports, drug manufacturing factories were intentionally closed down and investments into this sector were cancelled by the pharmaceutical industry as a method of applying pressure on South Africa and others who were arguing for patent relief. [311] The impact of this decision, and potentially the impact of the concern that generics drugs would not be able to produce new formulations for sale for twenty years following TRIPS led to a visual decline in the amount of companies that were actively manufacturing and selling drugs in the United States between 1995 and 2001.

[309] Laing, "Talking Essential Medicines," 4.
[310] Correa and Yusuf, *Intellectual Property and International Trade: The Trips Agreement*, 18.
[311] Swarns, "DRUG MAKERS DROP SOUTH AFRICA SUIT OVER AIDS MEDICINE."

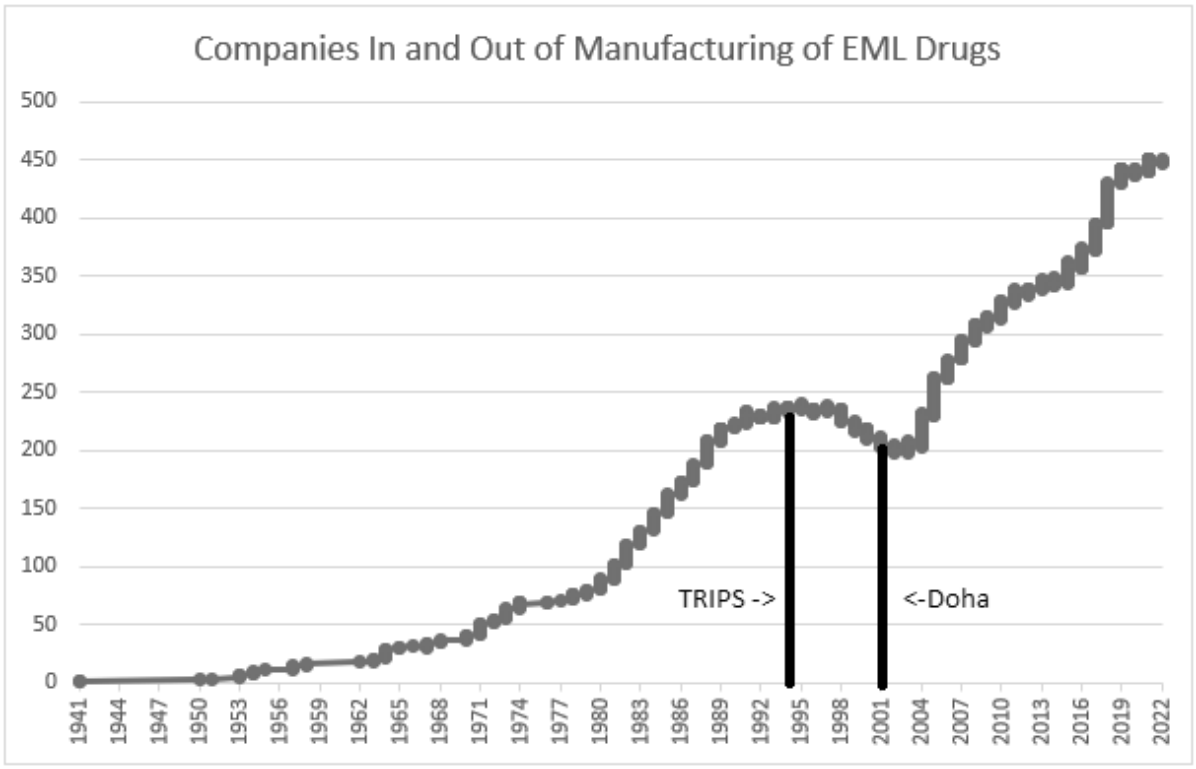

Figure 3 FDA Approved Manufacturers of EML[312]

The graph above, with data retrieved from the United States FDA Orange Book of market authorization, shows the general trend and trajectory of companies that have market authorization to sell an *antibiotic* that is on the WHO's Essential Medicines List within the United States specifically during any given year. Although there was a slowdown of new companies entering the market prior to 1994, following the implementation of the TRIPS agreement, and particularly after the announcement of South African 1997 Medical Act, there is a clear dip in companies developing generic essential *antibiotic* medicines – even though the South African case was largely focused on HIV/AIDS relief.

Despite the fact Doha was originally intended to assist LMICs in ensuring appropriate access to medications, immediately following its implementation the generic markets in the United States skyrocketed as a surplus of new manufacturers rushed to gain authorization for sale. Many of the companies (such as Dr Reddy's Laboratories or Salix Pharmaceuticals)

[312] Review Appendix 2 for the complete data set that was compiled to develop this chart. All data points sourced from FDA Orange Book.

gained FDA authorization sell their products globally, therefore their US authorization is an indication that they have a product that can be sold elsewhere – such as to LMICs. Therefore, this tangential data, reviewing the impact of TRIPS/Doha on the market approval in the United States can provide a potential insight to manufacturing practices abroad.[313]

There are some flaws with this example, and more research into the deeper meaning of the intentions and reflections of the companies doing this business would need to be conducted, but that is outside the scope of this project. Limitations to this data surround how short the time between TRIPS and Doha were, and while it's clear that there was a dip and a remarkable rebound, there is little qualitative information from the data points that point to reasons for why these companies left the business. While the timing with the punitive measures against the South African case match, a slowdown was indicated prior. These data points equally do not account for business mergers where an acquisition and continuance of sale does not disrupt the sale of products. Additional research and study into this time period would help provide clarity on the historical and practical data surrounding these companies and their intentions and reach, however, that is beyond the scope of this project. As a snapshot view, this chart suggests that there may be a relationship to the broader essential medicines' category and the influence of TRIPS/Doha. And what is clear for certain, is that post Doha the generics manufacturing market in the United States – and as a result, abroad, grew significantly.

Due to the political and economic ramifications of national and global legislation surrounding the response to HIV/AIDS medications, all essential medicines and the generics industry that supported those that were included on the Essential Medicines List – including

[313] It is important to note that he FDA's Orange Book only provides insight to pharmaceutical companies that have market authorization to sell a particular drug. It does not provide any insight whatsoever into the status of where those drugs get their active pharmaceutical ingredients (APIs) from. Chapter Five will discuss this discrepancy in more detail and reveal how a large number of pharmaceutical companies in one place does not mean there is great diversity when it comes to drug origins or an open and stable supply chain capable of managing access needs.

antibiotics were affected. The environment surrounding the EML's infrastructure had changed, and how it could best deliver its support changed as a result. This change was of great importance, because beyond the politics surrounding HIV/AIDS – the medical concerns of bacterial co-infections led to fierce debates and structural upheavals of antibiotics on the EML.

B. Medical Ramifications of HIV/AIDS on the EML: Co-infections and resistance

In 1986, Institute of Medicine, a non-government organization based out of in Washington, D.C., published a book entitled *Confronting AIDS: Directions for Public Health, Health Care, and Research*.[314] Published only five years after the HIV/AIDS crisis began, the book served as an initial form of guidance for the government on how to manage the epidemic, offering advice in terms of how the virus is contracted, what populations were at most risk, the status of the epidemic thus far, and national/international guidance.[315] Nestled within its pages lay one of the first public signs of relation between resistant strains of diseases and HIV/AIDS. "Probably because the immune deficit is so profound, in AIDS patients these infections are characterized by an aggressive clinical course, resistance to therapy, a high rate of relapse, and a high incidence of drug toxicity during treatment."[316] The bacteria of most concern, and seen with alarming regularity, was *mycobacterium tuberculosis*.

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[314] Established in 1970 by the National Academy of Sciences, the Institute of Medicine received its research funding for this specific project from the National Research Council (United States) Fund which includes a variety of private donors such as : Carnegie Corporation, Charles E. Culpeper Foundation, William and Flora Hewlett Foundation, John D. and Catherine T. MacArthur Foundation, the Andrew W. Mellon Foundation, the Rockefeller Foundation, the Alfred P. Sloan Foundation, the Academy Industry Program, as well as National Academy of Sciences and National Academy of Engineering endowments. There is no additional information regarding the individual authors or members of this particular committee, but more on their backgrounds and history can be found here: Institute of Medicine, *Confronting AIDS: Directions for Public Health, Health Care, and Research*. (Washington D.C., United States: National Academy Press, 1986).

[315] Institute of Medicine, *Confronting AIDS: Directions for Public Health, Health Care, and Research*. (Washington D.C., United States: National Academy Press, 1986).

[316] Institute of Medicine, *Confronting AIDS*, 47.

Eight years later, in 1998 (while James Love, the WHO, and South Africa were beginning to argue with pharmaceutical companies about HIV/AIDS drug pricing), the United States Department of Defense Global Emerging Infections Surveillance and Response System published a report discussing the impact of infectious disease and the need for an immediate reverse course on the laissez-faire attitude encompassed by national health policies in regards to such diseases. Although the intention behind the DoD's report is written with an overt militaristic concern of soldiers who may encounter viral or bacterial illnesses while deployed, the narrative of infectious disease as a global, and under-recognized threat, is clear. In this report, rather than TB, the resistant drug bacteria *campylobacter* is mentioned, as is the destabilizing factor of epidemics in a global context as areas with an HIV infection rate of 20+% were expected to become hotspots for militaristic conflicts.[317]

In both *Confronting Aids* and the DoD report, bacterial infections and their relationship with HIV/AIDS were being highlighted as areas of distinct concern for civilian and military populations both at home and abroad. Of particular concern to each was that there was a lack of drugs best suited for treating not only HIV/AIDS but the co-infections that frequently were seen with them, many of which were sexually transmitted infections (STIs). [318] The regulation of drugs, and the lack of proper antibiotic stewardship in LMICs heightened problems of resistance in all three referenced infections: TB, *campylobacter*, and STDs. The prevalence of these co-infections which were increasingly becoming resistance, was the impetus for calls for improved access to different drugs (i.e. reserve drugs) that could efficaciously treat these bacterial infections alongside HIV/AIDS.

In 1987, a journal entitled *AIDS* launched in an effort to collect and publish relevant medical research surrounding the epidemic. In 1989 it published an article specifically

[317] Department of Defense Global Emerging Infections Surveillance and Response System, "Addressing Emerging Infectious Disease Threats: A Strategic Plan for The Department of Defense," (Washington, DC, United States: Walter Reed Army Institute of Research, 1998), 2.
[318] Department of Defense, "Addressing Emerging Infectious Disease Threats," 8.

relating to the notion of STI co-infections experienced by those with HIV/AIDS. As a sexually transmitted disease, the idea of more than one STI occurring by those having sex with multiple partners is a likely possibility. Particular concern was placed with the co-infections of *treponema pallidum* (syphilis)*, chlamydia trachomatis*, and *Neisseria gonorrhoeae*.[319] The 1988 EML that would have been active at the time of this publication only recommends the use penicillin G benzathine, tetracyclines, spectinomycin, and the macrolide: erythromycin for treatment of these infections. [320] Both ceftriaxone[321] and azithromycin were both effective possibilities as well. [322] [323] [324] [325] However, it is with azithromycin in particular, that the EML's response to the HIV/AIDS crisis becomes most evident.

Azithromycin was discovered in the late 1970s by Croatian pharmaceutical company, Pliva.[326] By 1991, it had been approved for use by the US FDA and Pliva engaged in licensing agreements with Pfizer over the international sale of the antibiotic. Since then, azithromycin has been used traditionally to treat a range of bacterial infections from middle ear infections to malaria.[327] Azithromycin was first mentioned on the 1998 EML in regards to a research study as to its "clear advantage" in treating trachoma, a type of blindness resulting

[319] Jacques Pepin, Francis A. Plummer, Robert C. Brunham, Peter Piot, William D. Cameron, and Allan R. Ronald, "The Interaction of HIV Infection and Other Sexually Transmitted Diseases: An Opportunity for Intervention," *AIDS* 3, no. 1 (1989): 4-6, https://doi.org/10.1097/00002030-198901000-00002.
[320] Report of WHO Expert Committee. "The Use of Essential Drugs." Technical Report Series 770. Third Report of the WHO Expert Committee. Geneva: World Health Organization, 1988, 50-57.
[321] Added to the EML in 1998 under a restricted indication
[322] Report of WHO Expert Committee. "The Use of Essential Drugs." Technical Report Series 770. Third Report of the WHO Expert Committee. Geneva: World Health Organization, 1988, 50-57.
[323] Lola V. Stamm, "Global Challenge of Antibiotic-Resistant Treponema Pallidum," *American Society for Microbiology, Antimicrobial Agents and Chemotherapy*, 54, no. 2 (2010): 583–84. https://doi.org/10.1128/AAC.01095-09.
[324] Meenakshi Malhotra, Seema Sood, Anjan Mukherjee, Sumanthi Muralidhar, and Manju Bala, "Genital Chlamydia Trachomatis: An Update," *Indian Journal of Medical Research* 138 (2013): 312.
[325] World Health Organization, "WHO Guidelines for the Treatment of Neisseria Gonorrhoeae." (Geneva, Switzerland: World Health Organization, 2016), 3.
[326] Pliva would later become a subsidiary to Teva Pharmaceuticals in 2008.
[327] It has since been considered one of the most used antibiotics in the United States, and more can be found here: Azithromycin: Drug Usage Statistics, United States, 2013 – 2020, "Azithromycin," August 2022. https://clincalc.com/DrugStats/Drugs/Azithromycin.

from *chlamydia tracomatis* one of the potential noteworthy co-infections of HIV/AIDS.[328] In its report, the WHO declined to add azithromycin to that year's list as the results of clinical trials regarding trachoma had yet to be finalized (and up until that point: tetracycline was still determined as the drug of choice in these matters).[329] Azithromycin, crucially, was still on patent, and the EML had up until that point only recommended generic formulations as a cost saving measure to the LMICs it largely targeted.

Following the Doha declaration in 2001, however, and in support of a public push for access to needed medication despite the cost: the WHO re-evaluated azithromycin's health potential. Antiretrovirals capable of treating HIV/AIDS were the first on-patent medications to join the EML in 2002 as a direct response to the successful passing of Doha; only one year later azithromycin became the first on-patent antibiotic to join the list. It did so specifically to treat a co-infection commonly associated with HIV/AIDS. Without the public outcry surrounding HIV/AIDS, and the push for essential medicines to be made accessible to those with a significant health need despite the patent cost: it is entirely possible that azithromycin, like ceftriaxone, would have needed to wait until the end of its patent life before it joined the list and was recommended for use.

Instead, by 2005, companies were scrambling to develop generic versions of the drug. Two years after it first made its appearance on the EML, LMICs had access to four different generic options when it came to azithromycin, including those from the initial manufacturer, Pliva. More manufacturers have been joining the market every year since, and at the time of writing there are now twenty-three companies producing azithromycin in generic or brand name forms.

[328] Richard Laing, Interview by Erin L. Paterson, 11 November 2022.
[329] Report of WHO Expert Committee, "The Use of Essential Drugs," Technical Report Series 882, The Model List of Essential Drugs, (Geneva, Switzerland: World Health Organization, 1998), 65.

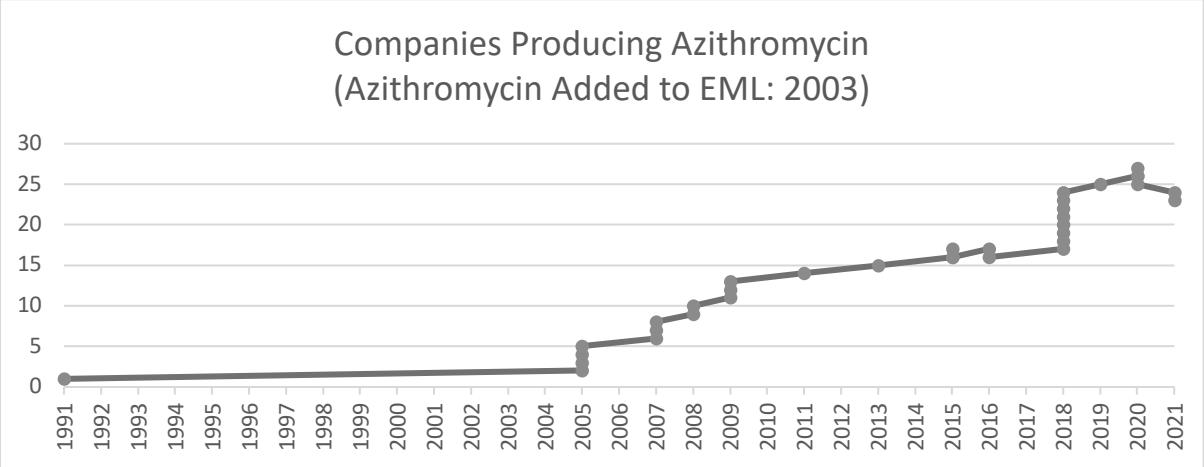

Figure 4 Companies authorized to manufacture and distribute Azithromycin in the United States according to the FDA Orange.[330]

What makes azithromycin such a uniquely important medication is that it can treat a wide range of infectious diseases in just a single dose, it comes in an oral form, can be taken outside of a healthcare setting, and is safe for use during pregnancy and amongst adolescents.[331] The previous drug of choice had been tetracycline, which could not be used in either case.

Despite the 2003 EML specifying that azithromycin should only be used in a "single dose treatment of genital C. trachomatis and of trachoma only," its capacity to be used as a single dose treatment led to medical practitioners with new access to the drug to use it in other instances. [332] Azithromycin quickly began to be used to treat multiple types of bacterial infections beyond C. trachomatis, including enteric infections and resistant strains such as *Neisseria gonorrhea* (another HIV co-morbidity). By 2008, rates of azithromycin resistant gonorrhea were being reported worldwide, particularly as it became clear that while a single

[330] See Appendix 2 for the data set used to develop this chart. All data points sourced from FDA Orange Book.
[331] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 920, The Model List of Essential Medicines. (Geneva, Switzerland: World Health Organization, 2003), 11-12.
[332] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 920, The Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2003), 12.

dose treatment was effective for C. trachomatis, it was not effective for gonorrhea, leading to, perhaps unintentional, inappropriate use of the drug within the treatment course. [333] [334]

As azithromycin experienced growing pains around the world, other co-infections of HIV/AIDS were equally being addressed by the WHO and its EML. Continual research studies and investigations into the medical impact of both HIV/AIDS, the antiretrovirals used to treat it, and the adverse effects of combination therapies for all the associated co-infections or co-morbidities associated with HIV/AIDS were happening worldwide. In the case of TB, one of the most lethal HIV/AIDS co-infections, a long standard recommended treatment (that had been on the EML) was the use of thioacetazone. Thioacetazone (also known as 'thiazina') had been used since the 1960s, and was considered a relatively cheap drug that was easy to produce. It had been added to the first EML in 1977 and was often used in combination with streptomycin and isoniazid.[335] In a 2004 Wellcome Trust Centre witness seminar on Short-Course Chemotherapy for Tuberculosis, Professor Janet Darbyshire recalled:

> The fascinating thing is that I remember in the early 1980s, that all of a sudden we started to get quite severe Stevens–Johnson reactions to the thiacetazone[sic], which was the serious skin side-effect. We thought that maybe it was the wrong concentration, maybe there was something wrong with it, but in retrospect it was probably the very early cases of HIV infection. In people with HIV infection the incidence of adverse reactions is much higher, and the more severe reactions are common, hence most countries now are not using thiacetazone[sic] if they have a high incidence of HIV infection. So that's interesting. These probably were some of the early HIV infections in Africa.[336]

[333] Liu-Feng Yuan, Yue-Ping Yin, Xiu-Qin Dai, Rachel V Pearline, Magnus Unemo, and Xiang-Sheng Chen, "Resistance to Azithromycin of Neisseria Gonorrhoeae From 2 Cities in China," *Sexually Transmitted Diseases* 38, no. 8 (2011): 764.
[334] John W. Tapsall, "What Management Is There for Gonorrhea in the Postquinolone Era?" *Sexually Transmitted Diseases* 33, no. 1 (2006): 9, https://doi.org/10.1097/01.olq.0000194599.97426.a3.
[335] Report of WHO Expert Committee, "The Selection of Essential Drugs," Technical Report Series 615, The Selection Essential Drugs. (Geneva, Switzerland: World Health Organization, 1977), 213.
[336] DA Christie and EM Tansey, eds. *Short-Course Chemotherapy for Tuberculosis*, Wellcome Witnesses to Twentieth Century Medicine, vol. 24, (London, United Kingdom: Wellcome Trust Centre for the History of Medicine at UCL, 2005), 13.

Her hypothesis matched reactions that other practitioners observed in their treatment of TB patients in the field at the time, and even as the witness seminar was taking place in London, thioacetazone was under consideration on the EML for that very issue.

First recommended for removal in 2003, in 2005 the WHO stated that although thioacetazone had known adverse reactions in general, when used with patients "co-infected with HIV, the frequency and severity of these reactions is increased, sometimes leading to death." By 2007, thioacetazone had been removed entirely, leaving the fixed dose combination sulfamethoxazole + trimethoprim as the key drug for the treatment of patients with HIV/AIDS and TB.[337]

The turn of the century, buoyed by the political ramifications of the HIV/AIDS crisis and then supported by increasingly noticeable health ramifications leading to different medical interventions and suggestions on the EML all contributed to an increased desire for the list itself to become restructured and more reflective of the changes occurring in the world. With rising co-infections, and increasing signs of adverse reactions with compounding illnesses, coinciding at a nexus point where the price and value of drugs and care were increasingly under question, the Essential Medicines department at the WHO underwent a massive upheaval.

C. Structural Ramifications of HIV/AIDS on the EML: Evidence vs Experience Based Medicine and a Reconsideration of Both Cost and Value

As the twentieth century ended, the impact of international organizations and global trade agreements became increasingly more relevant to the WHO's Expert Committee's arguments over the cost of medicines, patent regulations and requirements, and the method of how drugs should be considered and added to the list. Just after the lawsuit against the 1997

[337] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 933, The Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2005), 25-26.

South African Medicines' Act began, and the 1999 EML was published, the WHO Expert Committee responsible for the EML determined that there should be changes in how the EML was being constructed. So called "private 'brainstorming'" sessions…and an ad hoc Committee meeting" eventually led to the WHO proclaiming its intention to address the way new drugs were added to the EML in March 2001 (the same month the South African trial began).[338] Almost as soon as they announced these intentions though, the United States responded with a 35-page memo decrying every aspect of the WHO's suggestions.[339] Regrettably, after an exhaustive search of the available WHO archives, a request to the receiving parties of those who handled the request, and several United States government archives, I have been unable to find this memo in order to determine specifically what issues were brought up. Hans Hogerzeil, the Secretary of the WHO Model List of Essential Medicines at the time, recalls receiving the letter (written by William 'Bill' Steiger), but no other record of it has been found.[340] What Hogerzeil did recall from the letter and its contents was that in general,

> [The United States] didn't like the Essential Drugs concept, so they didn't like the Essential Drugs List. And when we were really strengthening the list, and basically saying it was valid for developed countries, also, the even less liked it. Well, not the government necessarily, but the industry in America of course didn't like it. I think it was George Bush's cabinet at that time. There were several ministers had a pharmaceutical industry background. It was a strong lobby. [341]

While the list may have grudgingly been accepted in the late 1970s, the timing and optics of new adjustments to the list happen concurrently with the South African trial as well as James Love and MSF's negotiations with CIPLA to make the essential antiretrovirals affordable, was, perhaps a final straw. The United States issued their rebuke, and the WHO responded by

[338] Government of the United States of America, "WHO Proposal for Revising the WHO Model List of Essential Drugs: Discussion of the Process for Involving Member States," Provisional Agenda Item 4.17. 43rd Directing Council Session of the Regional Committee (Geneva, Switzerland: World Health Organization), August 27, 2001, 1-2, https://www1.paho.org/english/gov/cd/cd43_05-e.pdf.
[339] Richard Liang, Brenda Waning, Andy Gray, Nathan Ford, and Ellen 't Hoen, "25 Years of the WHO Essential Medicines Lists: Progress and Challenges," *The Lancet* 361 (2003): 1724.
[340] Hans Hogerzeil, Interview with Erin L. Paterson, 2 February 2023.
[341] Hans Hogerzeil, Interview with Erin L. Paterson, 2 February 2023.

narrowing its changes to two key components only. First, moving forward, new medications added to the EML would rely on evidence-based recommendations and referrals rather than experience-based testimony, and secondly: cost would no longer be a prohibitive factor to inclusion onto the list.

Previously, the WHO Expert Committee on Essential Medicines made its selection of drugs based on "efficacy, safety, quality, stability, ease of storage, price and availability," in sort: accessibility.[342] Drugs were then graded based on the experiential information the Expert Committee had acquired during their personal use and understanding of the drugs, determining their value on the list and their usefulness overall.[343] This information was gathered based on known track records from the usage of the drug and its impact on communities while in use, however much of these track records were word of mouth or purely from an Expert Committee member's personal experience. The committee's decision making became colloquially referred to as the GOBSAT – or the Good Old Boys Sitting Around the Table, where experience drowned out any other information to be discussed.[344] Transitioning to evidence-based medicine ensured that randomized controlled trials, and data that observed the effects of 10-20,000 cases including age and gender variations would provide a fully documented and defendable standpoint for the EML moving forward, rather than individual observation.[345] No longer would the WHO permit drugs based on personal experience, now each drug on the EML would be fully supported and publicly discussed.

A part of these discussions was the development and dissemination of the WHO Essential Medicines Library, an electronic resource that was created to be published in tandem with the lists in order to fully document the information regarding suggested

[342] "A Scoring System for Selection of Essential Drugs," *Essential Drugs Monitor*, 1990, 19.
[343] Jonathan Quick, Interview by Erin L. Paterson, 11 November 2022.
[344] Jonathan Quick, Interview by Erin L. Paterson, 11 November 2022.
Hans Hogerzeil, Interview by Erin L. Paterson. 2 February 2023.
[345] Jonathan Quick, Interview by Erin L. Paterson, 11 November 2022.

medications. The Library came in two forms, CD-ROM and website, that were planned for publication in 2002 alongside the April 2002 EML.[346] The Library was intended to serve multiple purposes, both in terms of defending the drugs on the EMLs but also in terms of providing resources so that national formularies could be created based off of the EML's suggestions. There is a chart on the 2002 EML, which discloses the WHO's intentions with the Library as a whole.[347] In brief, the EML would serve as a template that could be used by other agencies to identify statistics, costs, and quality information. Similarly, outside groups or clusters would be able to inform the model list with guidelines, reviews, and references as such information became available. An infrastructure within the infrastructure was being more formally established and the black box of how the EML fully operated was slowly coming into the light.

While the Library was being created, the switch from experience to evidence-based medicine was being confirmed, and the 2002 list was being drafted, two new statements were released from the WHO and the European Council of the European Union in regard to antimicrobial resistance: the 2001 WHO *Global Strategy for Containment of Antimicrobial Resistance* and the European Council of Minister's *Recommendation on the prudent use of antimicrobials in Europe*. The former is a 99-page document detailing AMR as a crisis that needed to be addressed and initial methods that could be used in order to do so.[348] The latter is a council recommendation that was submitted to members of the Council of the European Union on 15 November 2001 that detailed the rise of antimicrobial resistance, the need to act, and precisely what steps member states should take in order to react effectively to AMR. The Council's recommendations detailed a need for stricter and more accurate surveillance of

[346] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 914, Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2002), 11.
[347] Report of WHO Expert Committee. "The Selection and Use of Essential Medicines." Technical Report Series 914. Model List of Essential Medicines. Geneva: World Health Organization, 2002, 12.
[348] World Health Organization, "WHO Global Strategy for Containment of Antimicrobial Resistance," (Geneva, Switzerland: World Health Organization, 2001).

antibiotic usage, infection prevention and control methods, increased research in terms of antibiotic used in both animals and humans, and proper understanding regarding prescription methods and quantities.[349] On the EML, that meant that any and all antibiotics that would be included on the list now and in the future would need to take these recommendations into consideration, furthermore, the evidence of impact, value, and use against AMR would be top of mind consideration when drugs were up for discussion.

Cost has long since been a barrier to the EML. The rules and regulations requiring a drug to have a generic formulation in order to be included was meant to ensure that LMICs would be able to afford the drug of choice. However, cost does not necessarily equate to overall health care value. If one drug costs $10 per pill, and fifty pills are required to complete a treatment course, the course costs $500. However, if another drug costs $300 per pill, and only one pill is required: despite being more expensive than the first drug, it is a less expensive treatment course overall. Added hospital expenses, various formulations or the need for in or out patient treatment etc. are all additional factors that can influence this level of valuation.

Hans Hogerzeil described this transition of thinking as having a several results. The first, was the understanding that not all diseases are going to be of the same fiscal cost. Malaria and tuberculosis will cost differently because their length of treatment, medications, and impact on daily quality of life are all different as well. However, within a specific disease class, the EML would now focus on what the most cost-effective treatment would be within that disease category.[350] If the drug was on patent, but was of the most health benefit, it would be added to the list. Next, the Essential Medicines department and the WHO was committed to adding these new, and potentially expensive, drugs to the list, but furthermore

[349] M. Aelvoet, "Council Recommendation of 15 November 2001 on the Prudent Use of Antimicrobial Agents in Human Medicine," Recommendation, (Brussels, Belgium: Council of the European Union, November 15, 2001).
[350] Hans Hogerzeil, Interview by Erin L. Paterson, 2 February 2023.

committed to ensuring that if a drug was considered essential – it had to become affordable.[351] If it worked with AIDS medications, it would work with others, and affordability changed from a selection criterion to the consequence of the selection" within the list as a result.[352]

Faced with a multitude of concurrent events, including the success of the South African trial and the announcement of the Doha declaration at the end of 2001, the WHO made the drastic step to completely revitalize their EML from scratch: implementing all the measures they could, but also redacting anything that they hadn't proven. New committee rules stated that deletions to the list were determined only "if no positive arguments for maintaining the medicine on the Model List were submitted."[353] However, considering the complications around antibacterials and the new top of mind awareness of AMR and its concerns, a far more draconic approach was made in response to maintaining the list: *all* of the antibacterial drugs were removed only to be added to the 2002 EML once they had been reviewed in full. It was, as Hans Hogerzeil put it, a way of potentially "forcing them to provide the evidence so the final decisions were more defendable and credible with the scientific/public health community."[354] As a result of this decision, the 2002 EML was the shortest of any list since 1988 with only nineteen listed antibiotics.[355]

[351] Hans Hogerzeil, Interview by Erin L. Paterson, 2 February 2023.
[352] Hans Hogerzeil, Interview by Erin L. Paterson, 2 February 2023.
[353] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 914, Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2002), 7.
[354] Jonathan Quick, Interview by Erin L. Paterson, 11 November 2022.
[355] In all iterations of the EML, certain antibiotics such as antileprotic and antituberculotic medicaments are separated from the other sections of antibacterial drugs. Although these disease focused drugs are antibiotics targeting bacterial infection, due to its unique structure and treatment plans, these drugs have been separated on the EML and are therefore not included in this or other calculation regarding antibiotics on the EML. These drugs will be discussed in this dissertation, but are still considered separate from other antibiotics as a result of this schism on the list itself.

L.11 2000	L.12 2002	L.13 2003
Amoxicillin []	Amoxicillin	amoxicillin
amoxicillin + clavulanic acid []	ampicillin	amoxicillin + clavulanic acid
ampicillin	benzathine benzylpenicillin	ampicillin
benzathine benzylpenicillin	benzylpenicillin	azithromycin []
benzylpenicillin	ciprofloxacin []	benzathine benzylpenicillin
ceftazidime	chloramphenicol []	benzylpenicillin
ceftriaxone []	cloxacillin[]	ceftazidime
chloramphenicol	doxycycline []	ceftriaxone []
chloramphenicol []	erythromycin[]	chloramphenicol
ciprofloxacin []	gentamicin[]	ciprofloxicin []
clindamycin	metronidazole	clindamycin
cloxacillin[]	nalidixic acid	dicloxacillin []
doxycycline []	nitrofurantoin	doxycycline []
erythromycin []	phenoxymethylpenicillin	erythromycin []
gentamicin []	procaine benzylpenicillin	gentamicin[]
imipenem + cilastatin	spectinomycin	imipenem [] + cilastatin []
metronidazole []	sulfadiazine[]	metronidazole []
nalidixic acid	sulfamethoxazole + trimethoprim []	nalidixic acid []
nitrofurantoin	trimethorpim	nitrofurantoin
phenoxymethylpenicillin		phenoxymethylpenicillin
procaine benzylpenicillin		procaine benzylpenicillin
spectinomycin		spectinomycin []
sulfadiazine []		sulfadiazine
sulfamethoxazole + trimethorprim []		sulfamethoxazole + trimethoprim
trimethorpim		trimethorpim
vanocomycin		vancomycin

Table 2 Reorganized list of 2000-2003 EMLs, see Appendix A for a complete look at all EMLs[356]

The alterations between the 2000 and 2003 list are relatively straight forward: chloramphenicol is listed twice on the 2000 list with one indication listed as complementary and as a placeholder for any drug in that therapeutic group as indicated by the box shape next to its name. It is only listed once in 2003. Cloxacillin was on both the 2000 and 2002 list, but was replaced by di-cloxacillin in 2003. Finally, azithromycin, discussed earlier in this dissertation, made its first appearance on the 2003 list after being recommended to the Expert

[356] The three lists of 2000, 2002, and 2003 have been reproduced here, color coded and organized alphabetically for ease of comparison. If it's green: all three lists have the same drug. If it's yellow, only the lists of 2000 and 2003 have the same drug. If it's blue, only the lists of 2000 and 2002 have the same drug. Red indicates only one list has that drug mentioned.

Committee by Médecins Sans Frontiers as a treatment for *chlamydia trachomatis* (the common co-infection for HIV/AIDS).

Between 2000 and 2002, only one fixed dose combination, sulfamethoxazole + trimethoprim was admitted. However, the other indications of imipenem + cilastatin and amoxicillin + clavulanic acid were successfully added back to the list in 2003. In an interview with expert committee members, Richard Laing, it was suggested that the transition itself was one that everyone wanted to approach cautiously, particularly in regard to fixed dose combinations (FDC).[357] Previously considered by pharmaceutical companies as a way of boosting their own sales, fixed dose combinations were largely struck down by regulatory authorities in the 60s as being unnecessary at best, and problematic at worst. [358] Forty years later, the Expert Committee was hard at work gathering the data necessary to prove that these combinations were not only trustworthy, but in some cases: superior to standalone formulations.

Both FDCs were initially added to the EML in 1998 (well after the crackdown of the 60s) as restricted indications, imipenem + cilastatin as a reserve agent for the treatment of *Acinetobacter,* and amoxicillin + clavulanic acid as reserve treatment for bacteria resistant to ampicillin. During the 1980s, multiple articles had been written about imipenem + cilastatin as an FDC, but another set of reviews were created in 2000 utilizing post-market data. One such study, published in 2000, specifically compared the FDC to the monotherapy meropenem. Meropenem would eventually be added to the 2017 EML, but in 2000 its purpose was directly compared to that of the efficacy of the FDC. Attansio et al. reported that from a health and consumer standpoint, imipenem + cilastatin could treat patients faster, cheaper, and had less chance of encountering antimicrobial resistance.[359] By contrast,

[357] Richard Laing, Interview by Erin L. Paterson, 11 November 2022.
[358] Podolsky and Greene, "Combination Drugs — Hype, Harm, and Hope,"490.
[359] EA Attanasio, PB Russo, GB. Carunchio, AC. Basoli, and LB. Caprino, "Cost-Effectiveness Study of Imipenem/Cilastatin versus Meropenem in Intra-Abdominal Infections," *Digestive Surgery* 17 (2000): 168.

amoxicillin + clavulanic acid were initially recommended primarily as a treatment of last resort to be used only in cases of noted resistance elsewhere. The reports that the WHO Expert Committee needed were ones that continued to support the idea that it could be used during these scenarios. And those reports did eventually continue to come in, particularly when it came to treating antimicrobial resistance.

Expert Committee members found that when FDCs were used, resistance pathways were less likely to develop as even if one of the antibiotics lost its efficacy, the second would destroy the bacterial threat before it could expand that resistance to both drugs. In short, As Richard Laing stated in a recent interview, "by combining…antibiotic[s] you would be able to reduce the frequency of resistance occurring." [360] Imipenem + cilastatin and amoxicillin + clavulanic acid may have been left off the 2002 list as the Expert Committee was finalizing its decisions, but by 2003 they had returned, and they remain on the EML to this day. The Expert Committee, likewise, continued to support the research and development of FDCs[361] – though thus far, there have been few new combinations to speak of.

Additional discussion regarding FDCs and their utility as access to essential antibiotics will be conducted throughout this dissertation. Although there have not been new FDCs added to the list since 2003, the potential for assisting in combating AMR cannot be overlooked. Combination therapies have long been associated with TB, and at this time there is work being done to develop new FDCs for new treatments that have yet to receive approval.[362] TB, however, takes several months to overcome as opposed to the short courses most bacterial infections require. Overuse, and the potential for increased sales prices as a result of multiple drugs needed to combat a single infection are all risks associated with

[360] Richard Laing, Interview by Erin L. Paterson, 11 November 2022.
[361] Richard Laing, Interview by Erin L. Paterson, 11 November 2022.
[362] Mel Spigelman, Interview by Erin L. Paterson, 21 December 2023.

FDCs. These concerns have not yet fully been addressed or rectified, and any new FDC would need to be carefully monitored to ensure appropriate compliance.

For the other drugs left off the 2002 list: vancomycin's indication and category level changed between 2000 and 2003. Considered a restricted drug only to be used in highly specific circumstances, vancomycin lost its restricted status once it made its reappearance on the 2003 list. It remained that way until 2017. For the third generation cephalosporins, ceftazidime and ceftriaxone, a similar process occurred as the use and efficacy of third-generation cephalosporins were compared to the other generations of cephalosporins and their projected use and efficacy in the future. Both these drugs remained in future iterations of the list. Clindamycin, the final drug that had been removed from the 2002 list, equally saw its return in 2003 and beyond as the committee acquired the evidence data it needed to scientifically defend its position.

By the time all the changes were complete, it seemed as if there were no adverse reactions to there being a temporary shortening of the EML. I was unable to uncover any complaints or disagreements associated with the list's shortening and eventual lengthening. Rather, because new iterations of the lists were published so quickly after the fact, the purchasing awareness and accessibility concerns were largely mitigated.

As the changes were being finalized though, the OECD/WHO continued to impress upon how important these actions were. They further proclaimed that the EML restructuring was one that took place within the context of an overall policy framework overhaul within all aspects of their institutions. In 2003, they published a report, entitled *Poverty and Health*, which reiterated each of the new millennium's previous outcries when it came to drug cost and availability by stating that:

> without money to buy vaccines and drugs, to build and equip facilities, to ensure adequate staffing, to manage the health system, and to increase investments in other

> sectors important for health, low-income countries will be unable to meet the health-related [Millennium Development Goals].[363]

Access to Essential Medicines and the ability to afford expensive, but necessary, drugs, was increasingly becoming a matter of public urgency and importance. The HIV/AIDS, the South African Trial, the push for parallel trade/cross licensing and access to affordable medication between 1998-2001 led to these changes on the EML. Despite being a viral illness, HIV/AIDS had a distinct impact on the structure of the EML as a result of the political action and medical experiences that were being felt around the world. Although it cannot be said for certain that HIV/AIDS exacerbated the existence of AMR, resistant infections were routinely found in HIV/AIDS patients and as a result calls for new drugs capable of addressing resistant strains (such as azithromycin) to be added to the EML began to increase throughout the beginning of the new millennium. Additional medications such as amoxicillin + clavulanic acid and vancomycin, were added to the EML specifically due to their effectiveness against strains of resistant bacteria, and as an infrastructure tool in the realm of public health: the EML was decidedly moving away from its previous measures of surveillance and stewardship recommendations only towards a medication response to a burgeoning health crisis.

V. Altering or restricting the use of antibiotics on the EML and warnings about AMR: child classifications and AWaRe.

Following the major structural changes that came as a result of the HIV/AIDS epidemic, the WHO's next major concerns when it came to updating the EML revolved around children. In 2006, following a joint meeting between UNICEF and the WHO on how to address child needs in terms of medicine, WHO's then Assistant Director General, Howard Zucker released a statement indicating that "Too often, the right medicines for children, in the right dosages and formulations are missing from the spectrum of available treatment

[363] *Poverty and Health*, DAC Guidelines and Reference Series, (Paris, France: OECD/WHO, 2003), 14.

options."[364] Since 1977 the drugs and dosages discussed on the EML had always been dedicated to adult patients, with little to no references to child quantitates or indications. While doses for adults were relatively simple (slight variations occurring amongst known gender divides), such translations do not easily apply to children who cannot receive the same doses or medications as their adult counterparts. The 2007 EML published the results of the debates that took place on this matter in March.[365] By October that same year (with the assistance of the WHO's Pediatric Expert Subcommittee) the 2007 EML was re-released with an additional section specifically designed for children (cEML).[366]

In all succeeding versions of the EML, drug indications would be split into different subsections or identifications. These "A" (adult) and "C" (child) designations appeared quite naturally on the antibacterial section as well, offering suggestions and alternatives depending on if the drug was suitable for C class individuals. The use of the symbol [a] indicated an age restriction on the drugs listed, where [R] indicated "Subcommittee has endorsed the medicine as essential but has requested a review of the efficacy and safety to confirm this decision, or to expand use to additional age groups."[367]

For the antibacterial section, thirteen of the antibiotics on the October 2007 EML were given an [a] or [R], and all of the tuberculosis treatments were given an [R].[368] By 2009, the [c] symbol was also in circulation to signify the medicine required "specialist diagnostic or monitoring facilities, and/ or specialist medical care, and/or specialist training for their use in

[364] Suzanne Hill and Hanne Bak Pedersen, "WHO and UNICEF Tackle Problem of Lack of Essential Medicines for Children," Media Centre, August 14, 2006. https://apps.who.int/mediacentre/news/releases/2006/pr42/en/index.html.
[365] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 946, The Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2007).
[366] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 950, The Model List of Essential Medicines, (Geneva: World Health Organization, 2007).
[367] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 950, The Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2007), 112-113.
[368] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 950, The Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2007), 118-121.

children." And when the symbol is next to an "individual medicine or strength of medicine it signifies that there is a specific indication for restricting its use to children."[369] These too would continue to mark specific drugs and indications throughout the antibacterial section regarding the treatment and efficacy and monitoring needs of childhood medicaments on the EML.

Access to effective antibiotics for children carries with it additional barriers and concerns. As children are dependent on their care givers to provide them with appropriate medications and doses, they are reliant on someone other than themselves to understand the drugs and delivery methods and provide such assistances. As a vulnerable class, they cannot be relied upon to manage their medication intake on their own and as such are dependent on others for their care. Furthermore, testing and data surrounding the impact and efficacy of drugs on children can be challenging as ethics committees and rigorous clinical trial regulations impose stringent standards on any prospective drugs in consideration.[370] When it comes to antibiotic use and misuse, failure to complete a drug regimen (for example if a child fusses and refuses to take more and a parent capitulates because their child seems to be doing better on their own) can lead to increased rates of resistance.

The focus on children and the ability for children to get access to effective medications in appropriate dosing was not specifically focused on antibiotics. It was a change encompassing all medications on the list. Stewardship and surveillance methods were working globally to in fact reduce prescriptions (particularly in children) and were

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[369] Report of WHO Expert Committee. "The Selection and Use of Essential Medicines." Technical Report Series 958, The Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2009).

[370] While not a priority in 2005, years later, the concerns surrounding child dosing and clinical trials for antibiotics when it comes to pediatric care would become an issue of discussion. More on neonatal and child doses can be found in the next chapter, and for specific insight into how clinical trial ethics and antibiotic lacks in this field are a cause of concern can be found in the sources below:
Naomi Laventhal, Beth A. Tarini, and John Lantos, "Ethical Issues in Neonatal and Pediatric Clinical Trials," *Pediatric Clinics of North America* 59, no. 5 (2012): 1205–20, https://doi.org/10.1016/j.pcl.2012.07.007.
John Rex, "Developing Antibiotics for Children: There Are No Easy Answers, " AMR.Solutions, April 7, 2021, https://amr.solutions/2021/04/07/developing-antibiotics-for-children-there-are-no-easy-answers/.

successfully managing to do so,[371] [372] though its continued and improved use in pediatric care was still strongly being recommended by those in the broader health community.[373] The final major change to take place on the EML, though, was one that targeted antibiotics and appropriate access and use of antibiotics specifically.

By 2015, concern over antimicrobial resistance was now reaching a point where the EML on its own may not be able to recommend the requisite antibiotics needed to address resistant strains as they arise. The WHO published its *Global Action Plan on Antimicrobial Resistance,* which continued to call for improved awareness, surveillance, and research into AMR, but also insisted on the need for the reduction of infections via infection prevention and control measures, the optimization of current antibiotics in both human and animal health, and finally: the "develop[ment of an] economic case for sustainable investment…[of] new medicines, diagnostic tools, vaccines and other interventions."[374] Similar calls for additional research and attention into AMR were being made in both the United States and Europe around the same time, and these measures will be discussed in more detail in Chapter Three. After consultation amongst Expert Committee members and with the focus and attention on antimicrobial resistance, the 2017 EML rolled out its AWaRe (Action, Watch, and Reserve) program.

AWaRe was an organizational tactic within the EML's standard infrastructure that segmented specific antibiotics off from the rest of the list. It is, what I would argue, a form of corrective maintenance rather than a purely preventative maintenance step. Although the

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[371]Katherine E. Fleming-Dutra, Adam L. Hersh, Daniel J. Shapiro, Monina Bartoces, Eva A. Enns, Thomas M. File, Jonathan A. Finkelstein, et al, "Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011," *JAMA* 315, no. 17 (May 3, 2016): 1864, https://doi.org/10.1001/jama.2016.4151.

[372] I.M. Gould, "Minimum Antibiotic Stewardship Measures," *Clinical Microbiology and Infection* 7 (2001): 24, https://doi.org/10.1046/j.1469-0691.2001.00082.x.

[373] John S. Bradley, "COMMENTARY: Antibiotic Stewardship in Pediatrics: A Necessity," *Pediatric Infectious Disease Journal* 26, no. 6 (2007): 538, https://doi.org/10.1097/INF.0b013e3180593184.

[374] World Health Organization. *Global Action Plan on Antimicrobial Resistance*, (Geneva, Switzerland: World Health Organization, 2015), 1-28, https://iris.who.int/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1.

reserve, complimentary, and children's categories had existed for some time prior to this point, AWaRe was specifically designed to ensure that anyone reading the list understood fully exactly when and how each drug should be used and in what contexts: all with AMR in mind. It specifically targets drugs, and indicates they should not be used in explicit circumstances – implying they certainly *had* been used in inappropriate or incorrect circumstances prior. It restructured the antibacterial section of the EML to list which drugs should be utilized in first-line defenses, which should be used in slightly more complex circumstances, and which should be utilized "only if no alternatives are effective."[375] As an example, ciprofloxacin was placed in the Watch group immediately, along with vancomycin and a large number of third-generation cephalosporins, all which previously had been considered "reserve antibiotics." This is a distinct departure from lists in the 70s or 80s which offered no such restrictions and left prescriptive advice to the practitioners themselves.

The new Reserve category had very few antibiotics, and all of them were very new by comparison. Furthermore, as a part of the general organizational structure of the new list, they only appeared on a complementary list rather than the main EML itself, further solidifying that they should only be used as a last resort.[376] The actual rollout of the AWaRe listing however was confusing. The Antibacterial section of the EML was restructured to have three charts where drugs were listed as a part of which group they were associated with. However, the structure of this section was clumsy at best, as the "Key Access" chart included drugs that were also considered part of the Watch Group with little explanation as to why they were included.[377]

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[375] "Classifying Antibiotics in the WHO Essential Medicines List for Optimal Use—Be AWaRe," *The Lancet* 18 (January 2018): 18.
[376] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 1006, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 2017), viii-xii.
[377] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 1006, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 2017), 432.

The Complementary List also was split into two sections, one for Watch Group drugs and one for the Reserve Group. [378] Finally, vancomycin is listed twice for two different treatments and indications – one considered complementary and the other considered a part of the main list. Both are still a part of the Watch Group.[379] A series of review articles published within the EML itself discusses vancomycin in great detail, as well as other reasons for the decisions the WHO took in developing the EML, but the structure and presentation is overly complicated and confusing to understand.

Two years later, the succeeding EML rectified these issues by streamlining their listings so that the drugs are strictly organized into their correct categories and with no evident crossovers (although the Reserve category is still considered entirely complementary). [380] However, there was a great deal of change between which drugs are considered Reserve or not between the two lists. Of the original five drugs listed on the 2017 EML's Reserve list, only one (polymyxin B) remained for the 2019 EML. The others were shuffled about into other categories or removed entirely. Between 2019 and 2021 there were no redactions in this section at all, and cefiderocol was added instead.[381]

Generally speaking, the addition of new antibiotics to the EMLs takes time, with only one to three modifications occurring per year. The greatest leap in new additions did come in 2017 as the list expanded from twenty-nine antibiotics to thirty-seven.[382] The additions that only lasted one year on the 2017 EML included: aztreonam, Daptomycin, fourth- and fifth-

[378] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 1006, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 2017), 438.
[379] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 1006, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 2017), 432-442.
[380] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 1021, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 2019), 480-490.
[381] Consult Appendix 1 for a complete comparison.
[382] It should be noted that some drugs, such as Vancomycin are counted twice as they are listed in additional sections on the 2017 EML. Vancomycin is co-opted as a complementary drug to be used in addition to another drug, thus changing its method of use. For this reason, I have counted it for each use that it has been given.

generation cephalosporins, and tigecycline.[383] All had been marked as Reserve Group antibiotics, and the reason given for their removal appeared directly associated to that status. Upon further review, the Expert Committee responsible for the EML determined that "these antibiotics did not meet the revised criteria for inclusion on the Model Lists as individual Reserve group agents …[and] fourth-generation cephalosporins should be re-classified as Watch group as they did not meet the revised criteria for classification as Reserve."[384] (Fourth-generation cephalosporins did in fact change Groupings, but they never re-joined the list. They were entirely removed despite the new classification they received, and as of the 2021 EML have not yet returned).

Conclusion

Since 1977 the World Health Organization's Essential Medicines List has served as tool for the 'rational use' and management of drugs. It is an infrastructure meant to assist hospital formularies and nations when it comes to the acquisition of essential drugs that can treat specific health care needs. Rationales change, however, as do the needs of the populace.

In 2004, the Dutch government issued a request to the World Health Organization to develop a list of priority medicines, not currently in existence, that should be developed over the next few years in order to address global health needs. While the story of the development and impact of the *Priority Medicines for Europe and the World*[385] will be discussed in the next chapter, the recommendation of new attention to be given to AMR led to the World Health Assembly (WHA) applying additional attention to the matter. In resolution WHA58.27 (entitled *Improving Antimicrobial Resistance*) the WHA stated that "the spread of

[383] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 1006, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 2017), 7.
[384] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 1021, The Selection Essential Drugs, (Geneva, Switzerland: World Health Organization, 2019), ix.
[385] Warren Kaplan and Richard Laing, "Priority Medicines for Europe and the World," Proposal. Geneva: World Health Organization, 2004.

antimicrobial resistance recognizes no national boundaries and has reached proportions that require urgent action at national, regional and global levels, especially in view of the decreasing development of new antimicrobial agents."[386] Previous WHO reference to AMR were in the vein of surveillance and control, with reserve drugs recommended should resistance be found in a patient population. This resolution, however, was now indicating that medical interventions may not be enough as if resistance continued there would come a day where there is no treatment left. While surveillance and stewardship remained the largest components of WHA 58.27, the reference to a potential lack of efficacious medications was a signal cry that the tone and tenor of AMR discussions was about to change.

Two years later, WHA resolution 60.16 on the *Progress of Rational Use of Medicines* continued the discussion by pointing out the various flaws within both the essential medicines list and the failure of repeated requests for attention to be given to AMR. It states, with some level of exasperation, "successful implementation of previous resolutions on antimicrobial resistance cannot be achieved without addressing the global problem of irrational use of medicines," then continues on to state that everyone consumers to providers and drug developers need to take responsibility to ensure appropriate use continues.[387] Twenty years after the EML had first discussed the need for rational use, WHA 60.16 states with impunity that the Assembly is "Convinced that it is time for governments, the health professions, civil society, the private sector and the international community to pledge their commitment, including adequate resources, to promoting the rational use of medicines."[388] Rational use,

[386] World Health Assembly, "Improving the Containment of Antimicrobial Resistance," Resolutions and Decision, Ninth Plenary Meeting, (Geneva, Switzerland: World Health Assembly, May 25, 2005), https://apps.who.int/gb/ebwha/pdf_files/WHA58/WHA58_27-en.pdf.
[387] World Health Assembly, "Progress in the Rational Use of Medicines," Agenda item 12.17, (Geneva, Switzerland: World Health Assembly, May 23, 2007), https://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R16-en.pdf.
[388] World Health Assembly, "Progress in the Rational Use of Medicines," Agenda item 12.17, (Geneva, Switzerland: World Health Assembly, May 23, 2007), https://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R16-en.pdf.

surveillance, and stewardship were no longer enough, and as the AWaRe categories indicated on the 2017 EML: efficacious drugs were increasingly more difficult to find.

Antibiotics have been on the EML since its inception, however the way those antibiotics have been categorized and recategorized, and the reasons for successive inclusions on the list were in direct response to the growing AMR threat after 1990. Surveillance and stewardship were the primary responses for AMR through the 90s and 2000s, but it becomes clear as time goes on that stewardship was not enough and that the tepid responses to implementing and managing stewardship protocols were insufficient.

Following the HIV/AIDS epidemic and the many co-relating incidences of political, medical, and structural changes taking place in and around the WHO and the EML, the list was updated to reflect a need to embrace evidence of medical impact as well as cater to new cost and valuation understanding. If drugs were going to join the list and be on patent at the same time, the WHO would commit to working on lowering those costs. The addition of child categories furthered the WHO's evident commitment in helping reach all at need populations, but it is the AWaRe category where the additional specifications added to antibiotics shows the most impact.

AWaRe's purpose was to forestall additional levels of resistance by offering advice on when and how to use the antibiotics on the list effectively. It supports stewardship efforts, but importantly, does not suggest limiting access to drugs entirely or prohibiting their sale. Rather, it says these drugs *should* be purchased but used only when circumstances dictate that use effectively. Purchasing options and availability, however, can be extremely limited. Chapter Five will discuss how access to specific medications on the EML influence use and the corresponding relationship with AMR as a result. In either case, AWaRe on its own is intended to highlight the intersection of access and appropriate use.

The antibacterial section of the EML is of vital importance to the work that is being conducted within the AMR space, but AMR itself was not an original priority of the EML. It, like HIV/AIDS before it, is a health crisis that is growing and is forcing modifications to the list as global health needs are changing. As it currently stands, any new class of antibiotic that is capable of addressing resistant strain(s) of bacteria will join the EML. Bedaquiline (to be discussed in more detail in Chapter Four), was put on the list only three years after its launch for this reason in particular, highlighting not only the need for such drugs but the value the EML has as a signifier of the dangers of AMR at this point in time.

As a part of the global health care infrastructure, the purpose of the EML was to provide a concise list of drugs to countries in need of guidance on drug purchasing with the goals of improving access to the most effective medications a country needed to suit its health care needs, now showed distinct frailty when it came to ensuring those needs could actually be met. Preventative and corrective maintenance measures (surveillance, stewardship, and AWaRe) have been put in place in attempts to address AMR and ensure the continued efficacy of the list. However, these measures have not been wholly successful in this goal, and rates of resistance continue to rise.

The antibiotic section, which (like the rest of the list) had been designed to take a dizzying amount of drugs and drug names and limit the number to only a specific few that will meet health care needs, is scrambling to find new drugs to add to its list and equally struggling to find a balance between recommending drugs capable of treating resistant strains and avoiding the potential for additional overuse or inappropriate use of those same drugs. In short: as far as the antibiotic portion of the list is concerned, these essential medicines transitioned from a concept meant to indicate a small selection of priority drugs that were of most need and use to acquire, to a select list of efficacious drugs that is in need of new additions as resistance continues to threaten the usefulness of the suggested medications. The

infrastructure meant to support global health, in this venue, has begun to start showing its cracks as AMR begins to outpace the suggestions that it offers.

Throughout the remainder of this dissertation, I use address the legacy of the EML, and the notion of essential antibiotics to show where that impact has become most evident. In Chapter Three, this entails looking into the offshoots of the Essential Medicine's department to help manifest the Priority Medicines for Europe and the World report (PMR) and how these actors called for the creation of essential antibiotics to be created. In Chapter Four, I look at the development of the only new antibiotic class to have made it to the market, bedaquiline, and explore the ways that it has struggled to reach patients effectively after the point of sale even with its presence on the EML. And finally, in Chapter Five I explore how the despite the WHO's best efforts: there are many countries around the world that cannot adequately maintain their national formularies of antibiotics that exist on the EML.

Chapter Three: Assessing access to new antibiotics through the implementation of Public Private Partnerships meant to correct a Dry Pipeline of antibiotic development

"I think it's like we were setting up a lemonade stand in the in the desert, and everybody was thirsty…The demand was extreme." – Kevin Outterson.[389]

"The model of PDP was something that looked like a structure, [where in it] we could address the issue of a pipeline." – Marie-Paule Kieny.[390]

Beginning in the early 2000s but becoming increasingly more evident by 2014, the evolution of antibiotics as an essential medicine was tempered by the effectiveness of those antibiotics in the face of AMR. Without effective medications to treat resistant strains of bacteria, naturally those who contract a resistant strain will have poorer health outcomes. Discussions amongst various WHO and global health experts at this time, thus began to migrate away from stewardship and surveillance of AMR only, and instead towards the development of new antibiotics.[391] In essence, if the support that the EML provides to global health is beginning to erode for antibiotics due to the rise of resistance, than one way to address that crumbling infrastructure would be to implement a steady development flow so that new antibiotics replace those that are becoming less efficacious overtime. As discussed in the Introduction and Chapter One, however, a seamless flow of new development (i.e.: the antibiotic pipeline) was no longer a present reality.

Pharmaceutical companies had since the 1980s been steadily departing from the antibiotic development space and were focusing on more lucrative or medically necessary directions as off patent antibiotics were (and are) still largely effective. To return to this developmental space, the market rewards needed to be incentivizing enough. But, with very

[389] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
[390] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 39.
[391] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 17-20.

effective low-cost generics already available, and the death toll for cases of AMR well below a critical mass – such incentivization was not going to find itself in the private sector.

This chapter assesses the formation of new antibiotic pipelines of development in the form of Public Private Partnerships (PPPs) and Product Development Partnerships (PDPs) from 2008-2023. This action is a form of corrective maintenance applied to the antibiotic pipeline in the sense that it is an attempt to fix problems that have prohibited the pipeline from continuing as it once was. Lack of investment or return on that investment were keeping companies from re-entering the space, thus, PPPs/PDPs are a method of correcting this gap and allowing for the infrastructure the pipeline supports to continue operating.

The WHO, EU (generally), United Kingdom, and United States were the primary drivers of these PPPs, and the United Kingdom in particular was involved in all three of the partnerships. It examines how this new developmental antibiotic infrastructure was created, the challenges that companies face in bringing new antibiotics them to market, and the priorities of those companies who produce them. It argues that as it presently stands, access to new (and essential) antibiotics depends on an influx of public funds rather than private business, and that a combination of stewardship guidelines that restrict the use or sales of these drugs with a general perceived lack of expected profit, limits the number of companies that are currently even attempting antibiotic development as well as the number of antibiotics currently in development.

Starting with the 1998-1999 Committee on Industrial Research Relations within the European Federation for Pharmaceutical Sciences (EUFEPS), this chapter tracks EUFEPS' concern over lack of innovation within the European Union, and their efforts in promoting research and development in Europe. It will then discuss the influence of the European Framework system, and its development of Technology Platforms and Joint Technology Indicatives that led to the formation of massive Public Private Partnerships (PPPs) or Product

Development Partnerships (PDPs). Additional context, particularly surrounding the continued impact of the essential medicines work discussed in Chapter Two, will be provided as the impact of the 2004 and 2013 "Priority Medicines for Europe and the World" are seen within the PPP space. Three major PPPs that emerged within this time frame, the Innovative Medicines Initiative (1 and 2), DNDi/GARDP, and CARB-X will be analyzed in regards to how and why they emerged in the moments of time that they did, amongst which alliance of actors did they rely upon to take shape, what agendas were each group focusing on, and what their impact on AMR research and drug development has been like over the past twenty years.[392]

For specific context within this dissertation, it should be noted that while PDPs and PPPs are exceptionally similar in form and presentation, their practice differs. While some corporations will consider themselves both a PDP and a PPP at the same time, others prefer to use only one indication. Public Private Partnerships operate under the precept of a partnership between a public and a private entity where public money funds a series of projects in hopes of a successful outcome (a rate of attrition, therefore, wholly expected within the project scheme).[393] An example of this is the Innovative Medicines Initiative, spoken about in depth later within this chapter. Product Development Partnerships, similarly take the shape of a partnership between a public and private entity where public money funds a project, however the money is provided to specific targets and specific projects that meet pre-set parameters with a pre-determined supposition of efficacy.[394] GARDP, also discussed later in this chapter, serves as one such example.

[392] It should be noted that this list is not exhaustive and other PPPs and PDPs have emerged in the health sector during this time frame in the public health space. These three entities, however, are the largest that exist within their individual sectors of influence: the United States, Europe, and WHO, and therefore are most representative of works produced and influence overall. The one PPP that has made a great deal of impact but is not mentioned as thoroughly in this chapter is TB Alliance. It will be discussed in far greater detail in Chapter Four as its product brought to market, bedaquiline, will be used as a case study of market factors and influence.
[393] Anonymous Expert, Interview by Erin L. Paterson and Mirza Alas Portillo, 2 February 2024.
[394] Anonymous Expert, Interview by Erin L. Paterson and Mirza Alas Portillo, 2 February 2024.

Neither model is better than the other, and weaknesses can be identified in both, whether in terms of not enough risk taken in the PDP sector as there is historically less funding applied to PDPs compared to PPPs, or far too much risk taken via PPPs due to their more flexible budgets. However, the form and function of both models are often interchangeable. For the purposes of this dissertation, I will generally be using the term PPP to discuss these types of models unless otherwise specified by the interviewees or their direct actions. This is in no way meant to discredit the more targeted work of PDPs, nor is it meant to cast a moral value judgement upon these actors and stakeholders. I am assessing the emergence of this mode of resolution in the context of AMR, alone.

I. Rising concerns over state of European pharmaceutical companies and their market presence leading to new public investment in developing medications

In 2006, the European Federation of Pharmaceutical Industries and Associates (EFPIA) reported that between 1990 and 2005 pharmaceutical R&D investment in the United States had grown by 4.6 times its starting value, dominating "the biopharmaceutical field, accounting for three quarters of the world's biotechnology revenues and R&D spending," whereas in Europe it had only grown by 2.8 times and was slowly lagging behind in profit margins.[395] 1996 marked the first year that the United States had pulled ahead of Europe in global sales, representing 33% of all pharmaceutical sales compared to Europe's 29%, and as the years continued, Europe appeared to be struggling to catch up.[396]

EFPIA described the situation as a complex matter. Stating:

> it would be too simplistic to attribute the relative lack of attractiveness of Europe for pharmaceutical R&D to one single factor. Contributing to this problem are the economic and regulatory framework, the science base, the investment conditions, and societal attitudes towards new technologies. [397]

[395] EFPIA, "The Pharmaceutical in Figures," (Belgium: European Federation of Pharmaceutical Industries and Associates, 2006), 3.
[396] Ole J. Bjerrum, "New Safe Medicines Faster: A Proposal for a Key Action within the European Union's 6th Framework Programme," *Pharmacology & Toxicology* 86, no. Supplement I (2000): 23.
[397] EFPIA, "The Pharmaceutical in Figures," 3.

Parallel trade and a lack of sales revenue as a result, however was one potential foil. [398] European countries were able to trade amongst themselves to lower the price of pharmaceuticals, whereas sales in the United States didn't see the same level of negotiation. Without more money being put into the pharmaceutical industry, there was some concern that the industry would not be able to continue to compete against the United States.

Even before EFPIA's reports could be published, though, the economic and corporate effects of this transition of power was already being felt. In 2000, two reports were published criticizing the state of European pharmaceutical progress. The first, *Global Competitiveness in Pharmaceuticals A European Perspective,* was funded by the EU Commission and has been cited elsewhere via a shorthand known as the 2000 Pammolli report after one of its authors, Fabio Pammolli.[399] The three Italian economists tasked with developing the report found that United States pharmaceutical companies had access to capital markets and stock exchanges that allowed for increased venture capitalism, where the companies in Europe lacked the same financial infrastructure.[400] They equally noted that the division of labor, and the general success rate of products developed in the United States was more profound than in Europe, with fewer failures and a wider variety of potential outputs. [401] The second report published in 2000, prepared by Ole J. Bjerrum and Hans H. Linden of the Committee on Industrial Research Relations (CIRR) within the European Federation for Pharmaceutical Sciences (EUFEPS), similarly found that while the United States sales were growing, European sales were shrinking with major corporations seeing a 10-15% drop in employees within the sector throughout the 90s.[402] This lack of productive workforce meant fewer

[398] EFPIA, "The Pharmaceutical in Figures," 3.
[399] Alfonso Gambardella, Luigi Orsenigo, and Fabio Pammolli, "Global Competitiveness in Pharmaceuticals A European Perspective," Report Prepared for the Directorate General Enterprise of the European, (Brussels, Belgium: European Commission, November 2000).
[400] Gambardella, Orsenigo, and Pammolli, "Global Competitiveness in Pharmaceuticals," 76.
[401] Gambardella, Orsenigo, and Pammolli, "Global Competitiveness in Pharmaceuticals," 82-84.
[402] Bjerrum, "New Safe Medicines Faster," 23.

scientists in labs, fewer molecules under consideration, and an overall brain drain as workers left to find employment elsewhere. Both reports provided the same kind of conclusive warning: if Europe wanted to stay competitive, something had to change.

A meeting was planned that same year with EFPIA, the Danish Medicines Agency, and EUFEPS alongside "approximately 115 representatives from the pharmaceutical industry, academic institutions, and regulatory authorities" to develop a plan on how to make "New Safe Medicines Faster."[403] Bjerrum argued for the necessity of research groups, particularly those that covered a variety of specialist areas that could work in consortium with each other and cover multiple avenues of discovery at the same time. The plan was to simultaneously work on rebuilding lost (or diminished) networks of researchers within Europe as well as emphasizing the importance of developing new medications in a concept he and Hans H. Linden called the "New Safe Medicines Faster" program. Their hope was to launch it within the EU's 6th Framework program meant to take place between 2003-2007.

Access to needed medications[404] was a part of this push from the start, but there was a high-level awareness of the low return on investment these medications would bring. "One of the problems" of developing appropriate medications that are needed by the public, Bjerrum argued,

> is that pharmaceutical companies are often pre-occupied with generating income to pay the expected two-digit dividends to their shareholders. This is probably the reason for sticking to a 'blockbuster' strategy and a conservative regulatory system, instead of developing scientifically based long-term strategies that could renew the drug development process.[405]

[403] Ole J. Bjerrum, and Hans H. Linden, "European New Safe and Innovative Medicines Initiative: History and Progress (through December 2009)," In *Translational Medicine and Drug Discovery*, edited by Bruce H. Littman and Rajesh Krishna, (Cambridge, United Kingdom: Cambridge University Press, 2011), 267.
[404] Not just antibiotics, but all drugs that were essential or in need.
[405] Bjerrum, "New Safe Medicines Faster," 395.

Chapter One discussed how this transition took place, with Victor Roy's "pricing escalator" analogy emphasizing the need for ever growing returns. [406] The Framework program could potentially help alleviate some of those concerns, though, as it would be an influx of public monies and public support which took the edge off of potential financial motivations.

The European Union launched the first European Framework program in 1984 with the hopes that an influx of public funds into research areas would make European industries more competitive.[407] The Framework program was therefore, naturally, an ideal spot for this new venture. In the 6th iteration of the program, the European Technology Platform formed a group of pharmaceutical industry led stakeholders to create a Strategic Research Agenda (SRA) with the goal of transforming how drug development worked in the European Union.[408] Named "INNOMED," more than €18 Million was committed to the development of this goal and to running a pilot program for two scientific projects: PredTox and AddNeuroMed.[409] Both would be used to see of such collaboration was possible and prove the efficacy of that collaboration if successful.

Although an extensive search was conducted for the original version of the SRA, I was only able to track down the second version published and disseminated on 15 September 2006. Its executive summary reads:

> The Innovative Medicines Initiative (IMI) is a unique pan-European public and private sector collaboration between large and small biopharmaceutical and healthcare companies, regulators, academia and patients. The aim of IMI is to support the faster discovery and development of better medicines for patients and enhance Europe's competitiveness by ensuring that its biopharmaceutical sector remains a dynamic high-technology sector…IMI proposes a number of clear, practical paths that will accelerate the discovery and development of more effective innovative medicines with fewer side-effects. IMI will implement innovative Patient Centred[sic] Projects that address the principle causes of delay or bottlenecks in the current biomedical R&D process. These

[406] Victor Roy, *Capitalizing a Cure: How Finance Controls the Price and Value of Medicines*, (Oakland, United States: University of California Press, 2023), 46-47.
[407] European Commission, "30 Years European Research Framework Programmes 1984-2014," *Horizon Magazine*, March 2015, 10, https://sfe.lnl.infn.it/wp-content/uploads/2015/11/Horizon-Magazine-EU-Research-Framework-Programmes-1984-2014.pdf.
[408] IMI Innovative Medicines Initiative, "History – the IMI Story so Far," Accessed February 15, 2024, http://www.imi.europa.eu/about-imi/history-imi-story-so-far.
[409] The Innovative Medicines Initiative, "Innomed – Integrated Project," Accessed July 31, 2008, http://www.imi-europe.org/pilot%20project/pages/default.aspx

> bottlenecks have been identified as: predicting safety, predicting efficacy, bridging gaps in knowledge management and bridging gaps in education and training.[410]

Interestingly, while it does highlight the need to work with academia, the causes for bottlenecks in Europe is not identified as licensing discrepancy between public and private work, nor even a financial concern at all. Rather, drug safety and efficacy, as well as future researcher shortages are highlighted as areas of needed development and improvement. The exact statistics provided by EFPIA between 1991 and 2000 revealed that project failures in Europe were most likely due to "a lack of efficacy (25%), clinical safety concerns (12%), [or] toxicological findings in pre-clinical evaluation (20%)."[411] Perhaps infuriatingly for those involved in producing the report, was the realization that between 1995 and 2004 while the cost of research had increased significantly, and the time to develop a new drug stayed relatively the same, the ability to actually produce a new drug and gone down. The Centre for Medicines Research Pharmaceutical R&D Factbook, published a figure in 2006 to identify the global R&D expenditure, development times and NMEs 1995–2004 and it was used within the IMI's SRA to exemplify this phenomenon.[412] [413]

While any type of innovative research experiences a rate of attrition where time and money invested into the development of a product may yield no viable results, EFPIA's concern over the attrition rate within European Pharmaceutical companies stands out in this

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[410] Innovative Medicines Initiative, EFPIA, "The Innovative Medicines Initiative (IMI) Strategic Research Agenda: Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society," Strategic Research Agenda, Innovative Medicines Initiative, September 15, 2006, 3.
[411] Innovative Medicines Initiative, EFPIA, "The Innovative Medicines Initiative (IMI) Strategic Research Agenda: Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society," 7.
[412] The Centre for Medicines Research was an expert in independent pharmaceutical industry R&D measurement. In 2006 it was bought by Thompson Reuters, and is now owned by Clarivate, a "leading global provider of transformative intelligence." Despite the IMI SRA's use of this graph, additional data into how it was developed, where the data came from, or its intentions are unavailable as the Centre's Factbook is neither accessible nor available. This graph is presented without much comment in the SRA, and is taken for granted that its meaning is clear as the SRA quickly moves on to which strategic areas will best address the problems the graph points out. To that end, I can only comment and speculate on the SRA's usage at this time. Information on Clarivate's current priorities and research focuses can be found on their website: Clarivate, "Clarivate - Data, Insights and Analytics for the Innovation Lifecycle," Accessed August 29, 2024, https://clarivate.com/.
[413] Innovative Medicines Initiative, EFPIA, "The Innovative Medicines Initiative (IMI) Strategic Research Agenda: Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society," Strategic Research Agenda, Innovative Medicines Initiative, September 15, 2006, 9.

moment. Their solutions and recommendations within the SRA indicated a desire for a bottom-up response to drug development in Europe. They also called for the creation of a European Medicines Research Academy to be formed so that a new generation of researchers could be specifically trained in pharmacovigilance and other forms of bio-safety and efficacy frameworks.[414] Pharmacovigilance is the "the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines."[415] Though pharmacovigilance is primarily conducted after registration and approval of a drug, the SRA's suggestions were made under the presumption that if the new generation of researchers was trained in advance with these aspects in mind, then the rate of attrition on NMEs would go down, and production of efficacious and beneficial molecules would go up. Furthermore, by being aware of pharmacovigilant practices, the overall health and well-being of society would be improved as only safe medicines would remain on the market overall. Meanwhile, the education gaps that the SRA called to be addressed included:

1. Improved interdisciplinary work, including greater understanding of pharmaceutical R&D, greater knowledge amongst researchers of the requirements of the downstream processes, and ensuring that specialists study additional fields beyond their original area of expertise.
   a. Specific attention is brought to the fact that universities tend to "silo" their scientific areas and thus researchers have little experiences outside their own segmented lanes.
   b. Improved communication/interaction between clinical scientists and human biologists to bridge gap between understanding of biology of a disease within a clinical setting.
2. A need for qualified specialists within the natural, technical, pharmaceutical, and medical sciences.
3. A need for ongoing training to keep them updated with scientific and technology developments.
4. A need for more interaction between scientists in academia, industry and regulatory authorities and an improved flow of expertise between the three parties
5. A need for more scientists who focus on:
   a. Safety in medicines beyond the role of the traditional toxicologist. Particularly with focus in:
      i. Pharmacology: primary and secondary, safety, non-clinical and clinical, systems
      ii. functional genomics, safety pharmacology, physiology, pathophysiology, physical chemistry, animal and clinical toxicology, cellular biology,

[414] Innovative Medicines Initiative, EFPIA, "The Innovative Medicines Initiative (IMI) Strategic Research Agenda: Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society," 89.
[415] European Commission, "Pharmacovigilance," Public Health, January 15, 2025, https://health.ec/medicinal-products/pharmacovigilance_en.

biochemistry and animal physiology, with all their specialist branches (including in vivo whole organisms)

iii. Postgraduate physicians specialised in pharmaceutical medicine; Scientists skilled in bioinformatics, biosimulation, knowledge management, systems biology, systems toxicology, pharmaceutical biotechnology, and in silico modelling; Medical statisticians and biostatisticians; Medical imaging is increasingly being used in both basic and clinical research.[416]

Each of these items would have been expected knowledge for those working as an inhouse pharmacologist prior to the 1980s, but with the exodus of researchers Bjerrum and Linden noted in their 2000 assessment, it was paramount that any newly trained scientist was meeting and exceeding previously established guidelines. Furthermore, this interdisciplinarity was seen as a research foundation that was now lacking in the present, and it was a lack Europe wanted to fill. Several interviews I had with various members of the drug development, regulatory, and accessibility communities all echoed the need for improved education and what the impact of that education could be on the drug (and, specifically, antibiotic) pipeline could be.[417]

Despite this call for academic and interdisciplinary improvement, the suggested European Medicines Research Academy never took off. It was last mentioned publicly in a 2012 *Euractiv* article that implied the Innovative Medicines Initiative (IMI1) intended to begin working on constructing it in 2013.[418] No other reference has been found since, and in an interview with IMI1 founder, Ruxandra Draghia-Akli, she described IMI1's intention with educationally as the following:

> In all the programs there is a component of education and training because grants include the salaries of doctoral fellows, of post-doctoral fellows, of the researchers that are involved in the program. De facto, one could bring new students within the program and have a true education during those formative years.[419]

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[416] Innovative Medicines Initiative, EFPIA, "The Innovative Medicines Initiative (IMI) Strategic Research Agenda: Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society," 90-91.
[417] John Quick, Interview with Erin L. Paterson, 11 November 2022.
John Rex, Interview with Erin L. Paterson, 1 March 2024.
Ruxandra Draghia-Akli, Interview with Erin L. Paterson, 11 March 2024.
[418] Euractiv, "€2 Billion Poured into EU Pharma Innovation," May 5, 2008, https://www.euractiv.com/section/innovation-industry/news/2-billion-poured-into-eu-pharma-innovation/.
[419] Ruxandra Draghia-Akli, Interview by Erin L. Paterson, 11 March 2024.

And fellow IMI1 workers and consultants, such as John Rex, highlighted the work IMI1 did when it came to ensuring that education thrived. It's structure and intention from the start was to bring together university, private sector, and governmental entities for the purpose of research and development within the medical sphere. 350 stakeholders participated in this discussion, many from the private sector who would likely be the receiving end of this influx of newly trained researchers, but many also from public spheres (both academic and national or EU level government included).[420] By providing a platform for these different groups to work together, it equally provided the opportunity for members of the academic field to understand the complexities of the private pharmaceutical development field and vice versa.[421]

The relationship between public and private work forces and collaboration set the groundwork for the formation of the Public Private Partnership (PPP) structure that was used for IMI. Under the overarching umbrella of the European Commission's Framework program as well as what was indicated as a Joint Technology Initiative (JTI), these partnerships were intended to bring together "private and public partners to define common objectives of wide societal relevance and to combine funding and knowledge in order to fulfil these objectives."[422] From the Commission's standpoint, anything that would qualify as a JTI needed to indicate:

- strategic importance of the topic and clear objectives;
- existence of market failure;
- added value of action at European level;
- substantial, long-term industry commitment;

[420] Ole J. Bjerrum, Jacques Demotes, Andriani Odysseos, Jurg Seiler, Ferran Sanz, and Karen Strandgaard, "How to Establish a European Technology Platform for Innovative Medicines," Report from Workshop. Sixth Framework Programme SCIENCES, GENOMICS AND BIOTECHNOLOGY FOR HEALTH (Barceló Hotel Sants, Barcelona, Spain: European Federation for Pharmaceutical European Clinical Research Infrastructure Network European Federation for Medical Chemistry European Federation of Pharmaceutical Industries and Associations Federation of European Toxicologist & European Societies of Toxicology University of Cyprus With financial support from the European Commission, September 9, 2005), 86-89, https://web.archive.org/web/20061009110918/http://www.eufeps.org/document/pdfs/nsmf_III_final_report.pdf.

[421] John Rex, Interview by Erin L. Paterson, 1 March 2024.

[422] European Commission, "Joint Technology Initiatives, a New EU Research Initiative: Frequently Asked Questions," Memo, Press Corner, (Brussels, Belgium: European Commission, December 11, 2007), https://ec.europa.eu/commission/presscorner/detail/fr/memo_07_570.

- inadequacy of existing Community instruments[423]

Innovative medicines was earmarked as one of the six needs both the Commission and the JTI intended to fill. Thus, in 2008, the world's largest Public Private Partnership, Innovative Medicine's Initiative, was launched.[424]

IMI's original mission statement in 2008 called for European figures to "significantly improv[e] the efficiency and effectiveness of the drug development process with the long-term aim that the pharmaceutical sector [will] produce more effective and safer innovative medicines."[425] The verbiage closely aligns to what Bjerrum had proposed with his "New Safe Medicines Faster" initiative, and continual call backs to the work within the SRA were evident in the handling of IMI1's overall structure. As a PPP, its business model depended on university researchers, public funders, and private corporations working together on shared goals. Those goals, however, varied drastically depending on which project focuses were being considered at any given moment, and antibiotic development was only one small section of the larger IMI conglomerate.

II. How Product Development Partnerships emerged as a response to the Pharmaceutical Industry's lack of antibiotic development: Priority Medicines Report and needed innovation

In 2003, the Netherlands was preparing to become president of the European Commission and discussions on how to best manage the upcoming Framework program were well underway. Not long before, the Dutch had discovered a large source of natural gas off their coast leading to an unexpected boost to their economy. With their presidency looming and excess funds available for investment, they turned their attention to matters of health. [426]

[423] European Commission, "Joint Technology Initiatives."
[424] Hilde Stevens, Geertrui Van Overwalle, Bart Van Looy, and Isabelle Huys, "Innovative Medicines Initiative (IMI) Case Study Analysis Reveals the True Added Value of Early-Phase Public-Private Partnerships (PPPs)," *Biotechnology Law Report* 34, no. 4 (2015): 153, https://doi.org/10.1089/blr.2015.29008.hs.
[425] IMI Innovative Medicines Initiative, "History – the IMI Story so Far," Accessed February 15, 2024, http://www.imi.europa.eu/about-imi/history-imi-story-so-far.
[426] Richard Laing, Interview with Erin L. Paterson, 11 November 2022.

They requested that the WHO prepare a research proposal to "help bridge the gap between public health needs and the development priorities of the pharmaceutical industry."[427] The end goal of this report, was to ensure that, when the time came, the public would have access to medications that can treat the health threats to come. The final result, entitled Priority Medicines for Europe and the World (PMR), was released initially in 2004,[428] and it was commissioned at the same moment that EFPIA had been working with the EU on the development of the SRA for IMI. While they were plotting *how* to ensure production improved, this report would be the basis of *what* that production should focus on.

Although it had originally been conceived as a European based document, the 2004 PRM expanded its remit to include "Europe and the World" in an effort to highlight intersectionality of medical need between Low- Middle-Income Countries and High-Income Countries. Its authors, Warren Kaplan and Richard Laing, were both Boston, Massachusetts based physicians who served the WHO in several professional capacities. Kaplan served as a Technical Officer at WHO for the Essential Drugs & Medicine/Policy and Rational Use Priority Medicines Project.[429] Laing was a medical officer, member of several Executive Committees, and editor of the WHO's *Essential Drug Monitor*. [430] [431] He also served as a participant in the WHO's development of a 2001 report, *WHO Global Strategy for Containment of Antimicrobial Resistance* which highly emphasized the need for surveillance and appropriate antibiotic use via antibiotic stewardship.[432]

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[427] Kaplan and Laing, "Priority Medicines for Europe and the World," 1.
[428] Warren Kaplan and Richard Laing, "Priority Medicines for Europe and the World," Proposal. Geneva: World Health Organization, 2004.
[429] Warren A. Kaplan, Academic Profile, 2021. https://www.bu.edu/sph/profile/warren-kaplan/.
[430] Richard Laing, Profile of Member of International Editorial Advisory Board, GaBI Journal, http://gabi-journal.net/authors/richard-laing.
[431] Laing was responsible for interviewing Jonathan Quick about his time during the TRIPS/Doha Declaration arguments as discussed in Chapter Two.
[432] World Health Organization, "WHO Global Strategy for Containment of Antimicrobial Resistance," (Geneva, Switzerland: World Health Organization, 2001), https://iris.who.int/bitstream/handle/10665/66860/WHO_CDS_CSR_DRS_2001.2.pdf.

From the start, the understanding of the project was based heavily in the knowledge both men acquired via their work on essential medicines, and the WHO ensured the framing and understanding of the PMR would be done so from an essential medicines concept. Following the publication of the PMR both the *Drug Monitor* and the EML itself reported on the PMR and how it had been "presented at a major meeting of the European Union in The Hague on 18 November 2004 [to be] used as a resource for the seventh framework programme of the European Community for research, technological development and demonstration activities."[433] For the WHO, the key difference between what would be considered a *priority* medicine versus an *essential* medicine, was only a matter of development.

Priority medicines were those which *had not yet been developed* but for which a need had been seen in order to meet the health care needs of a population. Therefore, these were drugs that required innovation in order to exist in the first place, and the management of that innovation was equally key within the PMR's analysis. Split into eight sections (excluding the introduction), the report provided a background, a list of approaches to its priority settings, elucidated its methodology, but perhaps of most interest, developed a "preliminary list of priority diseases" that required increased attention and awareness, and from there proposed links, cross-cutting themes between diseases, medicaments, and patient populations, and offered suggestions for new approaches to promoting innovation.[434] From a cursory glance, it becomes evident that despite the title evoking Priority *Medicines* for Europe and the World, it is the diseases that are brought to the forefront of inspection. Twelve years later, in 2017, the WHO would follow up with this concept and publish its Priority Pathogen List,[435]

[433] Report of WHO Expert Committee, "The Selection and Use of Essential Medicines," Technical Report Series 933, Model List of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2005), 8.
[434] Kaplan and Laing, "Priority Medicines for Europe and the World."
[435] World Health Organization, "WHO Publishes List of Bacteria for Which New Antibiotics Are Urgently Needed," Press Releases, World Health Organization News (blog), February 27, 2017,

but here this list served as a jumping off point for targeted medical research and innovation to be proposed. The initial diseases included in the PMR ranged from those impacting mental cognition, to chronic disorders, to infectious maladies with specific indications such as Antibacterial Drug Resistance. For the purposes of this dissertation, only the sections pertaining to AMR will be reviewed in great depth, though others may be mentioned for additional context.

The PMR matched the work the EFPIA had done in showing the ebb and flow of innovation but did so with a far greater timeline and scale. Kaplan and Laing split innovative bursts into specific eras with the 1820s-80s marked a chemical revolution, the 1880s-1930s as an era of sera and vaccines, the 1930s-1960: that of organic and natural products such as vitamin, antibacterial, and hormone research; the 1960s-1980s as a time of clinical trial study and life sciences as a result (this shift also included an increased focus towards chronic diseases rather than infectious diseases), and finally highlighting the modern era for its focus on biotechnology and "the production of physiological proteins" for diagnostic purposes.[436] Like EFPIA, they indicated that this final is less productive than those that came before it with fewer innovative medications, across the board, coming to market, and the cost of those innovations going up at a steady pace regardless of the ebb and flow of production.[437] They too highlighted the United States, and its absence of product price control, as the emerging global leader of antibiotic development during this time period, which it remains so to this day.

Where the Strategic Research Agenda (mentioned earlier) focused on the need for education to improve European pharmaceutical excellence, Laing and Kaplan target the financial system as the fault. They used the 2000 Pammolli report alongside other EU

https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.

[436] Kaplan and Laing, "Priority Medicines for Europe and the World," 7-8.

[437] Kaplan and Richard Laing "Priority Medicines for Europe and the World," 9.

Council initiatives such as the 2000 Lisbon call for "economic, social and environmental renewal in the EU" and 2002 Barcelona call for "investment in medicines research in the EU (both public and private) [to] rise from 1.9% to 3% of Gross Domestic Product (GDP) by 2010," to help lay out perceived policies that the EU intended to target in the coming years.[438] From there, they discussed the WHO's position and understanding of medical reform that could potentially match the EU's goals. For this, they turned to independent scholars and experts to draft background papers that would give credence to the conclusions they would publish in the 2004 PMR.

In the years before the development of the report, Laing had visited Uppsala on behalf of the WHO to discuss AMR with members of the ReAct/Strama teams.[439] [440] He would later ask Otto Cars,[441] pharmacologist Per Nordberg, and the coordinator for the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, Dominique L. Monnet to write a background paper discussing the specific priority of antibacterial drug resistance within the PMR to help bolster the report's claims.[442] Their paper addressed the full gambit of AMR as a global threat by defining its presence, its expansion, and the complications that came with treating it.[443] In stark terms, they revealed that in just one case of antibacterial resistance, MRSA, there were roughly 1,300 deaths per year in the European Union, and when put alongside the overall cost of treating bloodstream MRS infections (117 million Euro per year) these annual costs "alone already exceed the EU budget for antimicrobial

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[438] Kaplan and Richard Laing, "Priority Medicines for Europe and the World," 11-12.
[439] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 22.
[440] For more information on Strama, consult: S. Mölstad, O. Cars, and J Struwe, "Strama - a Swedish Working Model for Containment of Antibiotic Resistance," *Eurosurveillance* 13, no. 46, November 13, 2008, 1. https://doi.org/10.2807/ese.13.46.19041-en.
For more information on ReAct, consult: ReAct, "About Us," Accessed April 10, 2024. https://www.reactgroup.org/about-us/.
[441] ReAct, "Otto Cars," Accessed January 13, 2025, https://www.reactgroup.org/contact/react-europe/otto-cars/.
[442] Expert Witness, Interview by Erin L. Paterson, 17 April 2024.
[443] Per Nordberg, Dominique L. Monnet, and Otto Cars, "Antibacterial Drug Resistance: Options for Concerted Action," (Geneva, Switzerland: World Health Organization Department of Medicines Policy and Standards, February 2005).

resistance research for 1999-2002."[444] The cost of treating resistant strains of infection, was now outpacing what the potential cost of investment to develop a new drug might be in the first place.

This assessment led the PMR to promote four key recommendations in regards to AMR specifically: increased surveillance, prevention, research and product development, and international cooperation to get the crisis under control.[445] These recommendations would find themselves supported in the PMR's list of eight key conclusions; three of which directly relate to the growing concerns regarding antibiotics, research and technology gaps, and a need for a restructuring of markets and evaluations to ensure good drugs reached patients faster and more effectively rounding out the second half of the list, and one specifically calls for a new financing model to target this need for innovation.[446] Because private investment in antibiotic development and innovation has floundered,[447] [448] the PMR directly calls for public investment to be made in consortium with private companies in order to ensure effective products can make it to the market in the form of a Public Private Partnership (PPP).

PPPs, and their sibling Product Development Partnerships (PDPs), have been used in the field of antibiotic development almost since the advent of antibiotic usage. As physician Rosewell Quinn has pointed out, US government investment and involvement is what led to the production capabilities of penicillin during WWII, and this investment came in the form of a PPP.[449] The actual phrase itself though was one that emerged around the 1990s as more formalized and specific relationships between government entities and private businesses

[444] Nordberg, Monnet, Cars, "Antibacterial Drug Resistance: Options for Concerted Action," 23.
[445] Kaplan and Laing, "Priority Medicines for Europe and the World," 50-51.
[446] Kaplan and Laing, "Priority Medicines for Europe and the World," xv-xvi.
[447] Roswell Quinn, "Rethinking Antibiotic Research and Development: World War II and the Penicillin Collaborative," *American Journal of Public Health* 103, no. 3 (March 2013): 426, https://doi.org/10.2105/AJPH.2012.300693.
[448] For more detailed information on private investment in pharmaceuticals see Chapter Four.
[449] Roswell Quinn, "Rethinking Antibiotic Research and Development," 427-8.

began to form.[450] [451] At this time, and in response to several health crises, health-focused PPPs began to emerge, including International AIDS Vaccine Initiative (IAVI), Medicines for Malaria Venture (MMV), Malaria Vaccine Initiative, and TB Alliance.[452] The PMR draws attention to these PPPs and uses them as an assessment of whether the WHO should recommend them moving forward.

What the report determines is that as far as health and medicine focused PPPs are concerned, while the formation of a PPP can and should be put in place to help support drug development, the PPP on its own should not be expected to carry the entire financial burden of that drug development. Instead, they are considered a form of "push-incentive" that provides funds to incentivize innovation and enable private companies the opportunity to proceed with products of uncertain return on investment.[453] For those hoping to engage in a successful PPP venture, the goal would be primarily for public entities to form a partnership with a pharmaceutical company, and supply enough incentive funds that ensures an eventual product emerges onto the market.

III. Analyzing the Innovative Medicines Initiative: A Public Private Partnership with an end date

IMI officially launched in 2008 with an initial budget of €2 billion. It came as the result of many years of planning and collaboration, the SRA and its pilot program, the PMR and its push for PPP development, and a strong insistence on health and technology

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[450] Tony Bovaird, "A Brief Intellectual History of the Public–Private Partnership Movement," In *International Handbook on Public–Private Partnerships*, edited by Graeme A. Hodge, Carsten Greve, and Anthony E. Boardman, (Edward Elgar Publishing, 2010), 43, https://doi.org/10.4337/9781849804691.00010.

[451] Although PPPs pre-existed this decade, the United Kingdom does champion itself as the first country in the world to introduce the concept of PPPs in a health care setting, with government documentation declaring they began the process in 1991. UK Trade & Investment. "07 Public Private Partnerships." Healthcare UK. (London, United Kingdom: UK Trade & Investment).

[452] Hannah Kettler and Adrian Towse, "Public Private Partnerships: A Report for the WHO Commission on Macroeconomics and Health," CMH Working Paper WG2:21, 2001, World Health Organization, Commission on Macroeconomics and Health, Geneva, 15-16, www.cmhealth.org/docs/wg2_paper21.pdf.

[453] Kettler and Towse, "Public Private Partnerships," 32.

improvements within Europe to ensure its research, development, and production capabilities could match the United States market strength. Although the 2004 PMR was not mentioned specifically in the creation of the antibiotic research categories in IMI, those involved with IMI's roll out did state they had reviewed the PRM's nascent priority diseases (pathogens) list of suggestions (which included AMR, HIV/AIDS, and tuberculosis amongst others) as potential goals for researchers to address.[454] [455] [456] As a massive PPP, IMI was not specifically focused on any one particular path of interest. Rather, it was designed as a form of transit hub for multiple research focuses. The European Union invested half of the funding necessary to run its many research branches, with EFPIA supplying the second half.

Not long after the launch of IMI1, the Swedish presidency of the EU began in 2009. As with their involvement in assisting Sweden with Strama, ReAct (Otto Cars in particular) assisted the presidency again in discussions and negotiations with the EMA and ECDC on "to see whether they couldn't put up a document or a process to get some figures on the [AMR] burden."[457] The goal was to once again try to shape the perspective around what AMR was looking like at a continent level, as well as what the pharmacological response could be should such a thing be required. A conference was planned in 2010 that included several big pharma representatives, "notably Glaxo" to discuss the global needs of antibiotics.[458] These were

> the result of negotiations after the Swedish EU presidency. And that in turn challenged the EU Commission to come up with an action plan to include a strong component on fixing the pipeline… the sequence of events that emerged into the creation of new collaborations -New Drugs for Bad Bugs, included in the already existing Public Private Partnership (PPP) Innovative Medicines Initiative (IMI).[459]

[454] Kaplan and Laing, "Priority Medicines for Europe and the World," 47.
[455] Ruxandra Draghia-Akli, Interview by Erin L. Paterson, 11 March 2024.
[456] Expert Witness, Interview by Erin L. Paterson, 17 April 2024.
[457] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 23.
[458] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 23.
[459] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 22-23.

New Drugs For Bad Bugs (ND4BB), launched in 2013, was the largest branch of IMI1's antibiotic research program. It encompassed eight projects: TRANSLOCATION, ENABLE COMBACTE-CARE, COMBACTE-MAGNET, COMBACTE-NET, iABC, and DRIVE-AB. PreDiCT-TB, the sole outlier, was focused specifically on developing "a series of tools, which drug developers [could] use to increase the probability of them choosing the right drug-like compounds [for tuberculosis] and getting them through clinical trials successfully."[460] It stood apart from ND4BB due to its hyper focus on one specific disease. The others, were far more liberal in their intentions, allowing for a wide variety of bacterial targets or responses.

Each of the ND4BB programs, had slightly different points and purposes, and equally: slightly different investment schemes as a result. As an example, while COMBACTE-MAGNET focused on improvements to antibiotic surveillance and worked directly with hospitals and physicians to track and understand clinical data regarding AMR, ENABLE focused exclusively on the development of new gram-negative antibiotics as priority medicines.[461] ENABLE was set up to allow for a collaboration between multiple different scientists and labs, as well as data sharing on any information regarding the production of a new molecular entity. By 2019, ENABLE had established communication networks in 13 countries, connected 32 partners (including 11 Small- Medium Sized Enterprises [SMEs]), enabled the development of 70 new SMEs and research organizations, and assisted in 15 programs dedicated to this task (of which 5 were still in place).[462] The end goal was to find three antibacterial leads, two antibacterial development candidates, and move at least one

[460] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | PreDiCT-TB | Model-Based Preclinical Development of Anti-Tuberculosis Drug Combinations," May 1, 2012, http://www.imi.europa.eu/projects-results/project-factsheets/predict-tb.
[461] Hugh Laverty and Pierre Meulien, "The Innovative Medicines Initiative −10 Years of Public-Private Collaboration, *Frontiers in Medicine* 6 (2019), 6.
[462] Laverty and Meulien, "The Innovative Medicines Initiative," 6.

compound into preclinical and phase 1 clinical studies.[463] By 2021, when funding for ENABLE came to an end, they had more than surpassed that goal with six potential leads, three candidate declarations, two compounds in preclinical studies, and one compound that had completed phase 1 trials.[464] [465]

Very shortly after ND4BB's official launch, the WHO published its updated PMR in 2013. Written by Warren Kaplan, Richard Laing, and three new additional co-authors: Veronika Wirtz from Boston University, and Aukel Mantel-Teeuwisse and Pieter Stolk from Utrecht University, where Laing had been a frequent collaborator since 2004.[466] The new PMR included steep praise for IMI1's work so far, continued support for PPPs in general, and additional attention was given to ND4BB's launch and its call for papers as a way to encourage and incentivize new R&D.

In Pieter Stolk's background paper used in support of the PMR 2013, he references the development of IMI1's library of potential compounds as a key step taken in IMI1's work so far. This library, known as the European Lead Factory enabled companies, academics, and small enterprises to access molecules that were contributed by others within the IMI1 framework. They could screen the library for potential hits, and if something seemed particularly promising: remove the molecule from the library for continued research after paying a small fee.[467] This collaboration led to the unique sharing of 500,000 potential

[463] European Gram-Negative AntiBacterial Engine: ENABLE, "Welcome to ENABLE," Accessed March 7, 2023, http://nd4bb-enable.eu/.
[464] European Gram-Negative AntiBacterial Engine: ENABLE.
[465] A version of ENABLE has continued in Sweden and expects to continue for at least another couple of years, however it is in a much more reduced form and it is uncertain what (if any) additional outcomes will emerge from it. Expert Witness, Interview by Erin L. Paterson, 17 April 2024.
[466] Warren Kaplan, Veronika Wirtz, Aukel Mantel-Teeuwisse, Pieter Stolk, and Richard Laing. "Priority Medicines for Europe and the World 2013 Update," (Geneva: World Health Organization, July 9, 2013).
[467] Ruxandra Draghia-Akli, Interview by Erin L. Paterson, 11 March 2024.

compounds, while simultaneously opening doors for collaboration (particularly between academia and corporate entities).[468]

Collaboration remained the key component of the IMI structure beyond the doors of its library too. PreDiCT-TB, as an example, worked exclusively on developing a framework where screening for molecules or compounds would yield more likely targets with greater efficacy.[469] Its structure was wholly devoted to improving the parameters that went into screening efforts, and maintaining that research for future projects or scientists. All of their key research remained in the public domain following the closure of the PreDiCT-TB efforts, thus allowing for future researchers to pick up where they left off. The purpose was to encourage the production of data first and foremost, whether that data could eventually be patented and developed into a product, however, remained to be seen.

Less than a year after the publication of the 2013 PMR, the second cycle of the Innovative Medicines Initiative (IMI2) launched its own Strategic Research Agenda and trajectory for a new round of targeted research in European health. Its SRA directly cites the 2013 PMR, its goals and its insights, and used it as an additional resource in designing calls for future research platforms within IMI2,[470] thus solidifying and the link between the long trajectory of the work conducted by the team behind the Essential Medicines List in 2004, and its tangible impact in the IMI and PPP sphere.

It should be noted that both IMI iterations were faced with a unique feature that other PPPs in the field did not experience. IMI was always conceived of as a short-term partnership

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[468] Pieter Stolk and Elizabeth Ziemba, "Priority Medicines for Europe and the World 'A Public Health Approach to Innovation': Background Paper 8.1 Public Private Partnerships," Update on 2004 Background Paper, (Utrecht, Netherlands: Utrecht Institute for Pharmaceutical Sciences (UIPS), May 1, 2013), 8.1-6.

[469] Gerry Davies and Justin Green. 'This has been a critical investment for European researchers' – an interview with the PreDiCT-TB project coordinators, Corporate, September 26, 2018, https://www.imi.europa.eu/projects-results/success-stories-projects/has-been-critical-investment-european-researchers.

[470] EFPIA, Vaccines Europe, European Biopharmaceutical Enterprises, and Innovative Medicines Initiative, "The Right Prevention and Treatment for the Right Patient at the Right Time: Strategic Research Agenda for Innovative Medicines Initiative 2," (Brussels, Belgium: EFPIA, Vaccines Europe, European Biopharmaceutical Enterprises, Innovative Medicines Initiative, March 2014), 8, 11, 16, 27.

with a fixed budget that supported specific calls for projects in various fields. In IMI1, ND4BB stood out as the strongest collection of antibiotic related projects, but in IMI2 that project title went to the AMR Accelerator program[471] which housed AB-DIRECT, COMBINE, ERA4TB, GNA NOW, PRIMAVERA, RespiriNTM, RespiriTB, TRIC-TB, and UNITE4TB.[472] [473]

Seven of the projects were devoted to molecular development and grew on previous data inherited from ND4BB. COMBINE and PriMAVeRA were more research focused. COMBINE sought to improve understanding on the likelihood of molecular models' transferability from animal to human test subjects. By understanding which markers to be aware of, such research would be able to help shorten wasted time in clinical trial settings by rejecting the use of prospective models by knowing in advance that they would not work in human samples. PriMAVeRA, by contrast, looked into vaccine possibilities for bacterial infections and the possibility of pre-emptive care rather than responsive care as a result.

Imbedded in all nine projects, though, is the sense of finality as all of the projects came with an end date. IMI originally "ran" from 2008 to 2013 (with active projects running until the conclusion of their funding cycles). [474] [475] IMI2 was offered funding and support from 2014 through 2020. [476] [477] In 2021, the European Union adopted the Innovative Health

[471] IMI AMR Accelerator, "The AMR Accelerator," Accessed April 9, 2024, https://amr-accelerator.eu/amr-accelerator-project-portfolio/.
[472] More specific information on these individual projects can be found on the project website at: IMI AMR Accelerator, "AMR Accelerator Project Portfolio," Accessed April 5, 2024, https://amr-accelerator.eu/amr-accelerator-project-portfolio/.
[473] IMI AMR Accelerator, "AMR Accelerator Project Portfolio," Accessed April 5, 2024, https://amr-accelerator.eu/amr-accelerator-project-portfolio/.
[474] Innovative Medicines Initiative, "The IMI Funding Model," Europe's Partnership for Health, Accessed April 9, 2024, https://www.imi.europa.eu/about-imi/imi-funding-model.
[475] While on paper it is clear IMI was expected to run from only 2008-2013, several ND4BB initiatives did not start until after this date, leaving the particulars for why it was considered an IMI1 project rather than an IMI2 project relatively muddled. The latest to start/end was iABC which started in 2015 and ended in 2023. COMBACTE-NET and COMBACTE-CARE also ended in 2023.
[476] Innovative Medicines Initiative, "The IMI Funding Model," Europe's Partnership for Health, Accessed April 9, 2024, https://www.imi.europa.eu/about-imi/imi-funding-model.
[477] Like IMI1, IMI2 equally was publicly declared to run between these dates, though projects are continuing despite this "end."

Initiative (IHI), and pulled with it the ongoing projects leftover from previous IMI campaigns. ND4BB and AMR Accelerator can both be found on the IHI website, as can the projected end dates of their continued work. One, GNA Now, is scheduled to continue through 2025.[478] Past that point, its future is not certain.

While some supporters of IMI and its work have lamented its end, particularly in the closure of the ENABLE program which offered great support between academia and pharma,[479] the brevity of IMI was a feature not a flaw. John Rex, a founder of the ND4BB initiative explained the reasoning by saying that:

> The cyclical nature [is] an advantage because it forces you to come to a conclusion and then think about doing the next thing…Zombie projects are a real thing, and if there's an opportunity to stretch the funding out, try just one more experiment--you actually have to force people to make a decision and to move on because innovation only comes by being put in a pressure cooker to a certain extent.[480]

The fear in the development of IMI was that by creating an endless pool of funding, or something similar to an NIH program grand that could potentially reach up to 35 years in length, the need or desire for innovation would lag. Purposefully organizing projects in short bursts, and allowing for multiple calls to begin in succession with one another provided a slowly growing framework of sustainability where the research for one project fed into another, and the focus remained tightly specific throughout.[481]

This consideration, however, is unique to the IMI (and now IHI) lifecycle. Though the cyclical nature may have been seen as a boon to this particular series of initiatives, it was not replicated in other PPPs that emerged within this field. And, it is a decision that may not have restricted IMI from actually bringing a product to market. In interviews with outside observers, IMI's inability to lead an antibiotic compound to clinical trials or beyond remains

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[478] Lygature, "GNA NOW Consortium Expands Its Scope to Support the Under-Studied Condition of Severe Diarrhoea," Corporate, News, January 23, 2024, https://www.lygature.org/news/gna-now-consortium-expands-its-scope-support-under-studied-condition-severe-diarrhoea.
[479] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 24.
[480] John Rex, Interview by Erin L. Paterson, 1 March 2024.
[481] Ruxandra Draghia-Akli, Interview by Erin L. Paterson, 11 March 2024.

one of its most notable failings. Had it had more time, or had it received additional support, it is possible it could have done more. Despite the amount of work done in improving collaboration, and the training of new researchers that continued their work in the field of antibiotic development, an actual product was not created.[482] Too much emphasis on educational training and collaboration, or perhaps not enough time or structure to allow for actual product development, thus influenced the end output of one of the largest PPPs in this space.

Throughout IMI's existence, critiques on the programs involved and what the end goal was going to be circulated amongst academic and NGO communities. Friction between various factions: those pro-industry and those against had ripple effects within the partnership in varying degrees. As a matter of course, private corporations are a necessary component of Public *Private* Partnerships. However, who stands to benefit the most at the end of those partnerships is less clear.

IMI's emergence as the first major PPP that targeted antibiotic development is entirely unique to this early 2000s era. The United States' increasing pharmaceutical market presence is what drove European nations to develop IMI1/2 initially, but as we have already seen: antibiotic development in particular is not necessarily an avenue filled with expected high market returns. There are *many* other components to IMI that do not include antibiotic development, and an analysis on those branches of the PPP is outside the scope of this project, however, their mere existence does indicate that the fact IMI developed an antibiotic research focus should not be taken for granted. The funds dedicated to improving the educational awareness of researchers, the state of antibiotic molecular understanding, and

[482] Expert Witness, Interview by Erin L. Paterson, 17 April 2024.
Ruxandra Draghia-Akli, Interview by Erin L. Paterson, 11 March 2024.
John Rex, Interview by Erin L. Paterson, 1 March 2024.
Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.

even the start of actual physical new antibiotic development were not guaranteed from the outset.

As has already been discussed within this dissertation, although there had been continual attention and calls for concern regarding AMR, it wasn't until 2014 that discussions began to tilt towards the need for antibiotic innovation in specific. Prior, the work was largely focused on antibiotic stewardship and surveillance. The 2016 O'Neill report (*Review on Antimicrobial Resistance)* was hugely impactful when it came to encouraging actual product development, and members of IMI's antibiotic research team (ND4BB) such as John Rex, assisted O'Neill when he first began gathering data in 2014.[483] Once his report was published, O'Neill directly cited IMI by stating that "exciting progress" was already being made, and that the combination of public and private funding was essential to future needed antibiotic development.[484] The only other entity that was praised in such a manner was the United States' Biomedical Advanced Research and Development Authority (BARDA).

One of the most evident components of IMI, though, was its originally stated intention of creating an ecosystem where members from different groups were able to work or collaborate with each other in practical or meaningful ways. During the witness seminar I helped manage in January 2024, individuals of IMI's the DRIVE-AB program reflected on this and other aspects of IMI's impact.[485] Former DRIVE-AB coordinator, Stephan Harbarth, suggested that

> it was the early times when public academic leaders tried to match their perspectives and wish lists with the private sector…we were the catalyst of change, not only when it came to the ideas, [and] the desires, but also…how these different sectors interact… we learned

[483] Jim O'Neill, "Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations," Review on Antimicrobial Resistance, Wellcome Trust and Department of Health, 2014, 14.
[484] Jim O'Neill, "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations." Review on Antimicrobial Resistance, Wellcome Trust and Department of Health, 2016, 6.
[485]DRIVE-AB's mission statement reads that it is "tasked with defining responsible use of antibiotics, identifying the antibiotic-related public health priorities, calculating the societal value of having new antibiotics available for these priorities, developing and costing new economic models to promote the desired antibiotic innovation, and sustainable use of the resulting, novel antibiotics." More about DRIVE-AB's specific work can be found on their website: "About DRIVE-AB | Drive AB," Accessed May 16, 2024, https://drive-ab.eu/about/.

> to respect and to talk to each other in a very direct and unbiased way. Where everybody was clearly communicating what they thought. [486]

This collaboration was not without its difficulties, however. As IMI was first organizing ND4BB, that friction was already making itself known.

In Sweden, Otto Cars felt that "there [was] something missing in the New Drugs for Bad Bugs initiative. Namely what we call the controlled distribution and use, and access." He would go on to say that ReAct submitted a proposal "for an additional component of the IMI," to include such things, but that there was limited response and action to such a suggestion.[487] Although ReAct did take part in IMI's DRIVE-AB initiative, they backed out before the delivery of the final report due to a perceived lack of transparency regarding "how the partial de-linkage concept was born and promoted. And the strong industry voices around that."[488] [489] The passage in question was in relation to the notion market entry rewards and what kind of financial incentive should be provided to private corporations in this form.

The final report's verbiage does draw attention to the tensions between stakeholders, indicating that there were:

> two versions of this incentive– fully and partially delinked. In a fully delinked model, all developer revenues come from the reward payment(s) whereas in a partially delinked model, revenues are achieved both from the reward payment(s) and unit sales…Market entry rewards were judged to strongly stimulate innovation, with the partially delinked version receiving slightly higher support. There were concerns about the financial feasibility of the fully delinked model and thus sustainability and implementation…The fully delinked model was judged to strongly support sustainable use and equitable availability, but there were concerns that the partially delinked model would be less effective in these areas. [490]

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[486] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 71.
[487] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 72.
[488] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 72.
[489] The concern regarding promotion here was largely due to which voices were calling for the model to be used, and a frustration regarding whether the industry voices were being catered to in exclusion to the more public partners in the group.
[490] Christine Årdal, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John Rex, "Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access," Final Report, DRIVE-AB. Innovative Medicines Initiative, 2018, 92, https://www.imi.europa.eu/sites/default/files/projects/documents/DriveAB_Report_FINAL.pdf.

ReAct felt that the industry voices in the room overshadowed the call for a fully delinked MER, and that listening to these voices was to the detriment of real antibiotic stewardship and accessibility needs.

Kevin Outterson, founder of the PPP CARB-X and co-writer of DRIVE-AB's final report, stated that in those final moments of deliberation, DRIVE-AB "like every family it has some dysfunction…[But] it is interesting that today, really, the industry for antibiotics is more aligned with the position that ReAct was trying to make."[491] The PPPs that emerged in 2016, and the guidance provided by these PPPs have included accessibility concerns within the work that they do and discussions about delinking and price concerns have only continued in frequency.

IMI may not have been able to address everything, nor could it have done, but it had started a dialogue, and in the years after IMI's initial launch: that dialogue only continued to grow on both sides of the Atlantic.

IV. A trans-Atlantic response to developing antibiotics, how a United States and United Kingdom team up led to the creation of CARB-X

Founded in 2006, BARDA was initially developed in a time of paranoia in the United States surrounding drug safety and security. Lack of access to antibiotics, in particular, was seen as a national security crisis due to recent anthrax terrorist attacks and a national shortage of ciprofloxacin as a result (see Chapter Five for more detail).[492] Their remit, couched in militaristic terminology, indicated that BARDA was responsible for working

> with both public and private sector partners to support innovative solutions, advanced research and development, regulatory approval, and procurement of life-saving medical

[491] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 72.
[492] Jackson Landers, "The Anthrax Letters That Terrorized a Nation Are Now Decontaminated and on Public View," *The Smithsonian Magazine,* September 12, 2016, https://www.smithsonianmag.com/smithsonian-institution/anthrax-letters-terrorized-nation-now-decontaminated-public-view-180960407/.

> products—drugs, vaccines, therapeutics, diagnostics, and medical devices – that are known collectively as medical countermeasures.[493]

Early strategic research agendas for BARDA listed their intentions to ensure that a national stockpile of efficacious medications could be maintained at all times existed, but that new and important technologies and medical innovations would be developed to ensure future medical threats could be overcome without delay or undue burden on the United States' population.[494] [495]

Concurrently with these fears were various early 2000 publications from pharmaceutical companies indicating that despite screening for essential genes effective against bacteria, there was a growing dearth of prospective antibiotic candidates.[496] At the same time, was the unsuccessful launch of Sanofi-Aventis' antibiotic Ketek which was meant to be used against resistant strains of respiratory infections.[497] Although Ketek had shown distinct flaws in three different FDA trials, it was approved for use in the United States in 2004. By June 2006 "23 cases of acute severe liver injury and 12 cases of acute liver failure, 4 of them fatal, had been linked to Ketek. By the end of 2006, Ketek had been implicated in 53 cases of hepatotoxic effects."[498] Ketek eventually lost its FDA approval, and the fallout of the decision led to increased requirements on clinical trials and the necessary standards that must be met to receive regulatory approval in the future.

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[493] Department of Health and Human Services, "Administration for Strategic Preparedness and Response," Justification of Estimates for Appropriations Committee, (Washington DC, United States: Department of Health and Human Services, 2024), 74.
[494] Robin Robinson, "BARDA Strategic Plan," Powerpoint presented at the HHS PHEMCE Stakeholders Workshop, (Arlington, United States, September 25, 2008), https://medicalcountermeasures.gov/barda/documents/080925barda-strategicplan.pdf.
[495] Robin Robinson, and Assistant Secretary for Preparedness and Response Biomedical Advanced Research and Development Authority, "BARDA Strategic Plan 2011-2016," (Washington DC, United States: Department of Health and Human Services, 2011).
[496] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 29-30.
[497] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 30.
[498] David B. Ross, "The FDA and the Case of Ketek," *New England Journal of Medicine* 356, no. 16 (2007), https://doi.org/doi:10.1056/NEJMp078032.

For one BARDA representative, Ketek stood out as a triggering point that signaled a speedy exit of other companies interested in creating new antibiotics.[499] By 2010, while speaking with small to medium enterprises regarding their interests in developing drugs to address BARDA's specific concerns, the prevailing comment on the subject was that these companies "could not raise money for clinical development."[500] While large pharmaceuticals would have had the funds to develop an antibiotic in this climate, other companies were being priced out. Investment was needed, but what kind of investment and where it would go would be a flexible issue dependent on which congressional body was in power under which presidency.[501]

Initially, infectious diseases and specifications of disease statuses such as AMR were not a part of BARDA's oversight.[502] Congress would only permit investment into antibiotic/AMR research and development if there was a bioterrorism component associated with it.[503] Despite this, they did begin to fund enough projects to gain the attention of the UK's 2014 independent review on antimicrobial resistance (which would later go on to publish the O'Neill report). Later that same year, in the United States, under then president Barak Obama, released its National Strategy for Combating Antibiotic Resistant Bacteria.[504] By March 2015, the White House published its National Action Plan on the same subject, providing suggestions on how to address the strategy outlined in the 2014 document.[505] Both would provide increased flexibility to BARDA when it came to potential new companies to work with in the field of antibiotic development, doubling the amount of money, and funding, which was going to BARDA to support antimicrobials.[506]

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[499] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 30.
[500] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 30.
[501] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 30-32.
[502] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 31-32.
[503] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 32-34.
[504] The White House, "National Strategy for Combating Antibiotic Resistant Bacteria," (Washington D.C., United States: The White House, September 2014).
[505] The White House. "National Action Plan for Combating Antibiotic-Resistant Bacteria."
[506] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 74.

By 2016, five co-related events had begun to circulate. The O'Neill Report, calling for increased antibiotic production was published, the WHO had just published its own Global Action Plan on Antimicrobial Resistance,[507] the Davos Declaration unified pharmaceutical companies together in acknowledging AMR was a problem that needed to be addressed, [508] and IMI's work was quickly gaining attention as a PPP capable of generating increased research and awareness. In this climate of discussion, expectation, and competition, the United States decided to invest in a public private partnership dedicated to antibiotic innovation and they encouraged funding from any other countries or groups interested in taking part.

One such group was the Wellcome Trust. In the early 2000s, John Rex (a physician and drug developer who had experience in both the public and private sectors as well as IMI), joined and then ran a Wellcome Trust project entitled Seeding Drug Discover. Seeding Drug Discovery "was an open call for people to submit innovative concepts with an expert review panel," and select participants could receive from 1-10 million pounds to bring their project up off the ground.[509] In an interview conducted in 2024, Rex said that Wellcome was "not expecting them to all work, but expecting that most of them would fail, but recognizing the idea of seeding during discovery you actually have to roll the dice." [510] When the United States began to make calls for innovation, Rex collaborated with Boston University legal professor and health care advocate, Kevin Outterson, on designing the project. [511] Rex

[507] World Health Organization, *Global Action Plan on Antimicrobial Resistance*, Geneva: World Health Organization, 2015.
[508] More on the Davos Declaration will be found in Chapter Four, but its impact was also discussed during the Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 52-54.
To read the declaration in full, consult: "Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance," AMR Industry Alliance, January 2016, 2-4, https://www.amrindustryalliance.org/wp-content/uploads/2017/12/AMR-Industry-Declaration.pdf.
[509] John Rex. Interview by Erin L. Paterson. 1 March 2024.
[510] John Rex. Interview by Erin L. Paterson. 1 March 2024.
[511] Kevin Outterson had been known in access and availability circles prior to the launch of CARB-X. He worked alongside James Love, publishing papers relating to stewardship and drug availability in the early 2000s, and was involved with IMI through its DRIVE-AB program as well. A more comprehensive list of his publications in this field can be found on the Boston University website: Boston University, "Kevin Outterson, JD, LLM," University, Boston School of Public Health, https://www.bu.edu/sph/profile/kevin-outterson/.

admitted that they "actually imported some of the templates for how you call for proposals" to help get their PPP started, and the Wellcome Trust's interest in funding the whole program grew from there.[512]

The results of this collaboration and was the PPP known as Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X).[513] Two divisions of United States government offices, one UK government office, and a British funder were responsible for the initial investments. These included the United States National Institute of Health's (NIH) National Institute of Allergy and infectious Diseases (NIAID), the US Department of Health and Human Services' (DHHS) Biomedical Advanced Research and Development Authority (BARDA),[514] the United Kingdom's Antimicrobial Resistance Centre, and the Wellcome Trust.[515] Of these initial funders, BARDA and the Wellcome Trust (then under the direction of infectious diseases researcher Jeremy Farrar) were of most significance as they signaled the seriousness and the intention of the work about to be conducted. [516] The form and structure of CARB-X was, on the surface, somewhat similar to IMI's initial construction. A call for projects (CFPs) would be written, and prospective groups would write a grant request and submit to CARB-X for review. Those requests would be reviewed and, if the project was successful, they would receive funding from CARB-X to pursue their goals.

In the early years of its creation, the requirements for these CFPs were relatively minimal. "Proposals must be in scope, targeting: Bacteria (not viruses, fungi, mycobacteria or

[512] John Rex. Interview by Erin L. Paterson. 1 March 2024.
[513] Sarah Rimer, "BU Law School Guides Global Effort to Combat Antibiotic-Resistant Superbugs: $350 Million Aimed at New Antibiotics and Rapid Diagnostics," *The Brink*, (Boston, United States: Boston University July 28, 2016), https://www.bu.edu/articles/2016/carb-x/.
[514] BARDA is a component of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the Department of Health and Human Services.
[515] Sarah Rimer, "BU Law School Guides Global Effort to Combat Antibiotic-Resistant Superbugs."
[516] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 56.

parasites), Listed on the CDC 2013 Urgent or Serious Threat List, TRL 3-6,"[517] [518] and drugs that would address bacterial diseases on the WHO's Priority Pathogens List.[519] As more projects were added to CARB-X's pipeline of development, their standards and specifics became more focused. The initial list of requirements serve, at time of writing, as merely the bare minimum needed to "get in the door," as "specificity on syndromes…specific bacterial pathogens for that syndrome, and the specific types of resistance mechanisms" take precedence.[520]

One aspect of CARB-X that is unique to its composition is that all CARB-X projects must agree to create a plan on how they intend to make their product accessible after launch.[521] These companies do not need to have a locked-and-loaded ready to implement plan on day one, however they do commit to having an action plan for accessibility if their drug does make it through regulatory and eventual release. When asked, Kevin Outterson explained that, "every company signs the same paper whether it's a big company or small company… [But] obligations to publicly reduce and transparently publish the stewardship and access plan was moved closer…to drug approval so that we didn't waste the time with the 29 projects are going to die for science reasons along the way."[522] This locks in the commitment from the developer, but does not put undue pressure on that developer at stages of the research process where pre-emptively planning may cause an undue burden on the business.

[517] CARB-X, "CARB-X Funding," Corporate, October 24, 2016, https://web.archive.org/web/20161024172315/http://www.carb-x.org/funding.
[518] TRL here stands for "Technology Readiness Level" and indicates the 3-6 steps of a nine-step scale from base conception of a potential technology to actual in hand deliverability and use of that technology. Steps 3-6 generally span from initial proof of concept, through the validation in laboratory environment, to prototype demonstration. In essence, CARB-X does not accept any projects that are merely theoretical with no evidence to support eventual practicality, but it also does not accept projects that are fully realized. For more information on the TRL spectrum, please consult:
[519] CARBX 2016-2017 Annual report page 2
[520] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
[521] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
[522] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.

The implementation of the access requirement was met with some concern by funding organizations initially. Although the United States had shown hesitancy on delinking models or on models that leaned too heavily into access regulations in the past, by 2017 "every single recipient of every CARB-X award from the beginning" had "public-transparent stewardship access requirements" including in their remit "and that was with the US government's blessing, and obviously with Wellcome's enthusiasm and support."[523] This change echoed an evolving industry and governmental awareness of the need to include access to medicines within the Dry AP, and indicates just how clearly these two concepts were becoming more publicly intertwined.

Despite being hosted by a university, CARB-X projects do not experience the same kind of university/industry pairing that IMI projects experienced. There is no consortium of public and private enterprises coming together to work on a similar topic of interest. Rather, specific companies that are already well on their way to developing a feasible product approach CARB-X for funding and assistance, and CARB-X reviews their file for what is specifically in need. This can come in the form of start-up push funding, or it can also involve scientific experts, that the originator company may not have access to, being assigned to assist in the company's work.[524] This allows for the primary work to be undertaken by the originator/applicant with oversight, assistance, and financial support offered by CARB-X, with the end goal of advancing through to phase two or three clinical trials (and of course eventually a product on the market). CARB-X does not fund projects past phase one work, but qualifies and assists companies through that phase one work so promising molecules have a greater chance of success. It should also be noted that there is no preference to Boston University students or applicants interested in participating in CARB-X funded projects. An

[523] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 49.
[524] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.

external panel of scientists review the applications received, and to date there has been no BU project funded or sponsored by CARB-X. [525]

Growth for CARB-X was not slow. John Rex projected that in their first year they would be happy to end with five funded projects; they ended with twenty.[526] The constant growth required their original team size to double and expand each year until it reached its current count of roughly 29-30 people. [527] Similarly, its funders continued to expand. Eight years after its launch, CARB-X was receiving funding from four G7 countries and three major funding organizations including: ASPR, BARDA, NIAID, Wellcome Trust, the German Ministry of Education and Research, Novo Nordisk Foundation, United Kingdom's Department of health and Social Care and its Global Antimicrobial Resistance Innovation Fund, The Public Health Agency of Canada, Bill & Melinda Gates Foundation. [528] By 2024, they had funded 100 innovative projects, from thirteen different countries, leading to "fistfuls of patents,"[529] twelve projects that had advanced to human clinical trials, and two new pathways for diagnostic capabilities, for a combined total of roughly $454.2 million (roughly an average of $58 million per year) in investment funds. [530]

CARB-X's fourteen "graduates" (as those who successfully transition from phase one to phase two or three clinical trials are called) range from small-medium enterprises such as Cambridge, Massachusetts based Vedanta Biosciences, to large pharmaceutical companies like GSK. Not all companies that work with CARB-X graduate the program, however. A rate of attrition is naturally expected in science and there is no expectation for a 100% success

[525] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
[526] John Rex, Interview by Erin. L. Paterson, 4 March 2024.
[527] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
[528] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
and: CARB-X, "Funding Partners," 2024, https://carb-x.org/partners/funding-partners/.
[529] Of note, these patents do not belong to CARB-X but rather to the applicant and originator companies involved in the research, however as they are considered patents that were a result of CARB-X funding they are listed as a result of CARB-X interventions.
[530] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
and: CARB-X, "CARB-X," 2024. https://carb-x.org/

rate for funded projects. Termination of projects can come as a result of some kind of technical or regulatory failure, and a cessation of funds occurs when there is no clear path of efficacy for the product in question. [531] More than fifty projects have been terminated in this manner since CARB-X's founding.

For the companies that do manage to graduate the CARB-X program there are additional considerations that must be considered: where to find additional funding? And, should their product make it through regulatory approval, what steps do they intend to take to ensure that product's accessibility? For the first component, it can be a complicated matter of finding additional funding. While CARB-X graduate status does offer external funders the understanding that the work product has been vetted, supported, and reviewed by a team of experts throughout the product's development, there are no guarantees of additional funding options. BARDA, one of CARB-X's largest donors, is also one of the largest pull funders of antibiotics in the world, and it does consider CARB-X graduates. [532] AMR Action Fund, another large donor and funder of AMR research, has funded seven projects so far. Five have received prior CARB-X funding. [533] [534]

Where IMI had been concerned about potential zombie projects that continue forever with no clear end date, CARB-X's structure was not built with that in mind. Rather, CARB-X's work is supported via the donations of governments and funding groups, and therefore its longevity is guaranteed only so long as those entities are satisfied with the work that they do. There is no pre-determined end date to the funding, and funders are capable of renewing

[531] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
[532] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
and: Portfolio Company, "Spotlight Vedanta Biosciences," Corporate, November 20, 2020, https://carb-x.org/spotlight/spotlight-vedanta-biosciences/.
[533] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
and: CARB-X, "CARB-X," 2024, https://carb-x.org/
[534] AMR Action Fund, "Our Portfolio," 2024, https://www.amractionfund.com/investments#our-portfolio
These projects include: BIOVERSYS, Pattern, Vedanta Biosciences, Venatorx Pharmaceuticals, and ANTABIO.

without set termination being the expectation. So far, at time of writing, it has continued to be renewed and new government entities continue to be negotiated with. [535]

V. WHO and MSF response to developing antibiotics: DNDi and GARDP

Concerns about what happens post CARB-X sponsorship, however are still omnipresent. In one review, BARDA representatives observed between 2010 and 2020 the "successful clinical development of multiple products, and then subsequent commercial failures or bankruptcies that resulted because we were missing a holistic ecosystem of support." [536] The financial constraints that were limiting SMEs still existed and pull funding that supported these businesses through to regulatory approval were still necessary. At the same time that CARB-X was launching in the United States, though, another PPP directly targeting this aspect of the Dry AP was launching in Europe.

Like IMI, the Drugs for Neglected Diseases Initiative (DNDi) was not developed exclusively for the consideration of antimicrobial resistance. It was developed following Médecins Sans Frontières winning the Nobel Peace prize in 1999, the news of their win coming while members of MSF were gathered at an international meeting in Paris to discuss the potential for a research and development treaty.[537] And with the prestige of the award, came nearly $1 million in prize funds (nearly $2 million at time of writing).[538] Encouraged by James Love, the then President of the MSF International Council, James Orbinski, determined that the money would be dedicated to supporting the access and development of

[535] Kevin Outterson, Interview by Erin L. Paterson, 12 April 2024.
and: CARB-X, "CARB-X," 2024, https://carb-x.org/
[536] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 40.
[537] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 62.
[538] Charles Trueheart, "Medical Aid Group Wins Nobel Prize," *Washington Post*, October 15, 1999, https://www.washingtonpost.com/archive/politics/1999/10/16/medical-aid-group-wins-nobel-prize/7d899d39-9ec5-462f-9921-9b0d1061680e/.

new medicines targeting diseases without current/updated treatments.[539] [540] In 2003, MSF joined five other partners, the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia and France's Pasteur Institute, and the UNDP / World Bank / WHO's Special Programme for Research and Training in Tropical Diseases (TDR), to create DNDi.[541] It would be the first health care related product development partnership targeting neglected diseases specifically, and it began its product development with a treatment for sleeping sickness (Fexinidazole) in 2005.

The choice to develop DNDi as a PDP was not an easy one, and was the product of multiple conversations on how best to use the funds to create the greatest amount of impact. The research and development treaty that MSF had originally been meeting in Paris to discuss was not considered a likely treaty to pass due to different priorities of industry and government actors.[542] However, there was evidence that the PDP/PPP model worked. The Medicines for Malaria Venture and TB Alliance were already several years old by this point and were starting to show interesting results.[543] The model was seen to be something that "work[ed]" and therefore could get additional support and approval.[544] With the focus on neglected diseases especially, private companies such as Novartis, GlaxoSmithKline, and Merck Sharp & Dohme showed support for the initiative. Paul Stoffels from Novartis, is remembered to have said that "It is okay if you do what we as industry will not do because it is not commercially interesting."[545] In this way, DNDi was able to launch, with both the public and private support needed to provide it with enough capital to begin its work.

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[539] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 62.
[540] MSF Access Campaign, "MSF Access Campaign About Us," 2024. https://www.msfaccess.org/about-us.
[541] Julia Tuttle, "Drug Development for Neglected Tropical Diseases: DNDi and the Product Development Partnership (PDP) Model," (Thesis, Duke University, United States 2016), 39.
[542] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 62.
[543] For more information regarding MMV, consult: Medicines for Malaria Venture, "About Us," Accessed January 19, 2024, https://www.mmv.org/about-us.
[544] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 39-40.
[545] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 47.

DNDi's mission statement and goals were tightly aligned with MSF, and its method of operation was equally constructed with MSF's activism in mind.[546] On the MSF Access Campaign website, DNDi's mission statement reads that it:

> will develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Acting in the public interest, it will bridge the existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.[547]

From a purely results oriented perspective, it has made good on these promises. Since 2003 it has been responsible for bringing 13 new treatments to market (with a goal to reach 25 by 2028) in the fields of sleeping sickness, hepatis-c, malaria, Chagas disease, leishmaniasis, HIV-visceral leishmaniasis co-infection, and pediatric HIV.[548] Notably, though, it had not branched into the domain of antibiotic drug access development.

In 2014, the WHO released its report on antimicrobial resistance.[549] Following its release, member states requested that the WHO provide an action plan to be disseminated in 2015.[550] This action plan targeted the need for antibiotic production, and like the Priority Medicines Report before it, reiterated a need for public private partnerships as a financial model that would structure developmental needs.[551] Its mention, however, was limited in scope. Structurally, the Action Plan highlighted five key objectives, highlighting a need for awareness and understanding, communication and knowledge gathering, infection prevention and control, optimization of antibiotic use, before finally resorting to economic incentives.[552]

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[546] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 47-48.
[547] MSF Access Campaign, "DNDi, the Drugs for Neglected Diseases Initiative: An Innovative Solution," February 13, 2003, https://msfaccess.org/dndi-drugs-neglected-diseases-initiative-innovative-solution-0.
[548] DNDi, "Delivering Better Treatments for Neglected Patients," Treatments Delivered, 2023. https://dndi.org/research-development/treatments-delivered/.
[549] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 17. World Health Organization, "Antimicrobial Resistance Global Report on Surveillance 2014," (Geneva, Switzerland: World Health Organization, 2014).
[550] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 18.
[551] World Health Organization, *Global Action Plan on Antimicrobial Resistance*, (Geneva, Switzerland: World Health Organization, 2015), 19.
[552] World Health Organization, *Global Action Plan on Antimicrobial Resistance*.

Public Private Partnerships were only mentioned once, and only under the actions that an individual member state could invest in rather than something the secretariat or international/national partnerships could participate in. The concern being, that innovation and pipeline discussions regarding AMR were a high-income country problem, and not something that directly related to the actions LMICs could participate in effectively.[553]

For Marie-Paule Kieny (French virologist and head of vaccine research at the WHO) and Peter Beyer (German lawyer with a specialization in intellectual property rights and the WHO's commitment to access to medicines), the WHO as an institution needed to go farther. They, and members of their team, wished to create a huge product development partnership (PDP), "where innovation was rewarded to academia in biotech with prizes and grants, in order to fuel discovery." [554] The intention was not to reimagine a new form of enterprise where the public sector becomes a producer, but rather establish a business where public funds would enable the private sector to have "complete stewardship over the production and innovation," on a sub-contract basis.[555] If the industry did not wish to create an antibiotic because they saw no value in the development of that antibiotic, then they would be incentivized to do so via the subcontract with the publicly funded enterprise.

In 2016, the WHO tapped DNDi as the PPP they wished to partner with, and between them both, came the Global Antibiotic Research and Development Partnership (GARDP). The former senior project manager and head of clinical development at DNDi/former Executive Director of MSF's Access Campaign, Manica Balasegaram stepped in first as Director and then Executive Director of the new partnership at its launch in 2016. As PDP, GARDP is highly selective on the work that it engages in, and it is limited in its size and scale due to its funding being roughly 98% solely from governmental bodies.[556] While its

[553] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 18.
[554] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 19.
[555] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 20.
[556] Anonymous Expert, Interview by Erin L. Paterson and Mirza Alas Portillo. 2 February 2024.

largest funding partners are Germany and the UK, the Indian Council of Medical Research and South African governments have both been invaluable to their work as they both see a direct need for the products proposed by GARDP within their own communities.[557] GARDP's budget averaged to roughly 30 million euros per year.[558] IMI1/2 by comparison operated all of its projects within a span of around 400-546 million euros per year,[559] with specifically the entire ND4BB project costing around 700 million[560] and AMR Accelerator (at time of writing) costing 489 million during their runs.[561]

While these numbers seem deeply out of proportion, it is only due to the mass scale of projects within the IMI1/2 program lists. Below, I have generated a chart showing the span of all antibiotic projects (PreDiCT-TB, ND4BB, and AMR-Accelerator) within the IMI1/2 packages. Using their publicly posted budgets from the IMI website, I rounded the total funding to the nearest million for ease of convenience. Then, I calculated the date span listed under each project's work package and determined the exact budget per year allocated to those projects as a result.

[557] Anonymous Expert, Interview by Erin L. Paterson and Mirza Alas Portillo. 2 February 2024.
[558] Anonymous Expert, Interview by Erin L. Paterson and Mirza Alas Portillo. 2 February 2024.
[559] Innovative Medicines Initiative, "The IMI Funding Model," Europe's Partnership for Health, Accessed April 9, 2024, https://www.imi.europa.eu/about-imi/imi-funding-model.
[560] Innovative Medicines Initiative, "New Drugs For Bad Bugs The Innovative Medicines Initiative Response to Antimicrobial Resistance," IMI 2 Joint Undertaking, 2017.
[561] IMI AMR Accelerator. "AMR Accelerator Project Portfolio." Accessed April 5, 2024. https://amr-accelerator.eu.

Program Affiliation	Program Name	Date Span	Years Active	Total Funding in € Millions (rounded)	Budget Per Year in € Millions (rounded)
IMI1	PreDiCT-TB[562]	May 2012-October 2017	5.5	29 M	5.27 M
IMI1 ND4BB	TRANSLOCATION[563]	January 2013 – June 2018	5.5	30M	5.45 M
IMI1 ND4BB	COMBACTE-CARE[564]	March 2015-June 2023	8.3	84 M	10.12 M
IMI1 ND4BB	COMBACTE-MAGNET[565]	January 2015-December 2022	7	90 M	12.85 M
IMI1 ND4BB	COMBACTE-NET[566]	January 2013-October 2023	10.83	213 M	19.66 M
IMI1 ND4BB	COMBACTE-CDI[567]	November 2017-April 2021	3.25	4 M	1.23 M
IMI1 ND4BB	iABC[568]	August 2015-June 2023	7.83	56 M	7.15 M
IMI1 ND4BB	DRIVE-AB[569]	October 2014-December 2017	2.16	11 M	5.1 M
IMI1 ND4BB	ENABLE[570]	February 2014-October 2021	7.66	101 M	13.19 M
IMI2 AMR Accelerator	PRIMAVERA[571]	January 2021-October 2026	4.83	9 M	1.86 M

[562] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | PreDiCT-TB | Model-Based Preclinical Development of Anti-Tuberculosis Drug Combinations," May 1, 2012, http://www.imi.europa.eu/projects-results/project-factsheets/predict-tb.
[563] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | TRANSLOCATION | Molecular Basis of the Bacterial Cell Wall Permeability," January 1, 2013, http://www.imi.europa.eu/projects-results/project-factsheets/translocation.
[564] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | COMBACTE-CARE | Combatting Bacterial Resistance in Europe - Carbapenem Resistance," March 1, 2015, http://www.imi.europa.eu/projects-results/project-factsheets/combacte-care.
[565] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | COMBACTE-MAGNET | Combatting Bacterial Resistance in Europe - Molecules against Gram Negative Infections," January 1, 2015, http://www.imi.europa.eu/projects-results/project-factsheets/combacte-magnet.
[566] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | COMBACTE-NET | Combatting Bacterial Resistance in Europe," January 1, 2013, http://www.imi.europa.eu/projects-results/project-factsheets/combacte-net.
[567] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | COMBACTE-CDI | Combatting Bacterial Resistance in Europe - Clostridium Difficile Infections," November 1, 2017, http://www.imi.europa.eu/projects-results/project-factsheets/combacte-cdi.
[568] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | iABC | Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis," August 1, 2015, http://www.imi.europa.eu/projects-results/project-factsheets/iabc.
[569] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | DRIVE-AB | Driving Re-Investment in R&D and Responsible Antibiotic Use," October 1, 2014, http://www.imi.europa.eu/projects-results/project-factsheets/drive-ab.
[570] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | ENABLE | European Gram-Negative Antibacterial Engine," February 1, 2014, http://www.imi.europa.eu/projects-results/project-factsheets/enable.
[571] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | PRIMAVERA | Predicting the Impact of Monoclonal Antibodies & Vaccines on Antimicrobial Resistance," November 1, 2021, http://www.imi.europa.eu/projects-results/project-factsheets/primavera.

IMI2 AMR Accelerator	RespiriNTM[572]	May 2019-April 2025	6	8 M	1.33 M
IMI2 AMR Accelerator	TRIC-TB[573]	May 2019-February 2024	4.83	8 M	1.65 M
IMI2 AMR Accelerator	RespiriTB[574]	May 2019-April 2025	6	10 M	1.66 M
IMI2 AMR Accelerator	UNITE4TB[575]	June 2021-May 2028	7	185 M	26.4 M
IMI2 AMR Accelerator	ERA4TB[576]	January 2020-December 2025	5	208 M	41.6 M
IMI2	VALUE-DX[577]	April 2019-September 2024	5.75	4 M	0.7 M
IMI2 AMR Accelerator	AB-Direct[578]	July 2019-September 2023	4.16	4 M	0.96 M
IMI2 AMR Accelerator	COMBINE[579]	November 2019-October 2025	6	25 M	4.16 M
IMI2 AMR Accelerator	GNA NOW[580]	July 2019-June 2025	6	31 M	5.16 M

Table 3 IMI Programs and Budgetary Comparisons

The average budget allocated per project rested at € 8.7 million (strong outliers to this calculation include Value-DX and AB-Direct on the low end, and UNITE4TB and ERA4TB on the high end. Excluding these four projects drops the average annual budget to €6.38 million instead). With these figures in mind, GARDP's annual budget of €30 million would

[572] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | RespiriNTM | Progress Novel Assets (One FIH Start) for Non-Tubercular Mycobacteria That May Act Synergistically with Bedaquiline and Cytochrome Bc Drugs," May 1, 2019, http://www.imi.europa.eu/projects-results/project-factsheets/respirintm.
[573] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | TRIC-TB | Boosting Ethionamide Efficacy and Lowering the Dose with a Small Molecule Transcriptional Modulators, to Overcoming MDR-TB Infections and Define a New Place for Ethionamide in 1st-Line TB Treatments," May 1, 2019, http://www.imi.europa.eu/projects-results/project-factsheets/tric-tb.
[574] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | RespiriTB | Progress New Assets (One Pre-New Molecular Entity and One First-Time-in-Human Start) for Tuberculosis That Act Synergistically with Bedaquiline, Cytochrome Bc or Cytochrome Bd Inhibitors," May 1, 2019, http://www.imi.europa.eu/projects-results/project-factsheets/respiritb.
[575] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | UNITE4TB | Academia and Industry United Innovation and Treatment for Tuberculosis," June 1, 2021, http://www.imi.europa.eu/projects-results/project-factsheets/unite4tb.
[576] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | ERA4TB | European Regimen Accelerator for Tuberculosis," January 1, 2020, http://www.imi.europa.eu/projects-results/project-factsheets/era4tb.
[577] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | VALUE-Dx | The Value of Diagnostics to Combat Antimicrobial Resistance by Optimising Antibiotic Use," April 1, 2019, http://www.imi.europa.eu/projects-results/project-factsheets/value-dx.
[578] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | AB-Direct | Antibiotic Distribution and Recovery in Tissue," July 1, 2019, http://www.imi.europa.eu/projects-results/project-factsheets/ab-direct.
[579] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | COMBINE | Collaboration for Prevention and Treatment of MDR Bacterial Infections," November 1, 2019, http://www.imi.europa.eu/projects-results/project-factsheets/combine.
[580] IMI Innovative Medicines Initiative, "IMI Innovative Medicines Initiative | GNA NOW | Novel Gram-Negative Antibiotic Now," July 1, 2019, http://www.imi.europa.eu/projects-results/project-factsheets/gna-now.

safely cover the costs of three unique projects of similar size, potentially expanding to five with proper oversight and consideration. At time of writing, it is exactly five products that have been involved in GARDP's product development cycle.

The five products GARDP is working on span three different kinds of bacterial infection: serious bacterial infection & sepsis, neonatal sepsis, and sexually transmitted infections. In 2019, GARDP announced its intentions to deliver five products by 2025. By late 2024, it seemed evident they would miss that goal. While one of their new drug candidates, zoliflodacin (intended for treatment of *Neisseria gonorrhoeae),* continues through clinical trials with potential regulatory approval estimated for 2025, the carbapenem-resistant *Enterobacteriaceae* (CRE) drug they had hoped would gain approval in first, cefepime-taniborbactam, was instead rejected by the FDA in February 2024. [581] [582] Two other treatments listed in their 2024-2028 Pipeline agenda for treatment of sepsis related diseases were in state of trial and analysis in 2023, leaving only their work with cefiderocol remaining.[583]

Cefiderocol is a cephalosporin CRE drug that was originally marketed by Shionogi under the brand name *Fetroja* in 2020. Its unique feature comes from its method of utilizing an iron collecting siderophore to gain access through the bacterial cell wall. As the bacteria requires iron to survive, and is habituated to siderophore's retrieving iron and supplying the cell with energy as a result, the method of sneaking in via the siderophore's general access serves as a "trojan horse" entry for the antibiotic.[584] While siderophore research began in the

[581] GARDP, "2024–2028 Strategy: Putting Public Health Needs at the Centre of Antibiotic Drug Development," (Geneva, Switzerland: GARDP, 2023).
[582] Chris Dall, "FDA Rejects New Drug Application for Cefepime-Taniborbactam." *CIDRAP*, (Minnesota, United States: University of Minnesota February 27, 2024), https://www.cidrap.umn.edu/antimicrobial-stewardship/fda-rejects-new-drug-application-cefepime-taniborbactam.
[583] GARDP, "2024–2028 Strategy: Putting Public Health Needs at the Centre of Antibiotic Drug Development," (Geneva, Switzerland: GARDP, 2023).
[584] Takafumi Sato and Kenji Yamawaki, "Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin," *Clinical Infectious Diseases* 69, no. Supplement 7, November 13, 2019: S538, https://doi.org/10.1093/cid/ciz826.

1980s, Shionogi first identified the siderophore cephalosporin potential that would lead to cefiderocol in the 1990s.[585] With its unique features, it showed surprising stability against the three common β-lactamases which often triggered bacterial resistance in antibiotics such as carbapenems.[586] In the United States, the FDA approved it for use against complicated urinary tract infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia in 2019, with the European Medicines Agency granting regulatory approval for use against gram negative bacteria in 2020.[587] That same year, Shionogi submitted cefiderocol to the WHO's essential medicines list,[588] and it was subsequently included on the EML in 2021 as a reserve antibiotic.[589]

Shionogi developed cefiderocol with the support of British pharmaceutical company GlaxoSmithKline (GSK) and the venture capital work of Chinese insurance group, Ping An Insurance, under the auspices of creating a drug that would be accessible to those in LMICs.[590] When Shionogi, GARDP, and the Clinton Health Access Initiative began to discuss their potential partnership, GSK agreed to forgo its royalties on cefiderocol in all sales within LMICs.[591] Ping An's venture capital branch, Ping An-Shionogi Hong Kong,

[585] Takafumi Sato and Kenji Yamawaki, "Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin," *Clinical Infectious Diseases 69*, no. Supplement 7, November 13, 2019: S538, https://doi.org/10.1093/cid/ciz826.
[586] Takafumi Sato and Kenji Yamawaki, "Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin," *Clinical Infectious Diseases* 69, no. Supplement 7, November 13, 2019: S538, https://doi.org/10.1093/cid/ciz826.
[587] José Tiago Silva and Francisco López-Medrano, "Cefiderocol, a New Antibiotic against Multidrug-Resistant Gram-Negative Bacteria," *Revista Española de Quimioterapia* 34, no. Suppl 1, September 30, 2021: 41, https://doi.org/10.37201/req/s01.12.2021.
[588] Takuko Sawada, "Application to Request the Inclusion of Cefiderocol on the World Health Organization Model List of Essential Medicine," Cover Letter, November 30, 2020, World Health Organization. https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.7_cefiderocol.pdf?sfvrsn=db365d99_4.
[589] World Health Organization, "Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2021 (Including the 22nd WHO Model List of Essential Medicines and the 8th WHO Model List of Essential Medicines for Children)," WHO Technical Report Series, The Selection and Use of Essential Medicines, (Geneva, Switzerland: World Health Organization, 2021), ix.
[590] GARDP, "Shionogi, GARDP and CHAI Announce Landmark License and Collaboration Agreements to Treat Bacterial Infections by Expanding Access to Cefiderocol in 135 Countries," Corporate, June 15, 2022, https://gardp.org/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries/.
[591] Shionogi, "Shionogi, GARDP and CHAI Announce Landmark License and Collaboration Agreements To Treat Bacterial Infections by Expanding Access to Cefiderocol in 135 Countries," Corporate, News (blog), June

retained its exclusive development and commercialization rights for cefiderocol in Asian territories,[592] but beyond its scope GARDP and CHAI stepped into place. Although they did not assist in the development of the drug, their licensing agreement post development was dedicated strictly to the principle of ensure the accessibility of the drug on a global scale. Specifically:

> Under this agreement, GARDP will manufacture and commercialize cefiderocol through sub-licensees in a large range of countries that have delayed access (if any) to newer antibiotics. The license territory includes all low-income countries, most lower middle- and upper middle-income countries, and select high-income countries (135 countries total, almost 70% of countries worldwide). It includes a significant proportion of the world's population living in areas most affected by antibiotic resistance.[593] [594]

In this instance, the product *development* aspect of GARDP's structure gave way to the more MSF leaning commitments that drove DNDi (and eventually GARDP's) creation, e.g.: access and accessibility.

This licensing agreement offers a unique representation of how a public private partnership can facilitate access needs for antibiotics that do make their way through development pipelines. DNDi and GARDP were more conceived with product development in mind, but rather than stopping at mere product creation, they have worked to shore up the "second pipe" in my reconceived pipeline. Antibiotic development, with no ability to ensure that product reaches a patient fails in antibiotic accessibility, and in this case, despite the

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14, 2022, https://www.shionogi.com/us/en/news/2022/06/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries.html.

[592] Shionogi, "Execution of Sublicense Agreement with JEIL for New Siderophore Cephalosporin Antibacterial Drug Cefiderocol in South Korea," Corporate, News, July 28, 2022, https://www.shionogi.com/global/en/news/2022/07/20220728.html.

[593] Shionogi, "Shionogi, GARDP and CHAI Announce Landmark License and Collaboration Agreements To Treat Bacterial Infections by Expanding Access to Cefiderocol in 135 Countries," Corporate, News (blog), June 14, 2022, https://www.shionogi.com/us/en/news/2022/06/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries.html.

[594] A complete list of all countries was published in the publicly available version of the licensing agreement between Shionogi and GARDP in 2022. It can be located at: Shionogi and GARDP, "License and Technology Transfer Agreement (Execution Version)," Shionogi & Co., Ltd., 2022, https://gardp.org/uploads/2022/06/License-and-Technology-Transfer-Agreement.pdf.

delays in their in-house development GARDP's commitment to health care needs has been very clearly emphasized by their work with cefiderocol.

Shionogi and their private partners developed cefiderocol under financially difficult circumstances, and without public assistance to ensure drugs are financially accessible to LMICs. It is likely that those LMICs would have strained to provide access to cefiderocol without outside assistance. For watch dog groups such as the Access to Medicines Foundation, the work done to ensure cefiderocol's access has been of particularly admirable. Their "exciting partnership" highlights exactly the kind of benefits that PPP can have in ensuring access to future medication.[595] GARDP and CHAI's work here, eases the burden on the pharmaceutical manufacturer's side. Exact finances of the agreement, sales figures, and impact on the corporations is currently unavailable, and likely too recent to provide a clear picture on overall approval, quality, or impact, but the groundwork is set to review this partnership and its impact over the next few years. GARDP may not have reached its 5 by 25 goal as it had originally hoped for, but it has eased the way for at least one major drug to reach 70% of the world's nations by 2025 and it certainly makes a start for the overall "global public health mission" their organization as founded to address.[596]

VI. Discussion: the antibiotic pipeline as a part of an antibiotic access infrastructure and the funding necessary to keep that pipeline active

The Introduction and Chapter One both discussed the historical and practical perceptions of the antibiotic pipeline. This chapter revealed the state of that pipeline from the early 2000s through 2023. Rather than in-house development by a single (privately operated) pharmaceutical company, the creation of Public Private Partnerships has allowed for new antibiotic development in a space where relatively few unique molecules have successfully

[595] Martijn Van Gerven, Interview with Erin L. Paterson, 23 August 2023.
[596] Anonymous Expert, Interview by Erin L. Paterson and Mirza Alas Portillo, 2 February 2024.

made it through to marketing approval. Chapter Two emphasized the need for those new antibiotics to be made, as rising rates of antimicrobial resistance were causing the antibacterial section of the essential medicines list to lose some of its efficacy in practice. Lack of effective medications that can treat resistant strains, and an inability to fully support those health needs, revealed a gap – or a crack – in infrastructure meant to support antibiotics as a key component of health care. The antibiotic pipeline is a necessary part of that infrastructure, but its struggles – primarily driven by financial uncertainty, were profound.

The IMI was one of the first major PPPs that targeted antimicrobial resistance. Although TB Alliance pre-dates IMI, having been founded in 2002, TB Alliance's focus was on tuberculosis and resistant strains of TB only. IMI, with its variety of projects and programs beneath its ND4BB umbrella, was not nearly so precise. The pipeline that it targeted was one that balanced an educational pathway for new scientists to understand the bacterial research field, and in-depth pre-clinical research that could provide for greater understanding when it came time to actually develop a drug. As it was, however, no drug did emerge from IMI.

In 2011, the chief medical officer of the United Kingdom, Dame Sally Davies, published her perception on the status of infectious diseases in the UK. She stated that

> The supply of new classes of antimicrobial agents for future use has slowed over the last few decades in contrast to drug development for other conditions. This is in part due to the scientific challenge associated with the problem but is also partly due to the conditions of the market for new pharmaceuticals. Antimicrobial agents are used sparingly and for short duration. Over time, they are subject to diminished efficacy due to the development of antimicrobial resistance. Sometimes they are withheld for the future, limiting the profitability of a fixed term patent. Moreover trial requirements are onerous and costly. There are fewer economic incentives to produce new antimicrobial agents than there are for other classes of drug – a market failure. If we are to secure a 'pipeline' of new antimicrobial drugs for the future then we must align the private and societal risks, and the costs and benefits of research and development of these agents.[597]

[597] Davies, Sally C.: "Chief Medical Officer's Summary", in: *Annual Report of the Chief Medical Officer. Volume Two, 2011: Infections and the rise of antimicrobial resistance* (London, 2011), 20.

Her use of the words "market failure" and "pipeline" highlight the juxtaposition between the financial components of this infrastructure, and the actual outputs that are expected. In most cases, a product is developed and sold because a population requires that product. There is little doubt that antibiotics are a requisite part of society. Clare Chandler's work declaring the drug an infrastructure, supporting the health care and productivity needs of the world, make that clear. [598] But this is a product that should only be used in limited circumstances, and as rates of AMR are currently non-catastrophic, the sales potential and profit margins for these efficacious drugs are too low for private companies to take part.

During the 2024 witness seminar, these concerns regarding markets and market incentives highlighted the problems with IMI and its potential outputs as well as highlighting the tension within the pipeline discourse. If the market needed to be catered to, what did that mean for the kinds of drugs that could make it through the pipeline? How would they be funded? And furthermore – what kind of access would be seen on the other end?[599] In essence, how best can this infrastructure be supported and maintained to ensure continued development of and access to effective medication?

In all cases of PPPs, finances are managed via either a push or pull, where money is either injected into the company to help incentivize development, or added at the end of a product's life cycle to help pull it through clinical trials, market authorization and launch. The companies and individuals that help finance this work range from governmental bodies, NGOs, universities, or philanthropic donation schemes from private funders. As a matter of course, these PPPs are built around a public interest (in this case, the development of effective antibiotics that populations in need can access), but these public interests are not financially lucrative enough for private institutions to address them on their own without

[598] Chandler, "Current Accounts of Antimicrobial Resistance," 9.
[599] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 69-71.

public support. In each of these cases, the end products are, also, dependent on the patent monopoly system as it stands.

Since the 1990s, James Love and bioinformatician, Tim Hubbard, have been speaking with pharmaceutical companies, governments, and NGOs about alternative financial options that do not rely on this system.[600] Their suggestions have not been put into practice, and therefore are not the subject of this dissertation. However, understanding their ideas and the context in which they are given can provide insight to why the structure of antibiotic development has been formed the way it has, and where the pathways of resistance in terms of changing this structure have been most notable. Two of their most debated ideas included a prize fund or a Market Entry Reward (MER) that would be granted to a successful product reaching the market, and an open-source science dividend that would be provided to any group of researchers willing to make their research open source for the betterment and continuation of innovation for all.[601]

The MER is an outcome-based pull incentive that is intended to be a set fund known each year in advance. It would be a percentage of each participating country's GDP. For example, in 2012 Senator Bernie Sanders suggested a Medical Innovation Prize Act to the United States' 109th congress in the form of 0.55% of the US GDP amounting to then $86 billion.[602] Rather than the structure of the Longitude Prize which awarded a large financial reward for any company that met an increasingly difficult standard of accomplishment, James Love suggested that the prize be given to *any* company that developed a drug that received FDA approval and went on the market.[603] For ten years the drug would be entered into the prize fund competition and would receive money based on the drug's proven efficacy, the

[600] James Love, Interview by Erin L. Paterson, 30 April 2024.
[601] James Love, Interview by Erin L. Paterson, 30 April 2024.
[602] Ezra Klein, "What Happened to Bernie Sanders's Best Idea?" Vox, September 25, 2015. https://www.vox.com/2015/9/25/9397069/bernie-sanders-drug-prices.
[603] James Love, Interview by Erin L. Paterson, 30 April 2024.

number of patients treated, and its superiority to other drugs on the market.[604] The better the drug, the more money the company would receive. Should a drug be designed for a small population, such as the case with a drug with orphan disease status (see Chapter Four), that would be taken into consideration as well.

Resistance to this idea was stark from the perspective of the pharmaceutical industry. As it stands, the industry is largely in the business of acquiring promising molecules from either academic sources or SMEs, then (depending on the stage of molecular development) they either help bring those drugs through to marketing approval and sell them under their own name, or they begin the sales process directly.[605] If an academic/university or an SME is capable of preparing a drug and selling it directly to a government entity directly and establish a global patent free license that allows for the immediate generic manufacturing of that drug at a reduced rate – what would be the purpose or need of a large pharmaceutical company? [606]

The open-source science dividend places value on the role of science as a whole. It could take the form of an obligation on the part of patented drug sales, where 1-2% of drug sales revenue is set to the side in order to reward "persons who openly shared knowledge, data, materials and technology to drug developers," amounting to between $2.5-5 billion each year.[607] For scientific discovery, this dividend would encourage collaboration between scientists rather than the hoarding of so-called proprietary data. Arguably, the more eyes on the problem the more possibilities could emerge, thus innovation is stimulated. However, it is difficult determine the exact impact and *financial* value of each open-source contribution. As

[604] James Love, Interview by Erin L. Paterson, 30 April 2024.
[605] Stuart Hogarth, 2022, "The Fish and the Bicycle – antibiotic innovation and pharmaceutical firms," Paper presented at Boom, Bust and Antibiotics: Opening conference of the DryAP project, Oslo, 9 June 2022.
[606] James Love, Interview by Erin L. Paterson, 30 April 2024.
[607] Managing IP Correspondent. "The Value of an Open Source Dividend." *Managing IP*, October 15, 2014. https://www.managingip.com/article/2a5cj84o834chg3q8zaio/the-value-of-an-open-source-dividend.

James Love himself put it, “how do you value whether someone creates an open-source database or develops a reagent?”[608] This is particularly true in terms of long-term impact. If something put into open source is not utilized for several years, but then is used in great quantities as scientists discover new uses for it: how should the original scientist be compensated? These questions and complaints limited MERs and open dividends from even being seriously considered as growing fear about the lack of effective antibiotics began to outpace global standards of stewardship and surveillance when it came to AMR.

James Love’s alternative suggestions for developing a funding apparatus for drug or antibiotic development, have not yet come to fruition. But he has continued to discuss these ideas with industry and government representatives since the 90s. He has also reviewed and assessed the PPPs that have formed in lieu of his suggestions and worked with many of the actors discussed within this chapter thus far. In an interview on 30 April 2024, I asked Love perspective on the status of PPPs and the other financial options available, which he thought were better, and which he thought were more necessary. He responded by saying there was a need for both, and indeed a need for greater nuance or complexity in the discussions of both. However, “nuance is the death” of his field due to the deep desire to have one answer to cleanly fix all problems.[609] He then proceeded to cite a conversation he had with Duke law professor Jamie Boyle who responded to a similar question Love had posed to him by allegedly stating:

> Each of these instruments has its own strengths and weaknesses. And it's a mistake to think of which one is the best one and let's put all of our money into that system…A balanced system, where you use a combination of instruments is going to work better. There are obviously some areas where the grant system is the best way to go. If you want to develop a scientific basis of things, you want to keep certain kinds of institutions alive, if you want to sort of do a lot of things that are just too pre-competitive to really be thought of his products: if you don't have a grant system, it's going to be a real big problem.[610]

[608] James Love, Interview by Erin L. Paterson, 30 April 2024.
[609] James Love, Interview by Erin L. Paterson, 30 April 2024.
[610] James Love, Interview by Erin L. Paterson, 30 April 2024.

Grants, which form the basis of much of the push funding offered by BARDA and a large component of clinical trial coverage for drugs that do make it that far in the development cycle for other PPPs mentioned in this chapter, are enormously supportive of the work conducted by these enterprises.[611] However these grants may not be efficacious enough, and the need for more diversity in funding schemes to accentuate the PPP and antibiotic development sphere, particularly those that address accessibility issues once a drug is created, is evident due to the slow progress that is still being made.

Conclusion

The antibiotic research and development pipeline is a part of the infrastructure that allows for antibiotics to *be* an infrastructure. Without new drugs, there is a high likelihood that antimicrobial resistance will one day outpace our current stewardship efforts to the point that antibiotics could be ineffective leading to a post-antibiotic era.[612] The "dry pipeline" narrative, first discussed in Chapter One, shines a light on how a part of the antibiotic infrastructure was crumbling. New drugs were not effectively making their way through research and development or market phases.

In their book, *Le soin de choses,* Jérôme Denis and David Pontille state that to take care of something is a "fundamentally exploratory matter" (translation mine).[613] In other words, in order to maintain something effectively, new innovations and new understandings

[611] Himika Wasan, Devendra Singh, K.H. Reeta, and Yogendra Kumar Gupta, "Landscape of Push Funding in Antibiotic Research: Current Status and Way Forward," *Biology* 12, no. 1 (January 9, 2023): 101, https://doi.org/10.3390/biology12010101.

[612] For extended commentary on the potential for a post antibiotic era, please review:
Kristofer Hansson and Adam Brenthel, "Imagining a Post-Antibiotic Era: A Cultural Analysis of Crisis and Antibiotic Resistance," *Medical Humanities* 48, no. 3 (2022): 381–88. https://doi.org/10.1136/medhum-2022-012409.
Dominik Koesling and Claudia Bozzaro, "The Post-Antibiotic Era: An Existential Threat for Humanity," *Intergenerational Justice Review*, August 31, 2023, Vol. 8 No. 2 (2022): Existential and unknown risks for future generations (II), https://doi.org/10.24357/IGJR.8.2.1230.
Sara Reardon. "WHO Warns against 'post-Antibiotic' Era," *Nature*, April 30, 2014, https://doi.org/10.1038/nature.2014.15135.

[613] Jérôme Denis and David Pontille, *Le Soin de Choses : Politiques de La Maintenance,* (Paris : La Découverte, 2022) 225.

on how to address the needs of that thing are inherent to the process itself. The research and development pathway that was previously available, and the structure of pharmaceutical industries as a whole, had changed. With that change, came a need for a new way to develop antibiotics. Public Private Partnerships and Product Development Partnerships was the maintenance work applied to this infrastructure, and it is currently the maintenance that is most prevalent in the antibiotic development space at this time. These Partnerships serve as a method of financially easing the burden on corporations that had little interest in developing products with low returns on investment, and have been categorized as incentives that can both fix the market "failure" of antibiotics and the dry pipeline at once.

IMI, GARDP, and CARB-X each have incredibly different portfolios, as indicated in the Table 4 below. IMI was a European-wide PPP with a broad spectrum of individual programs. Its focus was not necessarily on the development of a product, but rather in educating a series of researchers so that they had a solid background in antibiotic development and were trained in inter-agency collaborations. While they do have a development branch that is still being funded by the Swedish government, as of time of writing: no product has made it past clinical trials or been launched onto the market. GARDP is a far smaller organization and is far more focused. It currently has several drugs still in development. As a younger organization, it is unsurprising that they do not yet have a drug on the market, but they have begun to submit their products to regulatory agencies for approval. It is likely they will succeed in bringing a drug to market within the coming years. In the meantime, they have invested in increased access to antibiotics via its partnership with Shionogi and have shown commitment to advancing access to antibiotics in general moving forward. Meanwhile, CARB-X has also not brought a drug to market as of time of writing. Created at the same time as GARDP, its funding apparatus has ensured over a dozen companies have managed to succeed through phase one clinical trials and are set up well for

future research success. Due to their partnership agreements that bind these companies to have a clear accessibility plan for any drugs developed, their impact on the dissemination future antibiotics will be of particular interest to those monitoring the antibiotic access space. The work of CARB-X and GARDP that followed IMI are complementary as one focuses on the early stages of development, and the latter focuses on later development. It will be interesting to see if future companies make use of this complementary nature in the future, by taking advantage of funding opportunities as they arise.

The purpose of detailing these initiatives and their work is not to critique their lack of producing an item ready for sale in 2024. In fact, considering that the expected time it takes to bring a drug to development is estimated to take 10-15 years,[614] each company has made commendable strides towards their stated goals. IMI's antibiotic development teams are still a work in progress, but its aim to educate a workforce capable of developing new antibiotics was clear from its start. Those involved in IMI projects have continued on to work in other antibiotic fields, supporting overall growth even if it cannot be directly linked back to IMI itself.[615] Without its own product in hand, GARDP has helped support antibiotic access with a needed new medication. And CARB-X's fourteen graduate programs far exceeds expectations for potential drug candidates developed in other spheres.

This chapter cannot make a final assessment on if the transition to PPPs has been a good move for antibiotic development compared to another pathway (such as Market Entry Rewards). However, it does provide a state of play as to what has happened since the early 2000s and what the current state of affairs are for antibiotics in this space at this moment.

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[614] Peter Corr and David Williams, "The Pathway from Idea to Regulatory Approval: Examples for Drug Development," In *Conflict of Interest in Medical Research, Education, and Practice*, edited by Bernard Lo and Marilyn J. Field, (Washington DC, United States: National Academies Press, 2009): 375, https://www.ncbi.nlm.nih.gov/books/NBK22930/.

[615] Ruxandra Draghia-Akli, Interview by Erin L. Paterson, 11 March 2024.
John Rex, Interview by Erin L. Paterson, 1 March 2024.

PPP/PDP	Date of Launch	Stated Goals	Financed by?	Drug Brought to Market?	Addressing Accessibility?
Innovative Medicines Initiative (IMI 1&2)	2008 (2013 – Launch of development branch, ENABLE)	"Improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need."	Funded jointly by the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations).	No	No
GARDP	2016	"Accelerates the development and access of treatments for drug-resistant bacterial infections."	Australia (DoH), Bill & Melinda Gates Foundation, Canton de Genève, EDCTP3, EU (HERA [via WHO]), Germany (BMBF and BMG), Jaman (MHLW), Leo Model Foundation, Luxembourg (Ministry of Health), Médecins Sans Frontières, The Netherlands (MOFA and VWS), Principality of Monaco, Public Health Agency of Canada, The RIGHT Foundation, South African Medical Research Council, Switzerland (SDC, SERI, FOPH), UK (DFID, DHSC – GAMRIF and NIHR), Wellcome.	Sort of – via its partnership with Shionogi, cefiderocol is now available to countries it wouldn't have been otherwise	Yes – Partnership with Shionogi in distribution of cefiderocol
CARB-X	2016	"A global non-profit partnership accelerating antibacterial products to address drug-resistant bacteria, a leading cause of death around the world."	ASPR, BARDA, Wellcome, Germany (Federal Ministry of Education and Research), UK DHSC - GAMRIF, Canada, NIAD, Novo Nordisk Foundation,	No	Yes

Table 4 Comparing Three PPPs

Pharmaceutical companies since the 1980s had largely been transitioning away from in-house product development in favor of corporate acquisitions of potentially lucrative products. The rise of these PPPs came about as a form of corrective maintenance to the antibiotic pipeline which serves as a key component of antibiotic access infrastructure. They emerged in a time of increased political pressure for pharmaceutical industrialization and a rise of AMR. They have served as ways for academic, government, and private actors to collaborate on projects with a spectrum of international support.

The involvement of universities, both in their ability to produce products that could eventually become patentable, and the training of researchers in a unique sphere of influence was essential as it instigated a competition for productivity and opportunity in the European sphere, and also sharpened financial interest in other-than antibiotic spaces that could be more profitable in the United States sphere. Profits and profitability is of chief importance in the private sector, but PPPs are an avenue where private work could be supplemented by public investment to ensure that antibiotic development was able to continue. What's more, is that there has been an increased focus on the education of scientists and inter-relation between University and private sector research as well as increased attention to the interdisciplinary collaboration between NGO and public sector partners as a result of these PPPs. These collaborations have coincided with more attention drawn to the awareness of AMR as a distinct threat.

The development of public private partnerships, and the use of the antibiotic pipeline by these partnerships and affiliated actors seems to be very clear here. The antibiotic pipeline is a component of greater antibiotic access infrastructure. Access to medicines requires access to effective medications. Had AMR not emerged, then it is possible that the present state of antibiotic innovation would not be cause for much concern. However, due to the rise of resistant infections, new medications capable of treating those infections became a priority.

The ability for those medications to emerge from pre-clinical research and successfully traverse the development "pipeline" to market approval equally gained importance as AMR became a more persistent threat. Decades of focus on stewardship and surveillance (Chapter Two) had informed global health populations there was an issue, but these interventions were losing the fight against continually rising rates of resistance. If antibiotics were to continue to be an infrastructure capable of supporting global health needs, and if the EML was to continue to be an infrastructure helping to ensure those needs were met: the pipeline needed to be functioning.

To extend the infrastructure and pipeline metaphor slightly: if the pipeline were an actual physical pipe, then its failure to allow for a flow of medications to continue through it indicates a break or crack in its physical components. Maintenance, the ability to address these concerns and ensure the pipe's optimal functioning, needs to be applied. The PPPs are one method of maintaining this pipe, as the financial components that seemed to be causing the leak in the first place allow for new development to continue. Continuing maintenance, meant to ensure the infrastructure remains sound, will need to be conducted throughout the pipeline's lifespan – as will continual assessment as to where the cracks are forming and *why* that is the case. In order to ensure continued access to effective antibiotics, this maintenance is essential.

Chapter Four: The Drug Trajectory of Bedaquiline

"It has to look like it's got a lot of scientific potential, meaning medical potential: that it could actually become a drug and be really helpful." – Melvin Spigelman.[616]

"When you work with a neglected disease, the resources are always limited. So, you always have the challenge in terms of getting best resources to the program, but also keeping the costs minimal. That's a very important lesson we learned that we really need to be cost effective when we are doing some of these neglected disease research." Anil Koul.[617]

On 1 February 2023, the pharmaceutical executives of Johnson & Johnson (J&J) held a town hall meeting with their staff. Many of those staff members had just been told they would be laid off, and the mood in the town hall was particularly bleak. As the head of J&J's infectious disease unit, James Merson, delivered his remarks on the status of the company's portfolio moving forward, a slide to his left displayed the grim fate of his department. J&J had already canceled its ongoing bacterial disease research, but it had now decided to wind down its interest in phage and small molecule non-tuberculosis mycobacteria. For viruses, HIV, hepatitis B and D, and Covid-19 research would similarly face either a cessation of research, a transition to so called "legacy studies," or prophylaxis care rather than treatments themselves.[618] J&J's decision came at the end of a series of stock buybacks, and with the announcement of a sweeping layoffs across multiple sectors as the vaccine and infectious disease research groups would be combined into one unit. James Merson's staff provided an update on his own status in a memo that described his desire to depart from J&J in order to "pursue the next opportunity."[619]

J&J's commitment to manufacturing and developing antibiotics has a complicated history. In 2016, following the publication of the O'Neill Report, they joined 80 other

[616] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.
[617] Anil Koul, Interview by Erin L. Paterson, 13 April 2023.
[618] Max Bayer and Fraiser Kansteiner, "J&J's Pharma Group Quietly Works through Global Overhaul, with Layoffs Expected to Reach Multiple Countries," *Fierce Pharma*, February 3, 2023, sec. Pharma. https://www.fiercepharma.com/pharma/johnson-johnson-quietly-works-through-global-overhaul-layoffs-spreading-multiple-countries.
[619] Bayer and Kansteiner, "J&J's Pharma Group Quietly Works through Global Overhaul."

companies and organizations in signing an industry drafted Declaration on Combating Antimicrobial Resistance (AMR).[620] Known colloquially as the Davos Declaration, these groups promised to conduct "enhanced" conservation of antibiotics (and indeed called for increased stewardship of antibiotics) and further elucidated on the commitments its signatories would be expected to carry out, including: working to reduce the development of AMR, ensuring global access to effective medicaments against AMR, and investing in "R&D that meets global public health needs with new innovative diagnostics and treatments."[621] For industry members, the Davos Declaration was something unprecedented, with one GSK representative elucidating it simply by saying: "companies rarely all get together and commit in public to a number of things like that."[622] Their public commitment came with public responsibilities, and later the Access to Medicines Foundation would begin tracking companies' commitment to antibiotic development and accessibility based on these goals.[623] In short, they would help invest into the development of needed a pipeline that would lead towards better access to needed medications that could address AMR.[624] When J&J announced its departure from antibiotic research seven years after Davos, it was clear that its commitment was on shaky ground. However, in spite of the murky circumstances of whether layoffs and collapsing of an R&D department can be seen as a sign of investing in global health needs, J&J did have the greatest antibiotic breakthrough in nearly forty years through its subsidiary, Janssen's, production of bedaquiline.

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[620] Johnson & Johnson, "Johnson & Johnson Joins First Industry-Wide Call for New Collective Action to Address Antimicrobial Resistance," Media Center, January 20, 2016, https://www.jnj.com/media-center/press-releases/johnson-johnson-joins-first-industry-wide-call-for-new-collective-action-to-address-antimicrobial-resistance.

[621] "Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance," AMR Industry Alliance, January 2016, 2-4. https://www.amrindustryalliance.org/wp-content/uploads/2017/12/AMR-Industry-Declaration.pdf.

[622] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 52.

[623] Martijn Van Gerven, Interview with Erin L. Paterson, 23 August 2023.

[624] Three signees of the declaration specifically mentioned the word 'pipeline' and their dedication to it. These quotes and their perspectives can be found here: AMR Industry Alliance. "AMR Declaration Launched." Accessed January 17, 2025. https://www.amrindustryalliance.org/mediaroom/launch-of-the-declaration/.

First discussed in 2004 and then sold on the market by 2012, bedaquiline is one of the few novel antibiotics that have been discovered and received market authorization since the 1980s. It is the first of a new class of antibiotics dubbed the "diarylquinoline" class, and it works by targeting the ATP Synthase Enzyme of TB mycobacteria.[625] The key researcher who discovered the method of action was Anil Koul, and in 2021 he described the methodology as the drug essentially stopping the motor of the bacteria from being able to turn and produce energy for the cell.[626] Bedaquiline's efficacy against tuberculosis was unprecedented and is the only treatment for XDR-TB (i.e. tuberculosis that is resistant to the previously established regimens of rifampicin, isoniazid, fluoroquinolone, amikacin/kanamycin/capreomycin). It also very nearly, did not pass clinical trials as the efficacy of the drug can only be seen after more than eight days of continued use.[627] It took continued rounds of assessment and extended clinical trials to reveal its potential on the market.

Market approval for bedaquiline was granted by the FDA in 2012. By 2015 it had made its way onto the WHO's Essential Medicines List. J&J subsidiary, Janssen, had applied for it to be added in 2013, but the Expert Committee rejected it "on the grounds of limited safety evidence and limited availability" as it was then only approved for use in the United States.[628] [629] By 2015 that story had changed. Within three years it managed to earn approvals in the "Philippines, the Republic of Korea, the Russian Federation, South Africa and…countries [in] the European Union" as well.[630] Furthermore, additional tests and a

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[625] Anil Koul, "The Discovery of Bedaquiline – Innovation in Tuberculosis Drug Discovery." Inaugural Address, London School of Hygiene and Tropical Medicine, February 2, 2021. https://vimeo.com/508781243.
[626] Koul, "The Discovery of Bedaquiline."
[627] Koul, "The Discovery of Bedaquiline."
[628] WHO Expert Committee, "The Selection of Essential Medicines," World Health Organization Technical Report Series 994, (Geneva, Switzerland: World Health Organization, 2015), 26.
[629] As noted in Chapter Two: following the changes to the Essential Medicine List continued efficacy and trial data and post market research from multiple countries was necessary in order to accept a drug onto the EML. While the application had been promising, the WHO could not accept the drug onto the list without additional approvals elsewhere.
[630] WHO Expert Committee, "The Selection of Essential Medicines," World Health Organization Technical

WHO analysis found that while previous treatments for MDR-TB yielded only a 32% success rate, with bedaquiline that figure rose to 61%.[631] By 2022, using a combination therapy of bedaquiline, pretomanid, and linezolid, that success rate has risen to 90%.[632] And, as an oral treatment, bedaquiline has easier storage and transport requirements and uninterrupted consumption is more manageable by the patient. Little wonder then, that within a year of its dissemination worldwide, local newspapers and medical journals in India (which sees roughly 124,000 cases of MDR-TB each year) both had begun hailing it as a "miracle" cure.[633] [634]

Bedaquiline was, and is, in many respects a success story. However, its success has been overshadowed by the presence of financial and market factors that limit the outreach possibilities of bedaquiline and cast a pall over the pharmaceutical industry itself. It is a medically successful drug that has turned into an accessibility failure. Only ten years after bedaquiline gained approval, and in the moment where Bedaquiline's patents have just started to expire, J&J has decided to restructure its interests and its attention as far as antibiotics are concerned. The researcher responsible for bringing bedaquiline to the fore, Anil Koul, like James Merson, is no longer working for Janssen or its parent company J&J. Investment into research and development has been cut, and there are few prospects on the horizon.

Why was this investment cut? And furthermore, why did bedaquiline, a veritable

Report Series 994, 29.
[631] WHO Expert Committee, "The Selection of Essential Medicines," World Health Organization Technical Report Series 994, 28.
[632] Francesca Conradie, Tatevik R. Bagdasaryan, Sergey Borisov, Pauline Howell, Lali Mikiashvili, Nosipho Ngubane, Anastasia Samoilova, et al, "Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis," *New England Journal of Medicine* 387, no. 9 (September 1, 2022): 810. https://doi.org/10.1056/NEJMoa2119430.
[633] The Indian Express, "The Roll out of a TB Curing Miracle Drug – Bedaquiline," March 22, 2016. https://indianexpress.com/article/explained/tuberculosis-bedaquiline-new-medicine-for-tb-cure/.
[634] Renuka Kandasamy and Subakeerthi Venkataramanan, "A Miracle Drug for Tuberculosis: Bedaquiline." *Pondicherry Journal of Nursing* 14, no. 1 (March 1, 2021): 23–24. https://doi.org/10.5005/jp-journals-10084-12174.

miracle drug for those with M and XDR-TB,[635] receive backlash for its pricing structure and overall lack of accessibility?

This chapter explores the drug trajectory of bedaquiline, the corporate history that brought it into existence, the financial circumstances that affected its launch and continued presence on the market, and the potential implications or concerns bedaquiline's experience has for other antibiotics in the antibiotic pipeline, particularly when it comes to access. It explores the historiography associated with relevant incentive programs such as the Orphan Drug Tax Credit and the Priority Review Voucher. It also challenges previously published presumptions regarding the investment Johnson & Johnson made into the development of bedaquiline. [636] Of key importance, is that despite having one of the largest potential patient populations in the world, bedaquiline failed to reach many of the patients that were in need after launch. [637] By looking at bedaquiline's story, potential safeguards or points of awareness regarding the effective nature of the antibiotic pipeline and the maintenance/repair efforts made to that pipeline (as discussed in Chapter Three), are put into focus. The pipeline is a part of the infrastructure that allows for new antibiotics to enter the market, if those drugs in turn are not accessible, however, then those drugs cannot go on to become a key component of health care infrastructure in turn. This chapter, therefore, focuses on what happens after a drug makes it through the pipeline, and how access and accessibility can be built into the antibiotic sphere to help ensure future antibiotics (either for tuberculosis or not) are able to reach patients more effectively in the future.

This chapter begins with a brief history and historiography of tuberculosis, setting the stage for understanding the impact of bedaquiline's drug trajectory. It then explores the

[635] Multiple and Extensively Drug Resistant Tuberculosis
[636] D Gotham, L McKenna, M Frick, and E Lessem, "Public Investments in the Clinical Development of Bedaquiline," *PLoS ONE* 15, no. 9 (2020): 6, https://doi.org/https://doi.org/10.1371/journal.pone.0239118.
[637] Médecins Sans Frontières, "As J&J Release Earnings, MSF Protests Price of Lifesaving TB Drug," Press Release, As J&J release earnings, MSF protests price of lifesaving TB drug in front of New York Stock Exchange, January 22, 2020, https://msfaccess.org/jj-release-earnings-msf-protests-price-lifesaving-tb-drug.

factors leading to the development of bedaquiline as one of the few novel antibiotics to emerge from the antibiotic pipeline, tracing its path from inception to deliverable. The chapter ends by comparing bedaquiline to the hepatitis C treatment sofosbuvir.

Although a virus, there are several similarities to the treatment of both hepatitis C and tuberculosis. They both have massive patient populations, and the treatment course can take several months at minimum. This requires drugs to be provided consistently, and the access to those drugs in an appropriate manner. Both drugs were priced at a particularly high price point, and the reactions to those price points ignited social disapproval amongst governments and patient populations alike. Discovered in 2007 and approved in 2013 (similar to bedaquiline's time frame) sofosbuvir acts as a dark mirror to bedaquiline by showcasing the market and policy clashes that continue to perpetuate the dry antibiotic pipeline, and providing contrast to experiences beyond the antibiotic space.[638] [639] Finally, with these two case studies at the forefront of this argument, this chapter provides a thorough examination of the integration of neoliberal capitalism within the pharmaceutical industry and what that means for access to essential antibiotics. In brief, this chapter highlights how even if an antibiotic can successfully be developed in a lab (with a PDP funding structure), the market factors that continue to influence corporate needs can still negatively influence that drug's accessibility potential.

From an antibiotic and access infrastructure perspective: if an antibiotic is made but never reaches a patient: it is not supporting the health care needs of society. The infrastructure is still weak, and needs maintenance or adjustment to become fully functioning once again.

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[638] According to one WHO study, there are 58 million people in the world with hepatitis C and an average of 290,000 people die of the disease each year: World Health Organization, "Hepatitis C," Hepatitis C, June 24, 2022. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.

[639] In another study, 1.8 billion people have tuberculosis worldwide, leading to 1.6 million deaths each year: TB Alliance, "TB Is a Pandemic," A Global Threat, 2023. https://www.tballiance.org/why-new-tb-drugs/global-pandemic.

I. Setting the stage: a brief history and historiography of tuberculosis prior to 2002

Tuberculosis is a disease that has walked side by side with humanity since antiquity, with some researchers believing the progenitor bacterial genus, *mycobacterium,* first evolved some 150 million years ago.[640] Evidence of TB can be found in ancient mummies and skeletal remains emerging in East Africa and Egypt, with the first written documentation being found in India and China as early as 3300 years ago.[641] Though often considered a respiratory infection, tuberculosis is capable of infecting and influencing the human body beyond the lungs, with skeletal samples being identified due to spinal deformities (Pott's disease). These incidences are considered extrapulmonary forms of tuberculosis, and though less common: they are no less lethal.[642]

Despite its presence alongside humanity for millennia, treatment for tuberculosis has been incredibly difficult to develop and implement. In 1882, Robert Koch was the first person to identify the tuberculosis bacteria (tubercle bacillus) in a lab setting and understand what precisely it was.[643] There was a presumption that because the bacteria had been identified, it could soon be treated, i.e.: "Find the cause, then find the cure."[644] Trouble came however, in the actual ability for that cure to manifest itself effectively, as targeting the bacillus was easier said than done. Christoph Gradmann's 2001 account of Koch's research into both tuberculosis and the development of a 'cure' (at the time: tuberculin) highlights how Koch struggled to manage both the public and scientific pressure placed on him following his

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[640] I. Barberis, N.L. Bragazzi, L. Galluzzo, and M. Martini, "The History of Tuberculosis: From the First Historical Records to the Isolation of Koch's Bacillus," *Journal of Preventive Medicine and Hygiene* 58, no. 1 (March 2017): E9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5432783/.
[641] Barberis, Galluzzo, and Martini, "The History of Tuberculosis," E9.
[642] Marjorie P. Golden and Holenarasipur R. Vikram, "Extrapulmonary Tuberculosis: An Overview," *American Family Physician* 72, no. 9 (November 1, 2005): 1761, https://www.aafp.org/pubs/afp/issues/2005/1101/p1761.html.
[643] Christoph Gradmann, "Robert Koch and the Pressures of Scientific Research: Tuberculosis and Tuberculin," *Medical History* 45, no. 1 (2001): 2. https://doi.org/10.1017/S0025727300000028.
[644] Christoph Gradmann, "This Is the End: Eradicating Tuberculosis in Modern Times," *Centaurus* 64, no. 1 (2022): 172, https://doi.org/10.1484/J.CNT.5.129633.

discovery of the bacillus. He describes Koch's initial research and presentation of tuberculin as "misleading" and "opaque," with Koch's results unable to be replicated and tuberculin's curative properties lacking in evidence.[645] Tuberculin did have an effect on tuberculosis, but as far as human treatment was concerned, it was highly reactive and patients could expect side effects including fever, shivering, pain in the limbs, nausea, and potentially necrosis of the flesh. [646]

Deprived of an immediate cure, treatment for tuberculosis instead turned to infection prevention and control measures. The disease, though relatively easy to acquire, was one that was capable of being overcome via the human immune system if the right conditions were met. Clean air, fresh sunlight, and a lack of crowded areas (which would prevent disease transfer) were all ways to both avoid infection and improve health.[647] Sanatoriums, meant to quarantine known infectious patients from the remainder of society, began to form in the late 1800s in an attempt to help manage this process.[648] These sanitoriums lasted through the 20th century, popping up in major cities across North America and Europe, and often faced over-crowding; despite this they played a large role in managing the disease as best they could despite the lack of efficacious treatment that could specifically target *mycobacterium tuberculosis.*[649]

Treatment, when it did come, emerged in the antibiotic era. Chapter One discussed the discovery and emergence of effective antibacterial chemotherapies, but for tuberculosis specifically, the first major antibiotics of note came in the form of streptomycin and para-

[645] Gradmann, "Robert Koch and the Pressures of Scientific Research," 23.
[646] Gradmann, "Robert Koch and the Pressures of Scientific Research," 27.
[647] John F. Murray, Dean E. Schraufnagel, and Philip C. Hopewell, "Treatment of Tuberculosis. A Historical Perspective," *Annals of the American Thoracic Society* 12, no. 12 (2015): 1750, https://doi.org/10.1513/AnnalsATS.201509-632PS.
[648] Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1752.
[649] M. Martini, V. Gazzaniga, M. Behzadifar, N.L. Bragazzi, and I. Barberis, "The History of Tuberculosis: The Social Role of Sanatoria for the Treatment of Tuberculosis in Italy between the End of the 19th Century and the Middle of the 20th," *Journal of Preventive Medicine and Hygiene* 59, no. 4 (December 15, 2018): E323–27, https://doi.org/10.15167/2421-4248/jpmh2018.59.4.1103.

aminosalicylic acid (PAS) in 1944.[650] Problems, however, once again arose when it came to treating patients. Both drugs had "significant side effects" on the patient and if either was used as a singular treatment tuberculosis proved adept at developing resistance; it was recommended that TB should never be treated with a single agent, but the combination therapies only added to the potential for adverse effects.[651] Isoniazid was discovered a few years later in 1951[652] and after a series of clinical trials to determine the most efficacious "triple therapy" with the fewest adverse effects, isoniazid, streptomycin, and PAS were considered the optimal combination treatment for TB.[653] Over the next two decades, additional therapies and combinations found their way onto the market. The rifamycins, cycloserine, ethionamide, kanamycin, and capreomycin all flushed out the different treatment pathways, and in all cases: combinations of these drugs made up the cocktails required for effective treatment.[654]

What should be noted about these treatment options though, is the length of time it took to cure tuberculosis. In 1952, the triple therapy of streptomycin, PAS and isoniazid could cure 90-95% of patients, but only if the course was followed for twenty-four months continuously.[655] [656] By the 1960s, when para-aminosalicylic acid was replaced by ethambutol, this treatment time was cut to 18 months. [657] Adding rifampicin helped bring treatment down to 8-9 months. Pyrazinamide combined with isoniazid and rifampicin allowed treatment reduction to 6 months.[658] Most treatment courses used today hover around this six-month

[650] Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1751.
[651] Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1753.
[652] Technically, the compound was discovered in 1912, and as a result of this discovery patent debates surrounding the drug between Hoffman-La Roche and Squibb and Bayer Chemical were laid to rest before they could get up off the ground. The drug was approved and marketed in 1951 by both companies without patent complaints. For more information: Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1753.
[653] Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1753.
[654] Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1754.
[655] "Improving the Health of the Tuberculosis Drug Pipeline," *The Lancet* 14, no. Newsdesk (February 2014): 102–3, https://www.natap.org/2014/HIV/PIIS1473309914700064.pdf.
[656] Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1753.
[657] "Improving the Health of the Tuberculosis Drug Pipeline," 102–3.
[658] Michele A. Riva, "From Milk to Rifampicin and Back Again: History of Failures and Successes in the Treatment for Tuberculosis," *The Journal of Antibiotics* 67, no. 9 (September 2014): 664.

benchmark. Most treatments, also, require roughly six pills a day, which at the end of six months would lead to over 1000 pills necessary for treatment.[659] Due to the extreme number of drugs taken, as previously stated within this dissertation: failure to complete treatment courses, inadequate dosing, or inappropriate diagnosis/use in the first place can lead to increased cases of resistance. Tuberculosis in particular, is a disease that is very susceptible to acquiring resistance.

Although HICs saw diminishing rates of tuberculosis as their communities experienced improvements in general health, hygiene systems, and cleaner air, tuberculosis was never completely eradicated from these population. Rather, as with LMICs, tuberculosis continued to be considered a disease of poverty that impacted those without access to those boons. In the 1970s, HICs began to dismantle tuberculosis sanitoriums, perceiving that the disease was no longer a threat. [660] [661] When HIV/AIDS appeared in the 1980s, these measures proved to have been too hasty. New York City, in particular, experienced a rampant tuberculosis outbreak that quickly accelerated to an MDR outbreak.[662] Treatment for MDR TB at that time was extraordinarily difficult, and as a result: many people died. If standard TB required 1000 pills to treat over the course of six months, MDR required 14,000 pills over the course of two years. [663] [664]

By the end of the 1990s, the WHO was actively working with countries around the

https://doi.org/10.1038/ja.2014.108.

[659] Mayo Clinic, "Rifampin, Isoniazid, and Pyrazinamide (Oral Route)," Accessed January 19, 2025. https://www.mayoclinic.org/drugs-supplements/rifampin-isoniazid-and-pyrazinamide-oral-route/description/drg-20062768.

[660] Murray, Schraufnagel, and Hopewell, "Treatment of Tuberculosis," 1751.

[661] Richard Coker, "Lessons from New York's Tuberculosis Epidemic," *BMJ: British Medical Journal* 317, no. 7159 (September 5, 1998): 616, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1113831/.

[662] Coker, "Lessons from New York's Tuberculosis Epidemic," 616.

[663] These results were provided by EndTB in 2023. EndTB emerged in 2016 as a clinical trial and research project dedicated to addressing MDR TB. Their focus is on the use of bedaquiline and delamanid to address TB concerns, and they are partnered with the Partners in Health, MSF, Interactive Research and Development, UNITAID, and MSF Transformational Investment Capacity. Though their work post-dates this section's analysis, the comparison and the perspective of the number of pills used over time is essential to make the impact and resource strain of both TB and MDR TB clear.

[664] EndTB, "Landmark Clinical Trial Redefines Multidrug-Resistant Tuberculosis Treatment Options," November 15, 2023. https://endtb.org/endtb-clinical-trial-results.

globe to determine the number of cases of tuberculosis active in the world. They determined that roughly 3.8 million new cases of tuberculosis were being reported each year, with higher incidents rates occurring as a result of being an opportunistic infection in relation to HIV/AIDS.[665] Despite this disease having existed for millennia, and despite treatment options available: tuberculosis was still an active threat worldwide, with rates of resistance continually on the rise. Meanwhile, discovery or interest in addressing TB fell by the wayside. Like other antibiotics, no new treatments had been discovered since the 1980s, but most of the testing and discovery relating to TB came from decades prior.

In 2000, the Product Development Partnership,[666] TB Alliance, was founded in Cape Town, South Africa. President and Chief Executive Officer of the PDP, Mel Spigelman admitted in an interview that the founding of TB Alliance likely came, at that time, as a result of the attention given to the New York City outbreak of MDR TB, as it brought TB back to a high income country, and divested it from solely being a problem in LMICs.[667] While TB Alliance has dedicated itself to assisting the development of any new drug capable of addressing TB, the circumstances of their formation highlight continual issues facing the TB field to this day. Because TB largely effects the poor, it is simultaneously neglected by those with the wealth and privilege to address it. Despite having one of the largest patient populations in the world, it is considered a "neglected disease" with low funding and low attention in the pharmaceutical space.

New medications, capable of lessening the length of time for treatment and addressing standard, MDR, and XDR TB is essential. Access to those medications, ensuring that they are

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[665] World Health Organization, "Global Tuberculosis Control WHO Report 1998," Global Tuberculosis Program. Geneva, Switzerland: World Health Organization, 1998, 24, https://iris.who.int/bitstream/handle/10665/63835/WHO_TB_98.237.pdf?sequence=1.

[666] As a reminder, PDPs and PPPs are exceptionally similar. PDPs focus primarily on the direct development of a product, but their existence is one which works to bring together public, private, academic, and philanthropic sectors to ensure the development of that product.

[667] Mel Spigelman, Interview by Erin L. Paterson, 21 December 2023.

both affordable and available, is an equal priority. Due to the extreme number of pills required for treatment, maintaining this accessibility requirement is a key component to treating tuberculosis effectively.

Johnson & Johnson's development of bedaquiline, therefore, should have been something of a roaring success for the company. However, the first novel antibiotic – and novel tuberculosis medication – in decades, struggled at launch, marking another uncertain chapter in the future of both this disease and its management.

II. How did Johnson & Johnson create Bedaquiline? Corporate and laboratory history leading to the first novel antibiotic since the 1980s

Johnson and Johnson (J&J) is not a recent company. However, after its launch in 1886, the company primarily spent its first century of existence creating consumer and hospital products/medical supplies that promoted health and sanitation (such as baby powder, face masks, lotions, and its tape/gauze adhesive: the Band-Aid, which quickly earned name brand supremacy in the United States).[668] J&J didn't expand its reach into pharmaceuticals until it acquired the Tylenol (paracetamol) manufacturer McNeil Laboratories in 1959, and Janssen Laboratories two years later.[669] J&J corporate historian, Margaret Gurowitz, describes this transition as one of uncertainty as the company feared acquiring an external entity that may stand at odds to their corporate credo.[670] The credo, written by General Robert Wood Johnson in 1943 highlighted that J&J's "first responsibility is to the patients, doctors

[668] Margaret Gurowitz, "1959: McNeil Laboratories Joins the Family," Johnson & Johnson Online Museum, Kilmer House (blog), December 16, 2009. https://www.kilmerhouse.com/2009/12/1959-mcneil-laboratories-joins-the-family.
[669] The New York Times, "Drug Concern Sold; McNeil Laboratories Bought by Johnson & Johnson," January 17, 1959, sec. Financial Business.
The New York Times, "Control of Bank in Virginia Sold," September 27, 1961, sec. Financial Business.
Margaret Gurowitz, "1959: McNeil Laboratories Joins the Family," Johnson & Johnson Online Museum. Kilmer House (blog), December 16, 2009. https://www.kilmerhouse.com/2009/12/1959-mcneil-laboratories-joins-the-family.
[670] Margaret Gurowitz, "The Writing of Our Credo," Johnson & Johnson Online Museum. Kilmer House (blog), December 18, 2013. https://www.kilmerhouse.com/2013/12/the-writing-of-our-credo.

and nurses…who use [their] products and services," as well as their commitment to an inclusive work environment that is responsible not only the communities they work in but the ones they live in as well. The final clause of the J&J credo further determined that their "final responsibility is to [their] stockholders. [As a] business must make a sound profit."[671] McNeil and Janssen Pharmaceutica were determined to have reflected these qualities admirably enough to justify the transition and they became the foundation for all of J&J's future pharmaceutical endeavors.

Of the two acquisitions, Janssen Pharmaceutica in particular had the most potential for pharmaceutical innovation. Established in 1956, Janssen Pharmaceutica was a small but proactive company founded by Paul Janssen (or Dr. Paul as he was known by his colleagues).[672] By the time J&J showed interest in acquiring the company, it had developed an antispasmodic that could treat menstrual pain, the fist antipsychotic that allowed home care for patients, and the anesthetic fentanyl.[673] In the years that followed, Janssen Pharmaceutica would remain at the forefront of cutting-edge medical development with ten of their eighty medications being chosen for the WHO's Essential Medicines List.[674]

Dr. Paul was a prolific researcher and he expanded his reach and influence to new scientists that were equally trying to make a name for themselves in the pharmaceutical development field. One such researcher was Rudi Pauwels who received a research fellowship from Dr. Paul and Janssen Pharmaceutica in the 1980s, and who enjoyed frequent collaborations with both the scientist and company in the years that followed. Both were deeply interested in HIV/AIDS and the potential cures or treatments that could be developed to address the disease. In conjunction with fellow HIV practitioner and researcher, Paul

[671] Margaret Gurowitz, "The Writing of Our Credo," Johnson & Johnson Online Museum. Kilmer House (blog), December 18, 2013. https://www.kilmerhouse.com/2013/12/the-writing-of-our-credo.
[672] R. Watson, "Paul Janssen," British Medical Journal 327, no. 7426 (2003): 1290.
[673] R. Watson, "Paul Janssen," British Medical Journal 327, no. 7426 (2003): 1290.
[674] Janssen, "Our History," Corporate, 2021. https://www.janssen.com/australia/about-us/our-history.

Stoffels, Pauwels's created the pharmaceutical company Tibotec Pharmaceuticals to more seriously address this goal.[675] Eight years later, the constant collaborations between Pauwels, Stoffels, and Janssen would lead to J&J officially acquiring Tibotec as a new subsidiary under Janssen's official oversight.

Purchased for $189 million USD, Tibotec joined J&J with an already present public-private partnership put in place with the International Partnership for Microbicides (IPM). [676] [677] Their task was to ensure "a royalty-free license to develop, manufacture and distribute" an HIV preventative compound identified as TMC120 (otherwise known as dapivirine).[678] [679] Despite the purchase and the eventual merger that would see Tibotec consolidated beneath the umbrella of Janssen Therapeutics, all agreements with IPM were still in place regarding production and J&J reiterated its commitment to HIV and Hepatis-C treatments in their 2002 Annual Report.[680] [681]The merger would be a success for all parties involved as not only dapivirine, but and three additional new HIV drugs would emerge from the labs as first, second, and third line treatments for HIV and vaccine candidates became more thoroughly understood and investigated.[682]

Then, in 2004, within Janssen Pharmaceutica, the drug "R207910" was discovered during a screening of roughly 70,000 compounds that could potentially show efficacy against

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[675] Erik De Clercq, "An Odyssey in Antiviral Drug Development—50 Years at the Rega Institute: 1964–2014," *Acta Pharmaceutica Sinica B* 5, no. 6 (November 2015): 529. https://doi.org/10.1016/j.apsb.2015.09.001
[676] Johnson & Johnson, "2004 Annual Report," (New Brunswick, United States: Johnson & Johnson, 2004), 33.
[677] IPM was founded in 2002 and was focused on determining ways to prevent the spread of HIV. Not mentioned in the last chapter due to its non-antibiotic related focus, it carries on with the traditions described in Chapter Three.
[678] Johnson & Johnson, "2004 Annual Report," 13.
[679] Johnson & Johnson, "Janssen Announces Expanded Collaboration with International Partnership for Microbicides for Development and Commercialization of Dapivirine for Prevention of Sexual Transmission of HIV," Media Center, 8 May 2014, https://www.jnj.com/media-center/press-releases/janssen-announces-expanded-collaboration-with-international-partnership-for-microbicides-for-development-and-commercialization-of-dapivirine-for-prevention-of-sexual-transmission-of-hiv.
[680] Johnson & Johnson News Release, "Johnson & Johnson Completes Acquisition of Tibotec-Virco," News, April 18, 2002. https://johnsonandjohnson.gcs-web.com/news-releases/news-release-details/johnson-johnson-completes-acquisition-tibotec-virco
[681] Johnson & Johnson, "2002 Annual Report," 2-5.
[682] Kristen Jill Kresge, "An Industry Leader in HIV Research," International AIDS Vaccine Initiative. Accessed December 11, 2023. https://www.iavi.org/demo/vol-22-no-3-2018/an-industry-leader-in-hiv-research.

mycobacterium smegmatis (a bacterium that shares a similar cell wall structure to *mycobacterium tuberculosis* and is thus often used in screening tests for potential new drugs).[683] The drug, key Janssen researchers Anil Koul and Koen Andries would discover, had a unique reaction when testing against *m. tuberculosis* in that it inhibited the bacteria's ability to access its fuel supply (or ATP synthesis).[684] It was immediately hailed by J&J as the first new TB medication to be "brought into the clinic in the past 40 years," and that the potential for this drug would be seen in its ability to work "better and faster than the current standard of care."[685] Janssen then passed control over the compound to Tibotec for the remainder of its research and development cycle.[686]

Tibotec at the time had no active experience with tuberculosis medication. However, due to its extensive work with HIV/AIDS and the understanding that tuberculosis was a common co-infection for this patient pool, they were considered best equipped to continue the research on the drug. They renamed the molecule: TMC207 and were responsible for all testing and clinical trials that followed. However, despite the transition to Tibotec, researchers such as Anil Koul who worked primarily in the Janssen Pharmaceutica component of J&J's teams, continued to work and contribute to the overall project reflecting the collaborative nature of the subsidiaries and acquisitions within J&J's profile.[687]

In vitro studies of TMC207 reflected bactericidal success against Tuberculosis and hopes for the drug to success in vivo quickly rose throughout the research team in both labs.

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[683] Hui Guo, Gautier M. Courbon, Stephanie A. Bueler, Juntao Mai, Jun Liu, and John L. Rubinstein, "Structure of Mycobacterial ATP Synthase Bound to the Tuberculosis Drug Bedaquiline," *Nature* 589, no. 7840 (January 7, 2021): 143. https://doi.org/10.1038/s41586-020-3004-3.

[684] Anil Koul, Luc Vranckx, Najoua Dendouga, Wendy Balemans, Ilse Van Den Wyngaert, Karen Vergauwen, Hinrich W.H. Göhlmann, et al, "Diarylquinolines Are Bactericidal for Dormant Mycobacteria as a Result of Disturbed ATP Homeostasis," *Journal of Biological Chemistry* 283, no. 37 (September 2008): 25273–74. https://doi.org/10.1074/jbc.M803899200.

[685] Johnson & Johnson, "2004 Annual Report," 13.

[686] Johnson & Johnson, "2004 Annual Report," 13.

[687] Anna C. Haagsma, Ioana Podasca, Anil Koul, Koen Andries, Jerome Guillemont, Holger Lill, and Dirk Bald, "Probing the Interaction of the Diarylquinoline TMC207 with Its Target Mycobacterial ATP Synthase," edited by Hendrik W. Van Veen. *PLoS ONE* 6, no. 8 (August 17, 2011): e23575. https://doi.org/10.1371/journal.pone.0023575

Classified now as a new class of antibiotics, the diarylquinoline class, and gifted with the official name: bedaquiline, TMC207 entered pre-clinical trials. The first, a series of mouse studies, found that bedaquiline was able to eradicate tuberculosis in the mouse within only two months, where other drugs required more time.[688] [689]

However, when clinical trials progressed to human patients, a problem occurred. When a human patient received the drug, there appeared to be no immediate effect.

During an Inaugural Lecture at the London School of Hygiene and Medicine in 2021, Anil Koul reflected on this complication by first referencing Professor Denis Mitchison. Tuberculosis, according Mitchison, exists in a heterogenous form in a patient. The *mycobacterium tuberculosis* stays in the body in three main states: rapid replication (alpha), semi-metabolic (beta), and dormant (gamma).[690] Historically, most tuberculosis drugs target the alpha and beta populations of tuberculosis but struggle to target the gamma states. However, to the surprise of the researchers, bedaquiline was far more successful against the gamma population of *m. tuberculosis.* When the first clinical trial patient received bedaquiline on 6 July 2005, clinicians were shocked to discover that the bacterial load after seven days showed minimal improvement compared to isoniazid and rifampicin. Something that had not occurred in the mouse studies.[691]

Fearing that the project would end there, the researchers at Tibotec and Janssen attempted to understand where the complication lay. They would eventually use video

[688] Koul, "The Discovery of Bedaquiline."
[689] Lounis, Nacer, Nicolas Veziris, Aurélie Chauffour, Chantal Truffot-Pernot, Koen Andries, and Vincent Jarlier. "Combinations of R207910 with Drugs Used To Treat Multidrug-Resistant Tuberculosis Have the Potential To Shorten Treatment Duration." *Antimicrobial Agents and Chemotherapy* 50, no. 11 (November 2006): 3543–47. https://doi.org/10.1128/AAC.00766-06
Anil Koul, "The Discovery of Bedaquiline – Innovation in Tuberculosis Drug Discovery." Inaugural Address, London School of Hygiene and Tropical Medicine, February 2, 2021. https://vimeo.com/508781243.
[690] Koul, "The Discovery of Bedaquiline."
[691] R. Rustomjee, A. H. Diacon, J. Allen, A. Venter, C. Reddy, R. F. Patientia, T. C. P. Mthiyane, et al., "Early Bactericidal Activity and Pharmacokinetics of the Diarylquinoline TMC207 in Treatment of Pulmonary Tuberculosis," *Antimicrobial Agents and Chemotherapy* 52, no. 8 (August 2008): 2833, https://doi.org/10.1128/AAC.01204-07.

microscopy, which allowed for a single cell time lapse of the efficacy of the drug, to conclusively prove that the drug was having an impact on the bacteria, but needed to extrapolate those results in vivo.[692] [693] Their conclusion, published in 2014, determined that when *m. tuberculosis* realizes that its ATP Synthesis is being inhibited, it attempts to mutate and defend itself, but it remains susceptible to bedaquiline, "on the long term."[694] That long term effect became particularly clear when gamma (i.e.: dormant) populations of *m. tuberculosis* were reviewed.[695]

However, the finalized publicized answer to the problems identified in the timing of bedaquiline's efficacy took nine years to be made known. As stated previously, the first patient trial began in 2005, and in the years between 2005 and 2014 there was a need to justify that this molecule was valuable enough to continue research, study, and eventually put on the market. Bedaquiline did eventually receive market authorization in 2012 and it went on the WHO's essential medicine list in 2015, but to get it there and to begin to have a market presence took time and investment from several entities.

As the scientists worked in the labs to prove bedaquiline's efficacy, the investment needed to continue the research required support. It is a truism that any product not actively on the market naturally is considered a loss for accounting purposes. Until a product can be sold and a company cannot begin to recoup the expenses accrued during the research and development phase. The longer that research and development phase drags on, the more the company will need to regain at the time of sale. This, naturally, would lead to either increased pricing of the product itself, or to a focus on fast rapid sales in large quantities to put the

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[692] Anil Koul, Interview by Erin L. Paterson, 13 April 2023.
[693] Anil Koul, Luc Vranckx, Neeraj Dhar, Hinrich W.H. Göhlmann, Emre Özdemir, Jean-Marc Neefs, Melanie Schulz, et al, "Delayed Bactericidal Response of Mycobacterium Tuberculosis to Bedaquiline Involves Remodelling of Bacterial Metabolism," *Nature Communications* 5, no. 1 (February 26, 2014): 3369. https://doi.org/10.1038/ncomms4369.
[694] Koul, "The Discovery of Bedaquiline."
[695] Koul, et al., "Delayed Bactericidal Response of Mycobacterium Tuberculosis to Bedaquiline Involves Remodelling of Bacterial Metabolism."

accounting back in the black. Key avenues of financial support for bedaquiline came from several areas: the forming of a product development partnership with TB Alliance in 2009, the Orphan Drug Tax Credit, the drug's donation program, and the Priority Review Voucher system, in addition to J&J's originator funds.

A. Financing Bedaquiline: how Johnson & Johnson brought a novel antibiotic to market

Chapter Three discussed how the financial burden and "market failure" of developing antibiotics led to many pharmaceutical companies abandoning the development of novel drugs, and that public private partnerships were one method of encouraging this development by injecting public funds into the private sector. In addition to the public funds offered by these PPPs there are other public incentives and options that can continue to add support to help bring that drug to market. In this section, I conduct a deep dive into the exact financial options that supported the ability bedaquiline's creation and distribution. I elucidate exactly how Johnson & Johnson's relationship with TB Alliance influenced research, development and production, and I detail the barriers and benefits of the government programs made available to bedaquiline.

As the first antibiotic class to make it to market using these options, it shows how the incentives that have been put in place specifically for this kind of drug innovation, research, and production have been implemented. It also shows where the pitfalls and complications come when the drug itself is in need of support or assistance.

a. Analyzing the relationship and impact of the Public Private Partnership, TB Alliance, and Johnson & Johnson

The Global Alliance for TB Drug Development (aka: TB Alliance) is a Product

Development Partnership[696] that was founded in 2000 with the goal of discovering, developing, or ensuring the delivery of "better, faster-acting and affordable tuberculosis drugs" to those in need.[697] It spawned from the Cape Town Declaration in South Africa, a summit meeting of like-minded individuals who called for increased and improved TB drug development,[698] with initial seed money coming from the Rockefeller Foundation.[699] By 2021 they had over 30 active programs in development, including 8 clinical trials.[700]

The methodology that TB Alliance uses to determine which drug or partnership to proceed with is a multi-step process. While TB Alliance naturally stays aware of developments around the world, it particularly focuses on innovative goals that seem to show the greatest potential. Following this cursory examination, a more thorough scientific appraisal of the developments is reviewed.[701] Melvin Spigelman, President and CEO of the TB Alliance, stated that the rate of new products or research brought to the TB Alliance's attention can sometimes reach once per week, and that following receipt they must each be ranked for their "attractiveness" to determine if they are worth investing TB Alliance resources into.[702] What that investment looks like, and the final form of the partnership that follows differs from arrangement to arrangement, but something that was key to Spigelman was the notion of ensuring that any drug development process could be done within the context of a drug regimen.[703]

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[696] For more on Product Development Partnerships and their impact on antibiotic drug development, please consult Chapter Three of this dissertation.
[697] "Who We Are In 2023," Video, New York, 2023. https://www.tballiance.org/about/who-we-are.
[698] Participants included The American Lung Association, Bill & Melinda Gates foundation, Stop TB Initiative, US Centers for Disease Control, US National Institutes of health, the Wellcome Trust, World Bank, and the World Health Organization, amongst many others. A full reading of the Cape Town Declaration can be found here: "The Cape Town Declaration," Working Alliance for TB Drug Development, February 8, 2000. https://www.tballiance.org/downloads/publications/CapeTownDeclaration.pdf.
[699] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.
[700] TB Alliance, "Building the Largest TB Drug Portfolio," August 2, 2021. https://www.tballiance.org/content/building-largest-tb-drug-portfolio.
[701] Developments in this case do not strictly need to be drug related, though for the purpose of this dissertation I will retain focus on drug development at this time.
[702] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.
[703] "TB Alliance: 20 Years of Impact," Video, New York, 2023, https://www.tballiance.org/news/20-years-impact

As mentioned earlier in this dissertation, combination therapies have long been considered an efficacious way to address bacterial infections, while simultaneously lowering potential risk for antimicrobial resistance. Spigelman's interest in drug regimens, however, was particularly important in the context of tuberculosis where treatments routinely required the use of multiple medications and compounds at once. Rather than develop one new drug and hope to use it to independently alter the TB treatment landscape, Spigelman suggested developing multiple drugs at once that could become a brand-new regimen with lower rates of resistance and higher rates of efficacy.

TB Alliance's first attempt at such a thing arrived in 2002 when it in-licensed pretomanid from PathoGenesis (later Chiron Corp and Novartis).[704] Under that arrangement, the TB Alliance "took over the development and the responsibility for pretomanid for all indications" and "owned all the rights to pretomanid."[705] This is a slight inversion of previously discussed PPPs, where in this case the not-for-profit enterprise, TB Alliance, retains the rights to the product rather than the private company. However, this still is a potential outcome of the relationship as the gathering of public funds and private company resulted in the development of a product.[706] Testing, trials, and compatibility work quickly proceeded, though the determination of the correct regimen took some time. But, by 2019, the FDA approved pretomanid as a treatment for highly drug-resistant TB, not as an individual drug, but rather as a single drug within a regimen that could only be used *as* a regimen; its fellow drugs were bedaquiline and linezolid.[707]

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[704] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.
[705] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.
[706] Of note, TB Alliance, although also considered a is– often describes itself as a product development partnership rather than public/private due to its intention to ensure that a product reaches the market first and foremost.
[707] GlobalData Healthcare, "TB Alliance's Pretomanid Receives FDA Approval for Tuberculosis," Pharmaceutical Technology (blog), August 28, 2019. https://www.pharmaceutical-technology.com/analyst-comment/tb-alliances-pretomanid-receives-fda-approval-for-tuberculosis/.
and: Centers for Disease Control and Prevention, "Provisional CDC Guidance for the Use of Pretomanid as Part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease," Government, November 21, 2023, https://www.cdc.gov/tb/topic/drtb/bpal/default.htm.

TB Alliance became aware of bedaquiline in 2005, following its first clinical trial. At this point, pretomanid was already being explored and developed by TB Alliance, and when asked, Spigelman agreed that the notion of using it in concert with bedaquiline was already considered in those early planning stages.[708] The final agreement between Tibotec (and therefore Johnson & Johnson) and the TB Alliance came in 2009, but it was not the straight forward arrangement that TB Alliance had with PathoGenesis in 2002. The press release of the announcement stated that

> the two organizations will share their expertise and resources in the development of TMC207, which could become the first TB drug with a new mechanism of action in 40 years… The agreement grants the TB Alliance a royalty-free license for the worldwide development and access to TMC207 in the field of drug-susceptible TB. In addition, Tibotec will collaborate with the TB Alliance on a discovery research program to identify new compounds for the treatment of TB. The rights for the newly discovered compounds for the treatment of tuberculosis will belong to the TB Alliance under a royalty free license. Costs for the development of TMC207 will be shared.[709]

Where TB Alliance had royalty-free usage, and indeed full control over pretomanid, the same could not be said for bedaquiline following their partnership with Tibotec or Johnson & Johnson. TB Alliance could only actively work with bedaquiline when it came to drug - susceptible TB, and it would share research and data with Johnson & Johnson that may be of interest to J&J's intentions of marketing it for MDR TB.

Exact details over what the specific financial contribution TB Alliance made to the development of bedaquiline is not publicly available. However, Spigelman did confirm that any "high level activities that would directly stand to benefit both drug sensitive and drug resistant development" would be included.[710] Potentially this would include any clinical trials, additional research, or long-term investigation (such as in the study on how bedaquiline effects *mycobacterium tuberculosis.*) While TB Alliance may have on the

[708] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.
[709] Johnson & Johnson, "Unique Collaboration between TB Alliance and Tibotec to Accelerate Tuberculosis Drug Development," Johnson & Johnson Media Center, July 17, 2009. https://www.jnj.com/media-center/press-releases/unique-collaboration-between-tb-alliance-and-tibotec-to-accelerate-tuberculosis-drug-development.
[710] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.

surface only been contributing to bedaquiline's susceptible TB program, any gains in that field would naturally have influenced the resistant field, and joint committee meetings and shared research between TB Alliance and Johnson & Johnson ensured the overall advancement of knowledge.

The return of TB Alliance's investment, however, would not be substantial. During an interview with Anil Koul in 2023, Koul admitted that Johnson & Johnson's intention with bedaquiline was *not* going to be drug susceptible TB, and it hadn't been since their phase 2 study of the drug.[711] The biggest unmet medical need in the TB field was drug resistant TB, and that had always been Johnson & Johnson's focus. Trying to create a new drug for drug susceptible TB was far more challenging, as the regulatory approval process was not in the developer's favor.

As mentioned previously, most cases of drug susceptible TB can be treated within six to twelve months, with the most common treatment is isoniazid, rifampin, pyrazinamide and ethambutol.[712] If a new drug is to enter the market, it must show that it is capable of treating tuberculosis *better* than the current treatment course. For instance: a shorter treatment time, fewer pills needed, or fewer side effects. Since 2012, the average cure rate for drug-susceptible TB was between 87-95%.[713] A new drug would need to prove it was superior in most if not all of these metrics.

For drug-resistant tuberculosis, the field is drastically different. In 2013, the cure rate for resistant strains of TB was closer to 48% (if the patient even received any form of treatment in the first place).[714] By 2020, that global success rate had only risen to 57% as a

[711] Anil Koul, Interview by Erin L. Paterson, 13 April 2023.
[712] Variations to treatment can occur based on tolerance levels as well. For more information, please consult: American Lung Association, "Treating and Managing Tuberculosis," November 17, 2022. https://www.lung.org/lung-health-diseases/lung-disease-lookup/tuberculosis/treating-and-managing.
[713] USAID, and TB DIAH, "TB Treatment Success Rate (TSR)," Data Hub, Accessed January 11, 2024. https://hub.tbdiah.org/pbmef/indicators/tb-treatment-success-rate.
[714] World Health Organization, "Global Tuberculosis Report 2013," (Geneva, Switzerland: World Health Organization, 2013), 45.

result of few effective medications, high price points for those medications, and general poor health outcomes for those with MDR-TB.[715] Side effects to many MDR TB medications can be excruciating. In one study, conducted at a South Korean hospital, side effects were found in the treatment of 37.1% of patients and included gastrointestinal disturbance, psychiatric disorder (uncategorized), arthralgia, hepatitis, peripheral neuropathy, hypothyroidism, epileptic seizures, dermatological effects, ototoxicity, and nephrotoxicity.[716] Elsewhere, one noted side effect includes permeant hearing loss, particularly in cases of co-infection with HIV.[717] In light of these devastating or debilitating side effects, new drugs that can potentially lead to better health outcomes are highly sought after – and regulatory requirements are less strict as a result.

A surrogate marker or endpoint, is used as a substitute for "treatment effects on the trial target outcomes of interest measuring how patients feel, function, or survive."[718] In the case of tuberculosis, this could be simply the length of time it takes a patient's sputum sample to turn negative.[719] Because treatment options were so rare, this minimum standard is all that stands in the way of a drug reaching the market. It would be easier for Johnson & Johnson to proceed with getting bedaquiline to market if it focused purely on resistant TB, and it would be far harder for TB Alliance to manage the same with susceptible TB. At time of writing, bedaquiline is still not approved for susceptible TB.

By 2019, however, TB Alliance did make good use of their partnership with Johnson

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[715] World Health Organization. "Global Tuberculosis Report 2020," xviii.
[716] Tae Won Yang, Hyun Oh Park, Ha Nee Jang, Jun Ho Yang, Sung Hwan Kim, Seong Ho Moon, Joung Hun Byun, Chung Eun Lee, Jong Woo Kim, and Dong Hun Kang, "Side Effects Associated with the Treatment of Multidrug-Resistant Tuberculosis at a Tuberculosis Referral Hospital in South Korea: A Retrospective Study," *Medicine* 96, no. 28 (2017): e7482, https://doi.org/10.1097/MD.0000000000007482.
[717] James A. Seddon, Peter Godfrey-Faussett, Kayleen Jacobs, Adam Ebrahim, Anneke C. Hesseling, and H. Simon Schaaf. "Hearing Loss in Patients on Treatment for Drug-Resistant Tuberculosis," *European Respiratory Journal* 40, no. 5 (2012): 1277, https://doi.org/10.1183/09031936.00044812.
[718] Oriana Ciani, Anthony M. Manyara, Philippa Davies, Derek Stewart, Christopher J. Weir, Amber E. Young, Jane Blazeby, et al, "A Framework for the Definition and Interpretation of the Use of Surrogate Endpoints in Interventional Trials," *eClinicalMedicine* 65 (November 2023): 102283, pg. 2-3. https://doi.org/10.1016/j.eclinm.2023.102283.
[719] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.

& Johnson by advancing their planned regimen of pretomanid, bedaquiline, and linezolid through the regulatory gauntlet at the FDA. Their partnership with J&J allowed them to have the research and trial data to determine if pretomanid and bedaquiline could be used in consortium with one another, and it allowed for their end goal of a new tuberculosis regimen that differed from the current standard of care to enter the field. Without the use of isoniazid or the key drug rifampicin, this combination therapy offers an entirely separate method of treatment that currently boasts an 84-93% cure rate for MDR TB.[720] [721]

TB Alliance will not make any money on the sale of bedaquiline in this regimen, as it is only used for resistant strains of TB.[722] However, their continued research, perseverance, and commitment to the treatment of tuberculosis despite this lack of profit has advanced the overall field. It also, naturally, has opened a pathway for Johnson & Johnson to generate additional revenue from additional sales of bedaquiline in the future as a result of the particulars of their regimen. In effect, TB Alliance's contribution has been one where they financially supported the development of bedaquiline, and have ensured its continued sale and distribution despite the lack of active license on the drug itself. A great bonus for Johnson & Johnson, but also, due to TB Alliance's dedication: a great benefit for the patients in desperate need of a new regimen for resistant-TB.

As a product development partnership, TB Alliance's main commitment was to the development of the product: bedaquiline.[723] Their financial investment and their collaboration allowed for the clinical trials to proceed effectively. They were able to bring

[720] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.
[721] Francesca Conradie, Tatevik R. Bagdasaryan, Sergey Borisov, Pauline Howell, Lali Mikiashvili, Nosipho Ngubane, Anastasia Samoilova, et al, "Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis," *New England Journal of Medicine* 387, no. 9 (September 1, 2022): 817. https://doi.org/10.1056/NEJMoa2119430.
[722] Bedaquiline is not approved for drug-susceptible TB at this time as the requirements to pass regulatory approval are more stringent for drug-susceptible TB as the treatments in that space are still very effective. As a result, TB Alliance which only has licensing authorization for drug-susceptible TB receives no royalties for any sales of bedaquiline when it is being used to treat MDR TB despite their investment in bedaquiline's success.
[723] Melvin Spigelman, Interview by Erin L. Paterson, 21 December 2023.

together public funds and private enterprise to ensure the product came to market. In following from Chapter Three, the aspects of their public private partnership with Johnson & Johnson emphasized that the type of business arrangement and financial agreements could serve as a viable option in bringing a new antibiotic through the pipeline – even if that pipeline includes seven years of trial work. As there was a great deal of uncertainty between 2005 and 2012 as to what bedaquiline's fate could be, this partnership helped alleviate the concerns Johnson & Johnson had about getting the drug out into the world. In this sense, this partnership was very successful. It was not, however, the only financial pathway used to get bedaquiline through to launch, and Johnson & Johnson made certain to take advantage of other mechanisms of financial relief wherever they appeared.

b. Impact of the Orphan Drug Tax Credit on bedaquiline's development

The Orphan Drug Tax Credit was established in the United States of America in 1983 as a method of increasing pharmaceutical investment in the development of treatments for rare diseases. During the 1970s, it was observed that pharmaceutical companies were naturally focusing on developing treatments or cures that addressed large patient populations.[724] This focus made sense for the general population, but it meant that individuals suffering from diseases that affected less than 200,000 people a year received little to no relief. By 1982 the Food and Drug Administration began looking into potential incentives to encourage pharmaceutical interest in targeting such diseases, and by the time the Orphan Drug Act (ODA) was finalized in 1983 those incentives amounted to:

> protocol assistance (written recommendations from the US Food and Drug Administration (FDA) on the preclinical and clinical studies necessary for marketing approval); tax credits equal to 50 percent of the qualified clinical testing expenses; waiver of Prescription Drug User Fee Act marketing application fee; orphan product development grants; and, most importantly, seven-year marketing exclusivity once the drug is approved by FDA.[725]

[724] John Swann, "The Story Behind the Orphan Drug Act," FDA, Feb. 2019. www.fda.gov, https://www.fda.gov/industry/fdas-rare-disease-day/story-behind-orphan-drug-act.
[725] Robert C. Griggs, et al, "Clinical Research for Rare Disease: Opportunities, Challenges, and Solutions," *Molecular Genetics and Metabolism*, vol. 96, no. 1, Jan. 2009, pp. 22. DOI.org (Crossref),

Protocol assistance, which at the time was seen as a form of olive branch to help ease application disagreements between industry and regulators, has been less useful in the past few decades as alternative measures have been put in place to assist industry move drugs through the development pipeline. After the Food and Drug Modernization Act of 1997, much of the advice and explanation that would have been included in the original dissemination of protocol assistance from the FDA were branched out into other programs that were more easily available to researchers and developers. These options included various agency meetings, pre-Investigational New Drug meetings, end-of-Phase I meetings, end-of-Phase II meetings, pre-New Drug Application meetings, and others.[726] All of these Tibotec eagerly took advantage of.

The details of Tibotec's relationship with the FDA in regards to bedaquiline were explicitly laid out in bedaquiline's request for market authorization in 2012. The medical reviewer assigned to their case, Ariel R. Porcalla, highlighted six such meetings that took place between 2006 and 2011, each preparing for the next step in the regulatory approval process. A complete timeline of these interactions has been recreated below, with meetings highlighted for additional clarity:

Date	Action/Issues
January 10, 2005	Orphan-drug designation was granted by FDA for bedaquiline as treatment for MDR-TB.
July 11, 2006	Face-to Face Pre-IND meeting between the Division of Special Pathogen and Transplant Products (DSPTP) and the Tibotec, Inc.
November 9, 2006	Submission of IND 69,600
September 28, 2008	Type C meeting between DSPTP and Tibotec, Inc to discuss results from Trial C208 Stage 1 and the bedaquiline treatment program to support an initial submission of a New Drug Application for bedaquiline for MDR-TB
June 3, 2009	Anti-infective Drugs Advisory Committee meeting was held to discuss issues related to the development of MDR-TB treatment
February 9, 2011	EOP2 meeting to discuss the proposal for overall development program for bedaquiline, including the adequacy of the data from Trial C208 Stages 1 and 2 and the confirmatory Phase 3 Trial C210 study design to support an accelerated and traditional approval for bedaquiline as treatment for MDR-TB. The Sponsor agreed to modify the Phase 3 study design based on concerns about the lack of

https://doi.org/10.1016/j.ymgme.2008.10.003.

[726] Jeff Fritsch, "Webinar on Orphan Product Development," (Transcript, United States of America Food & Drug Administration, January 23, 2009), 22, https://www.fda.gov/media/89129/download

	justification for the proposed non-inferiority margin.
April 22, 2011	Bedaquiline was granted fast-track designation
May 13, 2011	Teleconference on the two proposals for study design for the confirmatory Phase 3 trial. The use of a modified Bangladesh background regimen given 9 months with bedaquiline vs a Bangladesh background regimen with placebo could support traditional approval
October 7, 2011	Pre-NDA Meeting
June 29, 2012	Submission of the New Drug Application for bedaquiline

Table 5 Timeline of bedaquiline's NDA[727]

However, Porcalla's review of bedaquiline's New Drug Application clearly states that specific advice on trial data requirements that the drug would need to prove were provided to Tibotec during these meetings. This insight almost certainly ensured a smooth regulatory review and enabled the clinical trials to proceed in a manner that collected the exact data necessary to convince the FDA of approving the application. This is not to imply that bedaquiline would never have succeeded without such advice, or that the trials themselves were somehow altered to provide only a favorable result, but rather that the data collected from the trials was done so with the knowledge that those specific outcomes would be what regulators were keen to observe. Time, in this case, is what was saved by these meetings, as it limited the need for additional trial studies that could only be conducted after receiving a potential rejection for lack of satisfactory evidence.

The nebulous impact of the protocol assistance portion of the ODA leaves it as only potentially or implicitly useful as an incentive to the drug application process, however the remaining incentives the ODA provide far more fiscally tangible results. The tax credits that are supplied to a company can reach up to fifty percent of all "clinical research and testing expenses" that specifically occurs in human patients.[728] Any pre-clinical trials or in vitro studies would not be covered by this tax credit, only human trials. In the case of bedaquiline, the timing ad use of this tax credit is evident. On 10 January 2005, seven months before its first patient trial, bedaquiline received designated approval by the FDA as an Orphan Drug.[729]

[727] Ariel Porcalla, "New Drug Application: Bedaquiline," Medical Review. Maryland: Division of Anti-Infective Products/ Office of Antimicrobial Products, December 26, 2012.
[728] Fritsch, "Webinar on Orphan Product Development."
[729] U.S. Food and Drug Administration, "Bedaquiline," Database of Orphan Drug Designations and Approvals.

Of interest, considering the developmental history of the drug, the application was not submitted by Tibotec, but rather, Janssen Research & Development, LLC.[730] Six years later, Janssen would officially merge with Tibotec, consolidating the laboratories and all additional work under this umbrella title, but in 2005 the merger had yet to be finalized. The groundwork was clearly being set, however and this application marks one of the first times that developmental 'credit' of bedaquiline shifted away from Tibotec and became more firmly entrenched as a Janssen product. Johnson & Johnson announced the merger publicly on 22 June 2011,[731] and future clinical trials would retain Janssen as the study funders with no additional mention to Tibotec.[732] From the perspective of the US FDA, Tibotec officially alerted the agency to the transfer of drug sponsorship on 22 December 2011; moving forward sole responsibility of bedaquiline would belong to Janssen Research and Development LLC.[733]

Regardless of which company was officially responsible for the drug in the eyes of the FDA, for parent company Johnson & Johnson, the Orphan Drug Status was indeed the prize it most needed. Its human trial costs would now be halved because of this designation. This particular credit would be particularly valuable for J&J as clinical trials for bedaquiline stretched on for multiple years.

After the first 2005 attempt was made, two additional full-length clinical trials were conducted from 2007-2013. One trial, which for convenience has been separated into two

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Accessed 15 December 2023.

[730] The more bedaquiline began to emerge as a viable drug, the more Janssen's name became associated with its development rather than Tibotec. In future publications or references, Janssen (or Johnson & Johnson directly) would continue to be identified as the developer of the molecule.

[731] Pamela Van Houten, "Tibotec Therapeutics Becomes Janssen Therapeutics, Part Of The Janssen Pharmaceutical Companies," Johnson & Johnson Media Center, June 22, 2011, https://www.jnj.com/media-center/press-releases/tibotec-therapeutics-becomes-janssen-therapeutics-part-of-the-janssen-pharmaceutical-companies.

[732] Andreas H. Diacon, Alexander Pym, Martin P. Grobusch, Jorge M. De Los Rios, Eduardo Gotuzzo, Irina Vasilyeva, Vaira Leimane, et al, "Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline," *New England Journal of Medicine* 371, no. 8 (August 21, 2014): 724. https://doi.org/10.1056/NEJMoa1313865.

[733] Ariel Porcalla, "New Drug Application: Bedaquiline," *Medical Review,* (Maryland, United States: Division of Anti-Infective Products/Office of Antimicrobial Products, December 26, 2012), 27.

stages with unique identifiers, ran from 2007-2010 and was meant to test the efficacy of bedaquiline over time. Broken into two stages, the trial first treated patients with bedaquiline for eight weeks, and then conducted an additional 96 weeks of follow up to verify patient health and well-being after the treatment. In the second stage, patients were treated with bedaquiline for a total of 24 weeks, then received an additional 96 weeks of intermittent observation. Each patient therefore required a total of 104-120 weeks (two years-two years and four months) of observation depending on which stage of the clinical trial they were enrolled in. The FDA reports that the length of this trial lasted between 2007-2009,[734] but the Clinical Trial database indicates the final patient received a treatment in March 2010 with the studies officially closing in October 2012 after all review and analysis had been completed.[735] [736]

Trial Name	Trial Type	Study Start and End Date(s)	Treatment Duration	Population
TMC207-C202	Randomized, open-label, active-controlled	May 2005 – October 2005	7 days	DS-TB
TMC207-C208 Stage 1	Randomized, double-blind, placebo-controlled	June 2007 – March 2010 (Final completion: October 2012)	8 weeks	Newly diagnosed MDRH&R-TB/pre-XDR-TB
TMC207-C208 Stage 2	Randomized, double-blind, placebo-controlled	June 2007 – March 2010 (Final completion: October 2012)	24 weeks	Newly diagnosed MDRH&R-TB/pre-XDR-TB
TMC207-C209 (investigational treatment completed)	Open-label, uncontrolled	September 2009 - January 2013	24 weeks	Newly diagnosed or previously treated MDRH&R-TB/Pre-XDR-TB/XDR-TB

Table 6 Summary of bedaquiline's clinical trials[737]

[734] Porcalla, "New Drug Application: Bedaquiline," 37.
[735] "TMC207-TiDP13-C208: Anti-Bacterial Activity, Safety, and Tolerability of TMC207 in Participants With Multi-Drug Resistant Mycobacterium Tuberculosis (MDR-TB)," Clinical Trial Data, National Library of Medicine, April 29, 2014. https://clinicaltrials.gov/study/NCT00449644?a=39.
[736] Although the Clinical Trial database implies that Stage One testing would take place prior to Stage Two, it is not clear when Stage Two began or if certain countries (due to earlier recruiting capabilities) were able to move forward with their Stage Two testing earlier than others, for this reason the dates of these trials reflect the start and end date of both Stages from direct project origin to final terminus of work.
[737] Porcalla, Ariel. "New Drug Application: Bedaquiline." Medical Review. Maryland: Division of Anti-Infective Products/ Office of Antimicrobial Products, December 26, 2012, 37, 42.
Additional information provided by: "TMC207-TiDP13-C208: Anti-Bacterial Activity, Safety, and Tolerability of TMC207 in Participants With Multi-Drug Resistant Mycobacterium Tuberculosis (MDR-TB)." Clinical Trial Data. National Library of Medicine, April 29, 2014. National Library of Medicine.

The final Phase II trial conducted prior to its approval by the US FDA also spanned 120 weeks of patient treatment and observation, though initial documents requesting for early marketing access approval were delivered to the FDA at the 72-week mark.[738] Cumulatively, from the publicly available information I have been able to review, the amount of time needed to conduct all of these trials was roughly nine years and two months, including data analysis and review beyond patient treatment cycles. Thanks to the ODA's tax credit, half of all expenses accrued during this time were waived.

Similarly waived was the Prescription Drug User Fee Act (PDUFA) marketing application fee. During the 1980s, concern rose amongst American citizens and businessmen regarding the length of time it took a drug to make it through the FDA marketing approval process. At that time, the average length of time between application and response) lasted 29 months.[739] The FDA stated that it did not have the budget or the ability to manage the intense case load that was being set before their staff, and in response, congress passed the Prescription Drug User Fee Act to generate these funds. In 1992 when the law passed, these fees amounted to $100,000 per application.[740] By 2012 when bedaquiline's application had been submitted, that fee had risen to $1,841,500 along with the cost of doing business, increase in government workload, and inflation.[741] [742] This fee was automatically waived for

https://clinicaltrials.gov/study/NCT00449644?a=39.
And: "To Evaluate the Safety, Tolerability, and Efficacy of TMC207 as Part of an Individualized Multi-Drug Resistant Tuberculosis (MDR-TB) Treatment Regimen in Participants With Sputum Smear-Positive Pulmonary MDR-TB." Clinical Trial Data. National Library of Medicine, April 24, 2015. https://clinicaltrials.gov/study/NCT00910871?term=bedaquiline&intr=TMC207-C209%20&rank=1.

[738] Edward Cox and Katherine Laessig, "FDA Approval of Bedaquiline — The Benefit–Risk Balance for Drug-Resistant Tuberculosis," *New England Journal of Medicine* 371, no. 8 (August 21, 2014): 689. https://doi.org/10.1056/NEJMp1314385.

[739] Aaron P. Mitchell, Niti U. Trivedi, and Peter B. Bach, "The Prescription Drug User Fee Act: Much More Than User Fees," *Medical Care* 60, no. 4 (April 2022): 289, https://doi.org/10.1097/MLR.0000000000001692.

[740] Mitchell, Trivedi, and Bach, "The Prescription Drug User Fee Act," 290. 2

[741] Food and Drug Administration, Prescription Drug User Fee Rates for Fiscal Year 2012, § 76 FR 45831 (2011). https://www.federalregister.gov/documents/2011/08/01/2011-19332/prescription-drug-user-fee-rates-for-fiscal-year-2012.

[742] PDUFA user fees fluctuate overtime based on congressional approval, but key determining factors include the expected workload of the FDA, the status of the business that is submitting drugs for approval (i.e.: how many times has a company submitted a drug that year to the FDA for review). For critiques and analysis on how fees are determined and what the impact of these fees are consult: Joel Lexchin, "Drug Approval Times and

bedaquiline due to its Orphan Drug status. However, it is important to note that this is not money that directly goes to Johnson & Johnson, it is merely funds that J&J *did not have to spend.* The valuation here is not something that increased the coffers funding bedaquiline's progress through the pipeline, but rather the removal of a barrier that could have occurred at a future date in time.

A place where money does change hands, however, comes in the form of the orphan product development grants. These grants are advertised on the Federal Register via Requests for Applications and are posted on a yearly basis. In 2009, the yearly budget for these grants was $14.2 million and the average grant provided to Orphan Drug development ranged from $200,000-400,000.[743] It is unclear if J&J took advantage of these potential grants, but they would have been made available to J&J had they applied. The grant term lasts for four years, and an estimated $800,000-1,600,000 could have been received to help offset developmental costs associated with the development of bedaquiline throughout its clinical trials.

Finally, the ODA provides seven-year marketing exclusivity once the drug is approved by FDA. This was summarily granted to bedaquiline on three separate occasions. Market exclusivity was first granted to bedaquiline for the years 2012-2019 for its use in adult patients with MDR-TB, then between 2019-2026 for use in pediatric patients between the ages of 12 and 18 with MDR-TB, and finally from 2020 to 2027 for use in pediatric patients between 5-12 years old with MDR-TB.[744] This exclusivity is important in the context of the United States as it was expected to marginally extend past the end bedaquiline's patent term.

User Fees: An International Perspective in a Changing World," *Pharmaceutical Medicine* 22, no. 1 (2008); Susan Thaul, "Prescription Drug User Fee Act (PDUFA): 2012 Reauthorization as PDUFA V," CRS Report for Congress, (Washington DC, United States: Congressional Research Service, February 22, 2013);
And: Ke Dong, Garth Boehm, and Zheng, "Economic Impacts of the Generic Drug User Fee Act Fee Structure," *Value in Health* 20 (2017): 792–98, http://dx.doi.org/10.1016/j.jval.2016.05.003.

[743] Fritsch, "Webinar on Orphan Product Development," 33.

[744] U.S. Food and Drug Administration, "Bedaquiline," Database of Orphan Drug Designations and Approvals, Accessed 15 December 2023.

In 2014, UNITAID and the World Health Organization published a scoping report entitled "A Review of the Bedaquiline Patent Landscape" which identified each of the patents that had been submitted for bedaquiline. Five patents where submitted by Janssen Pharmaceutica N.V. between 2004 and 2008.

Patent 1	**Patent 2**	**Patent 3**	**Patent 4**	**Patent 5**
Substituted quinoline derivative compounds, including the free base, enantiomers and isomers of bedaquiline (This patent includes the base compound bedaquiline with antimycobacterial properties and blocks all manufacturing of the product if granted)	Use of substituted quinoline derivative compounds for the treatment of drug-resistant mycobacterial diseases (This patent covers the use of bedaquiline for the preparation of a medicament for the treatment of drug-resistant mycobacteria, in particular multidrug-resistant mycobacteria)	Use of quinoline derivative compounds, including bedaquiline, for the treatment of latent tuberculosis (This patent covers the use of bedaquiline for the manufacture of a medicament for the treatment of latent tuberculosis)	Process for preparing the enantiomer form of bedaquiline (This patent covers a process for the isolation of the enantiomer of bedaquiline from a mixture of stereoisomeric forms by optical resolution)	Fumarate salt of bedaquiline and the enantiomer of bedaquiline (This patent covers pharmaceutical compositions/ formulations for administration purposes)
International Patent Number: WO 2004/011436	**International Patent Number:** WO 2005/117875	**International Patent Number:** WO 2006/067048	**International Patent Number:** WO 2006/125769	**International Patent Number:** WO 2008/068231
Expected Patent expiration date: 18 July 2023	**Expected Patent expiration date:** 24 May 2025	**Expected Patent expiration date:** 8 December 2025	**Expected Patent expiration date:** 22 May 2026	**Expected Patent expiration date:** 3 December 2027

Table 7 Bedaquiline's patents and patent expiration dates[745]

Janssen applied for bedaquiline's patent worldwide, and UNITAID's estimations would hold true for some but not all of the possibilities that it had foreseen. In the United States, Patents 2-4 were abandoned by Janssen before a decision was made, however the final approved date for the end of the patent life was extended for both the first and fifth patent. The first is due to expire in 2026, with the fifth expiring in 2029.[746] [747] Neither of those determinations were known to Janssen at the time it had made its applications in 2004 and 2007 respectively. Had

[745] UNITAID Secretariat. "A Review of the Bedaquiline Patent Landscape: A Scoping Report." Geneva: World Health Organization, January 2014, 7, http://www.unitaid.org/assets/TMC_207_Patent_Landscape.pdf.
[746] Jean Francois Alexandre Lucas Hegyi, Wim Albert Alex Aelterman, Yolande Lydia Lang, Sigrid Carl Maria stokbroekx, et al., Fumarate Salt of (Alpha S, Beta R)-6-Bromo-Alpha- [2-Mythoxy-Alpha-1-Naphthalenyl-Beta-Phenyl-3-Quinoloneethanol, US Patent 20100028428A1, filed December 3, 2017, and issued May 22, 2009.
[747] Jozef Frans Elisabetha Van Gestel, Jerome Emile Georges Guillemont, Marc Gaston Venet, Herve Jean Joseph Poignet, et al., Novel Mycobacterial Inhibitors, Us Patent 20050148581A1, filed December 8, 2004, and issued July 7, 2005

their expiration dates been in fact what UNITAID had suggested, the seven-year market exclusivity granted by the Orphan Drug Act would have marginally extended their applicable term. However, in this circumstance: the seven-year market exclusivity did not overall contribute to improving or affecting bedaquiline status on the market due to its far lengthier patent term that it had run parallel with after approval.

Despite the lack of potentially lucrative investments due to a seven-year market exclusivity, the total impact of the ODA on bedaquiline should not be underestimated. With the fee waiver and clinical trial payments halved, along with associated other benefits via potential grants etc., the value of the ODA for bedaquiline has been estimated at $22-36 million.[748] This number is, however, one of the smaller portions of the investments made by outside (public) parties for the development of bedaquiline. As the following sections will explore in more detail.

c. Johnson & Johnson's Priority Review Voucher and its alleged economic potential

The Orphan Drug Act attempted to jump start research into the field of neglected or rare diseases. To a certain extent, it did succeed in reinvigorating research interest into this field. However, by 1999, the growth was still nominal. As Celine Aerts, Eliana Barrenho, Marisa Miraldo, and Elisa Sicuri have written, of the 118,634 new drug trials put in place in the United States between September 1999 and December 2011, only 1% were for neglected diseases, despite rare diseases encompassing 12% of the global disease burden.[749] The United States government proceeded to introduce a second inventive program, the Priority Review Voucher System, to help encourage development. On its face, the concept was relatively

[748] D Gotham, L McKenna, M Frick, and E Lessem, "Public Investments in the Clinical Development of Bedaquiline," *PLoS ONE* 15, no. 9 (2020): 6, https://doi.org/https://doi.org/10.1371/journal.pone.0239118.
[749] Celine Aerts, Eliana Barrenho, Marisa Miraldo, and Elisa Sicuri, "The Impact of the Priority Review Voucher on Research and Development for Tropical Diseases," *Pharmaceutical Medicine* 36, no. 3 (June 2022): 190. https://doi.org/10.1007/s40290-022-00427-x.

straight forwards. Applicants would provide data showing that a company is developing a drug that targets a neglected disease. In return, a Priority Review Voucher (PRV) would be given to the company. This voucher would cut down the amount of time that a drug sat waiting for an FDA agent to review the file (typically decreasing the wait from 10 to six months). However, the voucher also came with a unique twist: it did not need to be used for the drug that had triggered receipt of the voucher in the first place. The originator company could choose to either:

1. Use it on the application drug;
2. Use it on a different drug in their company's portfolio; or
3. Sell the drug to another company so *they* may use it as they saw fit.

With these possibilities, the value of a PRV quickly became a method of not only generating income that could offset development costs, but an avenue for speedy progress through the regulatory process as well.

David B. Ridley, Henry G. Grabowski, and Jeffrey L. Moe first pitched the concept of the Priority Review Voucher System in *Health Affairs* in 2006.[750] They estimated the length of time that a drug took to be reviewed by the FDA, then compared it to the length of time a priority drug received approval, calculating a potential of $300 million in additional value given to a blockbuster drug as a result of quicker approvals.[751] All three authors have been affiliated with Duke University in various capacities, largely as economists/health economists or professors of global health. Their intentions behind developing the PRV system that was eventually adopted by the United States federal government was multi-faceted as their report highlights both the public health good (particularly in the cases of neglected diseases such as tuberculosis) for low income countries, and the value the PRV can hold as an enticement for PPPs when entering negotiations with private partners, creating a trifecta of benefits for

[750] David B. Ridley, Henry G. Grabowski, and Jeffrey L. Moe, "Developing Drugs For Developing Countries," *Health Affairs* 25, no. 2 (March 2006): 313–24, https://doi.org/10.1377/hlthaff.25.2.313.
[751] Ridley, Grabowski, and Moe, "Developing Drugs For Developing Countries," 315.

manufacturers, developers, and people in need. [752] [753]

The utilization and impact of their PRV would not be without critics, however, particularly in terms of access. Although "it offers a financial incentive for firms to create new drugs for neglected diseases…unfortunately the incentive stops there—an innovator firm has scant reason to ensure that its new medicine is accessible to the patients who need it."[754] In Ridley et al.'s initial PRV suggestion, accessibility had been kept in mind, by "limiting the grant of PRVs to companies that developed drugs or biologics exhibiting clinical superiority to existing treatments, companies that had foregone patent rights to the product, and companies that had identified at least one manufacturer for the tropical disease product," however in the FDA's final version, these limitations were not included.[755] MSF Access Campaign in particular took umbrage to this change in the FDA's final version of the PRV, questioning why additional funds should be granted to a pharmaceutical company for creating a product ostensibly for people in need, but not ensuring they gain access to that product.[756] In a letter to congress, co-signed by TB Alliance, DNDi, and others, the MSF Access Campaign argued that the products emerging as a result of the PRVs were not actually assisting the communities at need.[757]

One of the co-signatories of that letter included the Treatment Action Group. [758] Only

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[752] Ridley, Grabowski, and Moe, "Developing Drugs For Developing Countries," 318-20.
[753] Henry G. Grabowski, David B. Ridley, and Jeffrey L. Moe, "Priority Review Vouchers to Encourage Innovation for Neglected Diseases," (Durham, United States: Duke University, September 2008) 6-11.
[754] M. Peterson, A. Hollis, and T. Pogge, "A Critique in Need of Critique," *Public Health Ethics* 3, no. 2 (July 1, 2010): 181, https://doi.org/10.1093/phe/php037.
[755] Hamming, Lesley. "The Promise of Priority Review Vouchers as a Legislative Tool to Encourage Drugs for Neglected Diseases." *Duke Law & Technology Review* 11, no. 2 (2013): 401.
[756] MSF Access Campaign. "FDA Priority Review Voucher Program," February 16, 2018. https://msfaccess.org/fda-priority-review-voucher-program.
[757] American Thoracic Society, Drugs for Neglected Diseases initiative, HIV Medicine Association, Infectious Diseases Society of America, Médecins Sans Frontières/Doctors Without Borders USA, TB Alliance, and Treatment Action Group, "Global Health Groups Appeal to Congress: Fix the FDA PRV for Neglected Diseases," Letter to Congress, (April 28, 2017). https://msfaccess.org/sites/default/files/MSF_assets/NegDis/Docs/NTDs_Letter_FixFDAPRVforNTDs_ENG_2017.pdf.
[758] Treatment Action Group is an HIV/AIDS activist organization that has been speaking on the need for improved tuberculosis treatment since 2002 due to its status as a frequent opportunistic infection with HIV/AIDS.

a few years after their signing, independent researchers associated with the Treatment Action Group, Gotham et al, would target the PRV's usage in bedaquiline specifically in a journal article critiquing the amount of public investment dedicated to bedaquiline and the lack of access and availability bedaquiline had despite these funds. In their estimates revolving around the PRV, they expanded the total value from what Ridley et al. had suggested the PRV could be worth in their initial 2006 article, determining that the value of the PRV that bedaquiline received to be between $300-400 million. [759]

Although Gotham et al.'s article was intensively researched and offers a particular critique with the use of public funds in private corporations, suggesting ethical concerns when the drug invested in does not reach the intended recipients, there could be an alternative explanation to their work. First, their methodology on how they assessed the value of the PRV is not clear. It has been several years since J&J received their voucher, and they did in fact use it, but Gotham et al. does not seem to have assessed the value of the voucher based off of what was done, but the potential value the voucher may have been able to provide. Even then, their estimation seems convoluted. At time of writing, of the 31 vouchers that have been delivered to pharmaceutical companies since 2009, only sixteen have ever been utilized. For those that have sold, sales data includes:

- BioMarin in 2014, who sold their voucher to an undisclosed buyer for $67.5 million.[760]
- United Therapeutics in 2015, who sold their voucher to AbbVie Inc for $350 million.[761]
- Retrophin in 2015, who sold their voucher to Sanofi for $245 million.[762]
- Ultragenyx in 2017, who sold their voucher to Novartis for $130 million[763]
- Mallinckrodt in 2022, who sold their voucher to Novartis for $100 million.[764]

[759] Gotham, et al., "Public Investments in the Clinical Development of Bedaquiline," 6.
[760] Jennifer Levin, "BioMarin Sells Priority Review Voucher for $67.5 Million," *Fierce Biotech*, July 30, 2014. Available from: http://www.fiercebiotech.com/press-releases/biomarin-sells-priority-review-voucher-675-million/)
[761] Reuters, "AbbVie Buys Special Review Voucher for $350 Million," August 19, 2015, sec. Healthcare & Pharmaceuticals, https://www.reuters.com/article/idUSKCN0QO1LP/.
[762] Pharmaphorum, "Priority Review Voucher Prices Fall Again after Spark's $110m Sale," Accessed January 11, 2024, https://pharmaphorum.com/news/spark-sells-priority-review-voucher-to-jazz.
[763] Pharmaphorum, "Priority Review Voucher Prices Fall Again after Spark's $110m Sale," Accessed January 11, 2024, https://pharmaphorum.com/news/spark-sells-priority-review-voucher-to-jazz.
[764] James Waldron, "Novartis buys priority review voucher from Pharming for discount price of $21M," *Fierce*

- Marinus in 2022, who sold their voucher to Novo Nordisk for $110 million.[765]
- BioMarin in 2022, who sold their voucher to an undisclosed buyer for $110 million. [766]
- Pharming in 2023, who sold their voucher to Novartis for $21.1 million.[767]
- Sarepta Therapeutics, Inc in 2023, who sold their voucher to an undisclosed buyer for $102 million.[768]
- bluebird bio, Inc. in 2023, who sold their voucher to an undisclosed buyer for $95 million.[769]

Aside from the astronomical sale between United Therapeutics and AbbVie, the average sale price for these vouchers hovers round $108 million, far lower than what Gotham et al. indicated.

Furthermore, for Janssen, the possibility of generating income with their PRV would have come with increased risks. At the time it had received the PRV, it was only the second company in the history of the program to receive it, and while the $67.5 million-dollar sale of the voucher that came before it may have been somewhat enticing, Janssen opted not to sell their voucher but to use it for a different project in the J&J portfolio. In November 2016, Janssen submitted its New Drug Application for Tremfya, a treatment of moderate-to-severe plaque psoriasis, receiving approval received eight months later.[770] In 2018, the FDA reported that the standard time to review a New Drug Application was 10 months, and so this voucher saved a potential two months of additional review time. Far less than the gap Ridley et al. had envisioned when they pitched the voucher system in 2006. Then, they had suggested whittling the review period from eighteen months to six months.[771]

Biotech. June 1, 2023, https://www.fiercebiotech.com/biotech/novartis-buys-priority-review-voucher-pharming-discount-price-21m.

[765] Waldron,, "Novartis buys priority review voucher from Pharming for discount price of $21M."

[766] BioMarin Investors, "BioMarin Sells Priority Review Voucher for $110 Million," Accessed January 11, 2024, https://investors.biomarin.com/2022-02-09-BioMarin-Sells-Priority-Review-Voucher-for-110-Million.

[767] Waldron, "Novartis buys priority review voucher from Pharming for discount price of $21M." m

[768] Tracy Sorrentino, "Sarepta Therapeutics Announces Sale of Priority Review Voucher for $102 million," *Sarepta Therapeutics*. July 5, 2023, https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-sale-priority-review-voucher-102.

[769] Businesswire, "Bluebird Bio Sells Second Priority Review Voucher for $95 Million," January 6, 2023, https://www.businesswire.com/news/home/20230106005087/en/bluebird-bio-Sells-Second-Priority-Review-Voucher-for-95-Million.

[770] Jason J. Jardine, "Janssen Biologic Tremfya Secures FDA Approval Following Use of Priority Review Voucher," *Knobble Martens*, July 25, 2017, https://www.knobbe.com/news/2017/07/janssen-biologic-tremfya-secures-fda-approval-following-use-priority-review-voucher.

[771] Ridley, Grabowski, and Moe, "Developing Drugs For Developing Countries," 315.

Tremfya did well as a drug on the market in its first year, earning $544 million at the start,[772] with $47 million just in the fourth quarter after it had received approval in July.[773] However these numbers and the potential value gained from Tremfya's priority approval do not seem to match the estimated value that Gotham et al. imply Johnson & Johnson received as a result of owning this voucher. Nor would this money be allocated to bedaquiline's production after the fact. This voucher, and however much it enabled J&J to earn on Tremfya would have been solely dedicated to Tremfya, and not to bedaquiline. And while the company may have indeed increased its sales for Tremfya as a result of this voucher, the totality of that impact may not be known without the public dissemination of sales data from the company itself.

Of key importance here, however, is the perception that the priority review voucher is something that is funded by public sector investments.[774] While there is potential for a company to gain additional money as a result of receiving an early approval, and while drugs that receive priority valuations do necessarily cause a delay in drugs that are utilizing the standard approval process as those drugs must wait their turn in line, the actual *monetary investment* by the public, with physical cash exchanging hands: is nil. The FDA agents would have reviewed Tremfya with or without the voucher, the only change came in the form of time. Actual tax payer or public money put into the development of bedaquiline neither increased or decreased from standard funds as a result. Gotham et al. created an infographic which highlighted the specific amount of public vs private sector investment that went into the development of bedaquiline withing their 2020 analysis.[775]

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[772] Pharmaphorum, "J&J Ends 2018 on a High, but Coming Year Looks Shaky," Accessed January 11, 2024. https://pharmaphorum.com/news/jj-ends-2018-on-a-high-but-coming-year-looks-shaky.
[773] Carly Helfand, "Johnson & Johnson's Stelara, Tremfya Step up in Q4 as Remicade's Decline Speeds," *FiercePharma,* January 24, 2018. https://www.fiercepharma.com/marketing/johnson-johnson-s-stelara-tremfya-step-up-q4-as-remicade-s-decline-speeds.
[774] Gotham, et al., "Public Investments in the Clinical Development of Bedaquiline," *6*.
[775] Gotham et al. "Public Investments in the Clinical Development of Bedaquiline," 6.

This framing casts the illusion that $300-400 million specifically went into J&J's coffers as a one to one trade. Had they *sold* the voucher, perhaps that valuation could be representative of additional potential income that bedaquiline achieved as a result of its development process. However, that still would not be considered a public sector investment as the sale would, more likely than not, have *not* been to a public sector entity. Furthermore, the valuation of what J&J received as a result of using it on Tremfya at that time is…limited. The drug only made $57 million in its first quarter. If we presume that the FDA's average response time of ten months is accurate, then Tremfya earned only two additional months on the market. At best, this voucher would have earned roughly only $28.5 million in those first two months. To suggest that $300-400 million of public sector investment directly went into bedaquiline via the priority review voucher is misleading, and it obfuscates the actual impact of public expenditures and support in drug development.

What this examination of the PRV in regards to bedaquiline shows is that the overall impact of a PRV should not be overestimated. The PRV did generate additional revenue for J&J. It was money that was not necessarily guaranteed to their corporation, but it was not near the Treatment Access Group's estimated valuation. Furthermore, historically, most PRVs were not sold for amounts greater than $300 million. A more thorough examination on the impact of all PRVs would help provide more clarity to the true value of a PRV within the dry antibiotic pipeline and other neglected disease research cycles. Within this specific context, the PRV is not a *bad* program, and more data would need to be collected on how the PRV has impacted other antibiotics that take advantage of it once such antibiotics make it through the pipeline. However, with bedaquiline in specific, its impact appears far less staggering than previous researchers have commented on thus far.

B. Assessing the relationship between a drug's trajectory and the use of a drug donation program

The final method of financing bedaquiline that will be discussed in this thesis is that

of the drug donation program tax break. While the PRV did not account for drug accessibility concerns, the drug donation program was a method of addressing such issues in advance. For this tax break, the terms specified that when a product is made, then offered to those in need without cost, this donation can be claimed as a charitable contribution and is thus tax deductible. This program, therefore, offers financial rewards for a product only after it receives market authorization.

Gotham et al. included the drug donation program in their analysis on bedaquiline, estimating that J&J likely received between $13-32 million as a result of their work within the drug donation program, though it is not clear what the actual receipt of such a tax break would amount to. Further, J&J themselves invested roughly $14-77 million into the drug donation program by Gotham et al.'s own admission.[776] While this helps understand what is involved in management of a donation program, it is important to consider that J&J did not *earn* money through tax credits for this program.

Gotham et al.'s analysis of the donation program, however, is restricted to the potential tax credits that were put in place. As their analysis continues to focus on *public* investment into bedaquiline, however, this limited view of the program as a whole hides additional contribution beyond tax credits that did go into the program's efficacy. Johnson & Johnson would not have received the funds that were involved, and in no way was responsible for managing those funds, and it is difficult to quantify the exact fiscal contribution of all public entities involved.

The donation program was developed in consortium with the United States Agency for International Development (USAID) and was originally conceived as a four-year project where J&J would donate 30,000 treatments to more than 100 countries on the Global Fund's

[776] Gotham, et al., "Public Investments in the Clinical Development of Bedaquiline," Appendix S1 pg. 6.

2016 eligibility list.[777] [778] Georgia was the first country to receive the donations in 2015, with 23 additional countries having applied for approval by the time the first USAID press release on the project's launch had gone out.[779] A section discussing the program could be found on USAID's website from 2016-2022, but by 2023 it had been removed. There is no mention as to why it is no longer publicly accessibly, however, in their 2020 Tuberculosis national action plan, USAID praised the expansion of their program, stating that by the end of their work in 2019, 105,000 treatments in 72 countries had been disseminated.[780]

To manage the product flow, USAID/J&J collaborated with the Stop TB Partnership's Global Drug Facility (of which several United States public, private, and NGO institutions donate to including the United States Air Force and – USAID as well as multi-laterals that *also* receive US funding such as the World Bank). Stop TB Partnership then, in turn, consulted with the Global Fund (which equally receives donations from the United States), to determine which countries needed access to the medicament and had the greatest need.[781] As a result of these multiple funding schemes and initiatives, the total understanding of which percentage of public investment contributed to the donation program is nearly impossible to quantify.

Finally, there is a separate impact to the donation program that could have indeed earned J&J additional funds in a faster rate. As a result of both the program and bedaquiline joining the WHO's essential medicine list, countries were quick to apply for access to their

[777] U.S. Agency for International Development, "USAID to Reach Patients in More than 100 Countries with Life-Saving Medicine for Drug-Resistant Tuberculosis," July 12, 2021. https://www.usaid.gov/basic-page/usaid-reach-patients-more-100-countries-life-saving-medicine-drug-resistant-tuberculosis.
[778] E. Rutta, C. Kambili, and Y. Mukadi, "The Bedaquiline Donation Program: Progress and Lessons Learned after 4 Years of Implementation," *The International Journal of Tuberculosis and Lung Disease* 24, no. 10 (October 1, 2020): 1039. https://doi.org/10.5588/ijtld.20.0134.
[779] U.S. Agency for International Development, "USAID to Reach Patients in More than 100 Countries with Life-Saving Medicine for Drug-Resistant Tuberculosis."
[780] USAID, "Combating Multidrug-Resistant Tuberculosis: Year Three of the National Action Plan Report," Year Three Report, (Washington DC, United States: USAID, National Institute of Allergy and Infectious Disease, Center for Disease Control and Prevention, 9, October 2019).
[781] All of these institutions also receive funds from non-United States partners as well, and in this case tracking the total global "public investment" is therefore rendered even further abstract as a result.

donated treatments. In order to gain access to the drug, however, they would need to ensure their country approved the drug being used in the first place. It is unknown how long drug approvals in each individual country may have taken otherwise, but by 2020 sixty-three countries had approved bedaquiline for use against MDR-TB[782] and this would eventually lead to J&J having the option to sell the drug on the open market once the donation program ended. It is, in its own way, another version of accelerated approval and fast tracking that ensured that their drug could sell sooner rather than later.

As a part of the overall drug trajectory story, by including a donation program in the first place, there is a sense of accountability to the extreme financial burden that is associated with the development of a new drug. For bedaquiline, from the start Johnson & Johnson had discussed the potential and implementation of a donation program as the tax benefit could be rewarding. Increased sales due to the wider access to countries where the drug had been approved was also a positive, and that did eventually impact accessibility as a result. But the actual act of donating is a precarious one, and it requires continual charity. It also was not sufficient to cover the needs of the population. Accessibility therefore was only a tentative component of this process, and for the drug itself: its trajectory as an accessible drug faltered slightly as a result.

C. Financial overview of Bedaquiline and what its economic expectations meant for its launch

On 4 June 2018, Adrian Thomas (Vice President of Global Public Health at Johnson & Johnson) delivered a prepared statement at the Interactive Civil Society Hearing on the Fight Against Tuberculosis stating that both J&J and another pharmaceutical company, Otsuka, had "both invested about $500 million each to bring one molecule to the

[782] Rutta, Kambili, and Mukadi, "The Bedaquiline Donation Program: Progress and Lessons Learned after 4 Years of Implementation," 1044.

market…and we need a lot more than that."[783] This comment is not entirely precise. Lacking any specific reports or data from Johnson & Johnson directly, Gotham et al. developed an estimate on the known expenditures and investments that had been involved in the creation of the molecule. My concerns regarding Gotham et al.'s estimation of the public investment into bedaquiline likely ranging between $455-747 million have already been stated above, but it is their estimate on J&J's specific investments that now bear additional consideration in light of Thomas's $500 million proclamation.[784]

J&J's total *out of pocket* (money actually spent) investment is calculated to be between $76-163 million.[785] There is no explanation for this figure. Gotham et al state that $500 million that Thomas projected was "likely a risk-adjusted and capitalized cost estimate,"[786] but without a clear breakdown of how precisely they produced their own estimate of J&J's expenses there is little certainty in either figure. Pharmaceuticals rarely, if ever, reveal the exact expenses accrued during the research and development phase. But estimations over what that expense total could be are not uncommon. In October 2001, just as research on bedaquiline was about to kick off, TB Alliance issued a report on *The Economics of TB Drug Development* breaking down various factors influencing TB drug creation and estimates costs needed to develop and bring a drug to market. [787] Johnson & Johnson did not help collaborate with the project, however multiple pharmaceutical companies (including GlaxoSmithKline and Enanta Pharmaceuticals), the WHO, CDC, and RTI International

[783] Adrian Thomas, "Statement," 72 Session, Interactive Civil Society Hearing on the Fight Against Tuberculosis. (United Nations, New York, June 4, 2018). Video, minutes 21:48–22:03. https://webtv.un.org/en/asset/k1y/k1y7oh47cp . Accessed 14 December 2023.
[784] Gotham, et al., "Public Investments in the Clinical Development of Bedaquiline," 6.
[785] Additional breakdown of the costs include: "tax credits at US$22–36 million, tax deductions at US$8–27 million, administration of a donation programme at US$5 million, PRV revenues at US$300–400 million. Total public investments were US$455–747 million and originator investments were US$90–240 million (if capitalized and risk-adjusted, US$647–1,201 million and US$292–772 million, respectively)." Gotham, et al., "Public Investments in the Clinical Development of Bedaquiline," 1, 5-6, 9.
[786] Gotham, et al., "Public Investments in the Clinical Development of Bedaquiline," 9.
[787] The Global Alliance for TB Drug Development, *The Economics of TB Drug Development*, (New York, United States: October 2001).

Research Institute, did.[788] They concluded, that as of 2001:

> Without considering the costs of failure…the costs of successfully developing an NCE for TB have been estimated to total approximately $36.8 million to $39.9 million (U.S. costs). This estimated range covers preclinical development ($4.9 million and $5.3 million), pharmaceutical development (at least $5.3 million), and Phases I through III of clinical development ($26.6 million). These efforts are designed to reach regulatory approval.[789]

If the cost of failures is added to that figure, the report estimates that the grand total cost of successfully developing a New Chemical Entity rests between $115-240 million.[790] Adjusted for inflation, this calculation made in 2001 would have been closer to $149-312 million in 2012 when bedaquiline received FDA approval, still significantly lower than J&J's $500 million claim.

Other estimations on total drug development cost have been made by many economists over the past six decades, with notable publications by Joseph DiMasi and the Tufts Center for the Study of Drug Development, often referred to or inspected for veracity. In 2003, one of DiMasi's publications, determined that the "average out-of-pocket costs of an NCE estimate" was $403 million, while the "average economic cost of an NCE" was $802 million."[791] Independent researchers seeking to verify whether such costs were reasonable, determined that it often depended on the drug itself, with one paper reporting that in *2014* for HIV/AIDS medications, the cost was closer to $ 479 million, compared to rheumatoid arthritis's $936 million.[792] Considering the estimates provided by TB Alliance, it would seem likely that Tuberculosis medication, similar to HIV/AIDS medications would be on the lower end of this economic spectrum.

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[788] Additional independent researchers, including Henry G. Grabowski of Duke University who first suggested the notion of the PRV were also a part of creating the report. A full catalogue of all participants can be found at The Global Alliance for TB Drug Development, *The Economics of TB Drug Development*, ix.
[789] The Global Alliance for TB Drug Development, *The Economics of TB Drug Development*, 37.
[790] The Global Alliance for TB Drug Development, *The Economics of TB Drug Development*, 38.
[791] Joseph A DiMasi, Ronald W Hansen, and Henry G Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (March 2003): 329, https://doi.org/10.1016/S0167-6296(02)00126-1.
[792] Christopher P. Adams, and Van V. Brantner, "Estimating The Cost Of New Drug Development: Is It Really $802 Million?" *Health Affairs* 25, no. 2 (March 2006): 427, https://doi.org/10.1377/hlthaff.25.2.420.

Without clearly documented evidence that explicitly reveal the out of pocket expenses accrued by J&J or its subsidiaries for the development of bedaquiline, however, what is clear is that as far as the public is concerned: $500 million is the amount that J&J *themselves* invested into this product, and it is the amount they would at minimum seek to recoup upon the sale of said product.

Throughout this chapter I have detailed the ways in which public financing has played a role in the development of this drug. With the TB Alliance's support, the various tax credits/deductions, and even the PRV, have had a financial impact on the development of bedaquiline. Whether or not Gotham et al.'s financial assessment is accurate to the penny does not distract from the fact that the public investment was there and it provided financial assistance to J&J when it came to ensuring it brought bedaquiline to market and tax relief after the fact.

It is here that J&J faced a particularly complicated challenge. Tuberculosis is a disease that primarily affects those who live in impoverished communities. Regardless of the high patient numbers, to make an efficacious treatment or cure for tuberculosis is to do so for those who either cannot pay or can only pay with difficulty.[793] J&J's solution to this matter was to institute a tiered pricing system, designed to pass the greatest financial burden to high income countries. Exclusive of the drug donation program which was discussed earlier in this chapter, *sales* of bedaquiline were priced via six-month treatment courses with high income countries paying $30,000 USD per course; medium income countries paying $3,000; and, low income countries paying only $900 per course.[794]

This pricing scheme was seen as incomparably prohibitive, and equally incompatible to the global market. Although the tiered pricing for national income levels has been the norm

[793] Hans Hogerzeil, Interview by Erin L. Paterson. 2 February 2023.
[794] WHO Expert Committee, "The Selection of Essential Medicines," World Health Organization Technical Report Series 994, (Geneva, Switzerland: World Health Organization, 2015), 29.

following the TRIPS and Doha Declarations and the various drives for increased access to medicines, the prices themselves were still too high for patients to afford them. In High Income Countries, some insurance companies balked at such fees.[795] In Low to Middle Income Countries, they were simply non-starters.

Independent research groups and organizations, such as Médecins Sans Frontières, immediately began to protest the pricing scheme. Following bedaquiline's addition to the Essential Medicines List and the natural routine of the EML serving as a method of lowering pricing, J&J did follow suit.[796] But it was continually harangued for not lowering the price *enough.* In 2017, one research group estimated that the drug could be sold for as little as $8-17/month ($102 for six month treatment) and still make a global profit,[797] but by 2020, the price had only dropped for low-income countries from the original $900 to $340 (roughly $1.50/day of treatment), with the added bonus that for every confirmed purchase: a 20% discount would be applied to another supply.[798] In other words, every five purchases led to one course of bedaquiline being made available for free, dropping the "total" cost to roughly $272/course of 188 tablets.[799]

Despite this and *including* the drug donation program, in the first seven years after bedaquiline's launch only 37,000 patients had even *received* the drug.[800] This is despite the fact that an additional 10.6 million individuals are estimated to have contracted tuberculosis

[795] In the United States, one narrow study indicated that only 36% of insurance companies covered bedaquiline. For more information on the complete breakdown review: Sundari Mase, Terence Chorba, Samuel Parks, Ann Belanger, Felicia Dworkin, Barbara Seaworth, Jon Warkentin, Pennan Barry, and Neha Shah, "Bedaquiline for the Treatment of Multidrug-Resistant Tuberculosis in the United States," *Clinical Infectious Diseases* 71, no. 4 (August 14, 2020): 1010–16. https://doi.org/10.1093/cid/ciz914.
[796] Hans Hogerzeil, Interview by Erin L. Paterson. 2 February 2023.
[797] Dzintars Gotham, Joseph Fortunak, A. Pozniak, Saye Khoo, Graham Cooke, Frederick Nytko III, and Andrew Hill, "Estimated Generic Prices for Novel Treatments for Drug- Resistant Tuberculosis," Journal of *Antimicrobial Chemotherapy* 72, no. 4 (April 1, 2017): 5-6, https://doi.org/doi: 10.1093/jac/dkw522
[798] STOP TB Partnerships, "Bedaquiline Is Accessible through GDF at a Price of US$ 340 for a Bottle of 188 Tablets," Access Bedaquiline, 2019, https://www.stoptb.org/new-tools/access-bedaquiline.
[799] STOP TB Partnerships, "Bedaquiline Is Accessible through GDF at a Price of US$ 340 for a Bottle of 188 Tablets."
[800] Médecins Sans Frontières, "As J&J Release Earnings, MSF Protests Price of Lifesaving TB Drug," Press Release, As J&J release earnings, MSF protests price of lifesaving TB drug in front of New York Stock Exchange, January 22, 2020, https://msfaccess.org/jj-release-earnings-msf-protests-price-lifesaving-tb-drug.

in 2021 alone, with 399,000–501,000 cases registered as MDR-TB cases.[801] [802] Each of those MDR-TB cases could have conceivably received the drug as a treatment plan, but for many: the drug never reached them. Facilities may have had the drug via the donation scheme, but actual treatments seemed scarce. Uncertainty regarding how to use bedaquiline, as well as fear of bedaquiline resistance has led to a crisis where patients in need frequently go without. And from a sales perspective: it is slow to move off the shelf.

Further complicating bedaquiline's situation has been the slow climb of regulatory approvals in a country by country level. Although Johnson & Johnson vocally provided its support and willingness to donate bedaquiline for compassionate use, confusion over how those it can be administered, what the logistics of moving bedaquiline into countries looks like legally has created delays or total stops at border crossings that refuse to allow the drug into the country or to the patients in need. Regulatory challenges of these kind are known areas of concern throughout the Dry AP, particularly when it comes to improving access.[803] When asked specifically about this concern, TB Alliance's Melvin Spigelman stated:

> The access issues are huge…The challenge there, is not that it won't happen, but how quickly it happens…We're not dealing with very well oiled regulatory or health care systems in most of the low to middle income countries. It's one thing if all you have to deal with is the US and Europe where the regulatory systems and the legal structures and everything else are relatively straight forward and we understand them well. But we're talking about some of the most underdeveloped countries in the world that have the biggest TB problems… [But] at the end of the day if you can't get the drugs into the hands of the patients who need them, you've failed totally, no matter how good the drug is.[804]

Suggested methods of improving these regulatory hurdles (and as such apply corrective maintenance) have included a pre-qualification review of medications by the WHO which

[801] World Health Organization, "2.1 TB Incidence," Global Tuberculosis Report, 2.1 TB incidence, 2021. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence.
[802] World Health Organization, "Global Tuberculosis Report 2022," (Geneva, Switzerland: World Health Organization, October 27, 2022), 15.
[803] Erica Lessem, Helen Cox, Colleen Daniels, Jennifer Furin, Lindsay McKenna, Carole D. Mitnick, Thato Mosidi, et al., "Access to New Medications for the Treatment of Drug-Resistant Tuberculosis: Patient, Provider and Community Perspectives," *International Journal of Infectious Diseases* 32 (March 2015): 56–7, https://doi.org/10.1016/j.ijid.2014.12.012.
[804] Melvin Spigelman, Interview with Erin L. Paterson, 21 December 2023.

analyzes new drugs and informs individual country medicines' agencies whether the drug is one that should be approved based on set factors. This pre-qualification scheme, known as the Collaborative Regulatory Procedure, and supported by groups such as the Access to Medicines Foundation as well as pharmaceutical companies such as GlaxoSmithKline, limits not only the country by country approvals of medications within pipelines, but also the financial cost to the pharmaceutical company which needs to apply in each country for these approvals.[805] The Collaborative Regulatory Procedure launched from the WHO initially in 2013, but true pilot test programs began in 2019. As of time of writing, it has not been fully implemented to affect the near fifty low to middle income countries that it hopes to in the future. Its impact, and potential is yet to be seen.

In the meantime, in absence of regulatory bottlenecks and potential confusion by purchasers, prohibitive pricing remains a key issue that has kept bedaquiline from those legally able to receive the drug but physically incapable of doing so. Had J&J started their production of bedaquiline using the $102/course treatment option from the start, bedaquiline would have been available to a large patient pool where regulatory approval did exist. Multiple groups, including the Global Fund and WHO have pledged support for the STOP TB Partnership's goal of ending TB by 2030.[806] With the only short course, oral treatment, high efficacy drug on the market, J&J could have had hundreds of *millions* of supply purchases. But such a venture, would run counter to the very nature of the financial market system that Johnson & Johnson, its subsidiaries, and bedaquiline exist in.

[805] Martijn Van Gerven, Interview with Erin L. Paterson, 23 August 2023.
James Anderson, Interview by Erin L. Paterson, 9 May 2024.

[806] STOP TB Partnerships, "Welcome to the Stop TB Partnership Partners' Directory," Directory, Partners, 2023. https://stoptb.org/partners/.

III. Understanding the Market Landscape of J&J and Bedaquiline: pricing escalators and rentier capitalism

This discussion thus far has detailed how bedaquiline maneuvered its way through the antibiotic development pipeline. Each financial option and opportunity contributed to the ability for this component of infrastructure to succeed. Many of these options were the effect of maintenance efforts: the Orphan Drug Act and Priority Review Vouchers were specifically designed to jump start attention and encourage innovation in neglected fields. They are forms of corrective maintenance specifically applied in the hopes of ensuring that drugs make it through the pipeline effectively. However, all of these maintenance efforts neglect to take into account the market system as a whole.

In his 2020 book, *Rentier Capitalism,* Brett Christophers discusses how in order to make and sustain profits, pharmaceutical companies of the post 1980s era engage in a particular kind of fiscal behavior. Still deeply entwined in neoliberal philosophy, rentier capitalism relies on the production of intellectual property (IP) protections to control a monopoly of a good for a set period of time.[807] Christophers identifies two versions of rent seeking, one: when a company manufactures or sells its own patented product, and two: when a company licenses a second company to manufacture the patented product for a royalty or fee.[808] Pharmaceutical companies engage in both versions of this in exchanges called in-licensing and out-licensing.

In-licensing is the act of one company purchasing the IP of another company in order to market it for themselves. In practice, this can be seen tangentially through Johnson & Johnson's purchasing of Tylenol, Janssen, and Tibotec as well. Out-licensing by contrast is a form of sharing information, resources, and knowledge sets with the result of an agreed upon

[807] Brett Christophers, *Rentier Capitalism: Who Owns the Economy and Who Pays for it?* (London, United Kingdom: Verso Books, 2020), 139.
[808] Christophers, *Rentier Capitalism*,141.

license between the companies in question once the product is created, as with J&J's partnership with TB Alliance on the production of bedaquiline and TB Alliance's royalty free license as a result.[809] Out-licensing alliances have increased steadily since the 1990s, with one report suggesting that between 1995 and 2008 saw such alliances grow from 600 to 1600 arrangements.[810]

Regardless of the licensing agreement involved, the act of purchasing or trading in licenses is a form of rentiership that has restructured the way pharmaceutical industries address innovation as a result. Universities and small biotechs often are responsible for creating, testing, and developing drugs, whose licenses are then traded or sold on the market. A pharmaceutical company can either buy the license, or in the case of many small-medium sized enterprises (SMEs) or biotechs, buy out the business that developed the drug in the first place. The more patents involved, the greater potential asset leverage the company has, and the higher the intrinsic potential value.

Possibilities of what could be patented also expanded from the 1980s through the 1990s. "Methods of treatment, mechanism of action, packaging, delivery profiles, dosing route, regimen and range, drug combinations, screening and analytical methods, drug chirality, biological targets and field of use" were all now patentable possibilities that companies around the world took advantage of.[811] The United Kingdom in particular has seen an uptick in patent applications from its various markets, and of its top ten patent filers: three are pharmaceutical companies—Johnson Matthey, GlaxoSmithKline, AstraZeneca.[812] Lobbyists in the UK similarly pressured EU lawmakers to agree on a 1998 ruling that granted

[809] Alberto Matteelli, Anna CC Carvalho, Kelly E Dooley, and Afranio Kritski, "TMC207: The First Compound of a New Class of Potent Anti- Tuberculosis Drugs," *Future Microbiology* 5, no. 6 (2010): 853. https://doi.org/10.2217/fmb.10.50.
[810] Oliver Gassmann, Carol A. Krech, Martin A. Bader, and Gerrit Reepmeyer, "Out-Licensing in Pharmaceutical Research and Development," In *Value Creation in the Pharmaceutical Industry (The Critical Path to Innovation),* edited by Alexander Schuhmacher and Markus Hinder, (Weinheim, Germany: Wiley VCH, 2016), 363.
[811] Christophers, *Rentier Capitalism*, 151.
[812] Christophers, *Rentier Capitalism*,, 146.

patent protection for "biotechnological inventions, including plant varieties and gene sequences,"[813] thus ensuring that pharmaceutical companies can continue to rely on this kind of revenue in the future.

With the TRIPS agreement in place and the economic monopoly afforded to patent owners, companies can balance out the amount of profit and return on investment they would will within their patent years. But this is a risk, one that involves a great deal of speculation on the part of investors. How many years remain on the patent, and can the company recoup the expense accrued from purchasing the IP in the first place (i.e.: their new "research and development" cost)? Is the perceived value worth investment now, when investment into a different product can provide even higher return on investment? These hypothetical figures and expectations determine the end price of the drug well and beyond cost of goods sold to the company and depend solely on what shareholders and traders believe they can extract as a price for the product itself.[814] The end of the patent equals the end of the "value" because the "value" had been inflated by its existence as a monopoly alone.

Several studies on the patent cliff have revealed that companies can lose up to 80% of their expected revenue once a generic enters the market.[815] That drop off is an expected and planned event however, and one that companies and shareholders collectively can mitigate with the release of a new product. The two methods of doing so are via in-house development, or acquisitions. Acquisitions of new products generally in line with when patent expiration occurs, providing cycles of potential growth for companies that is dependent around expected declines.[816] Companies that have a strong internal production

[813] Christophers, *Rentier Capitalism*, 155.
[814] Aeron Davis, "Defining Speculative Value in the Age of Financialized Capitalism," *The Sociological Review* 66, no. 1 (2018): 5-6, https://doi.org/https://doi.org/10.1177/0038026117711637.
[815] Marta F. Arroyabe, "The Role of Patent Expiration in Acquisition Decision and Target Selection in the Pharmaceutical Industry," *R&D Management* 51, no. 5 (November 2021): 523.
[816] Arroyabe, "The Role of Patent Expiration in Acquisition Decision and Target Selection in the Pharmaceutical Industry," 528.

base tend to acquire less, but they still are a part of the general flow of purchasing new licenses to increase their product line.

Within these patent and licensing exchanges and decisions, lies the key concern of shareholders: continued growth. This growth demand leads to what physician and sociologist Victor Roy has described as a "pricing escalator."[817] In essence, whenever a new drug comes to market, its price is valued not only to include its cost of manufacturing, but the expected loss of profit that the company believes it will experience when another drug in their portfolio loses its patent profit, including any prophesized expenses that will be accrued between the next product launch. This speculated and ever-increasing price retains this "value" only so long as the patent monopoly holds. Once generics enter the market, the price falls and the cycle continues again. However, at time of launch: each new drug must be able to generate the continued growth of a company or it will be deemed a failure, and so the drug pricing will continue to rise irrespective of the actual cost to the company itself.

These market facets create a multifaceted quandary when it comes to antibiotic innovation and market compatibility. First: pharmaceutical companies make the bulk of their revenue off of the rent of their IP; second: when patents begin to expire, the proprietary company must replace it with a new product to continue generating revenue; third: universities and biotechs are targeted as a pipeline by pharmaceutical companies for the production of innovative medicines; fourth: in order to sell to a company, it needs to prove it can be a lucrative enough acquisition for the buyer to recoup not only its license sale cost but also to generate revenue throughout the remainder of the patent lifetime; and finally, fifth: for a company to be considered successful by shareholders there must be continuous predictable growth.

For universities and biotechs, the incentive for developing high value treatments

[817] Roy, *Capitalizing a Cure*, 46-47.

geared towards long-term care are more likely to earn a pharmaceutical company bid. These decisions aren't made from a medical perspective in so far as: which drug could the group deliver effectively or which ideas are most medically relevant to the team at hand, but rather from the managerial standpoint of: which drug can be sold most effectively to supply increased purchasing power.[818] I say "managerial" here as a manager is the one making the decision to invest, but these decisions themselves follow the neoliberal economics that have been discussed throughout this chapter. The fiscal choice is one that is determined by the profit that will be passed on to the shareholders: i.e. the university, biotech owners, or other investors to each depending on the public/private nature of the institution. While they may not be considered "shareholders" in the sense of having stock within the institution, they serve as the beneficiaries of the profit or value derived from the successful sale of a developed product. As Takuji Hara states in his 2003 work *Innovation in the Pharmaceutical Industry:* medical innovation is not achieved simply due to a solo effort or brilliant scientists, but is a heterogeneous consultation among scientists, corporate managements, academics, patients, government officers, politicians, activists, materials, instruments, facilities; as well as "institutional and structural factors" including funds, markets, and regulations.[819]

The nature of pharmaceutical companies at this time has diverged from in-house research and development of products meant to serve a public health need, to broad scale health-focused marketing institutions that acquire SMEs and prospective products in order to package and sell under their brand names.[820] Whatever needs to be done to ensure that the product sells is prioritized over others, and most drugs that sell are reformulations of successful drugs rather than new drugs themselves.[821] These reformulations help extend

[818] Takuji Hara, *Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development*, (Cheltenham, United Kingdom: Edward Elgar Publishing, 2003), 31-33.
[819] Hara, *Innovation in the Pharmaceutical Industry,* 33-34.
[820]Stuart Hogarth, 2022, "The Fish and the Bicycle – antibiotic innovation and pharmaceutical firms," Paper presented at Boom, Bust and Antibiotics: Opening conference of the DryAP project, Oslo, 9 June 2022.
[821] Catherine Matraves, "Market Structure R&D and Advertising in the Pharmaceutical Industry," *The Journal*

patent protection to keep a drug on the market without competition, a form of ever-greening that ensures continued profit to recoup the costs of the development. Marketing expenses geared to promote the sale of drugs often dwarf the research and development budget. As an example, between 2011-2021, Johnson & Johnson's total production budget (not strictly exclusive towards that of bedaquiline) found that "selling, marketing, and administrative expenses" were consistently double that of its research and development expenses.[822] Similarly, Pfizer reported an average 27.6% of its budget dedicated to "Selling, informational, and administrative expenses," with only 15.4% of its budget being allocated to research and development expenses.[823] Exact marketing/advertising figures within that 27.6% cannot be determined, nor is it clear which drug campaigns received that advertisement assistance.[824]

Advertising comes in many shapes and forms. Although direct to consumer marketing for medications is still banned in the European Union, a 1997 change in policy guidelines at the FDA permits such marketing to consumers in the United States. However, the United States consistently ranks as the largest market for pharmaceutical drugs. The system allows for patients to ask their doctors about whichever new medicament they happen to come across on the radio or television. Although the pricing differential between the amount of money being spent on advertising versus research and development has decreased consistently year by year (1994's advertising budget was 4.7 times that of its research and development budget), the sheer *amount* of both figures has risen exponentially.[825] As too, has

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of Industrial Economics XLVII, no. 2 (June 1999): 173-174.

[822] The difference decreases from its highest in 2011 at 2.77 times greater, to only 1.7 times greater in 2021.

[823] Pfizer Inc, "Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 For the Fiscal Year Ended December 31, 2019," Form 10-K, (Washington DC, United States: United States Securities and Exchange Commission Financial Report, 2019), 16.

[824] J&J Expenses consolidated from annual reports: Johnson & Johnson. "Johnson & Johnson Annual Report 2019." Annual Report Pursuant to Section 13 Of the Securities Exchange Act of 1934. New Brunswick, New Jersey: Johnson & Johnson, March 2020, 15. AND Johnson & Johnson. "Johnson & Johnson Annual Report 2021." Annual Report Pursuant to Section 13 Of the Securities Exchange Act of 1934. New Brunswick, New Jersey: Johnson & Johnson, March 2022, 42.

[825] J&J Expenses consolidated from annual reports: Johnson & Johnson. "Johnson & Johnson Annual Report

the share price. Lifting from $1.00/share in 2000 to an average of $148.20 in 2021.[826] [827] However there have been increasing calls from medical professionals within the United States to curb these kinds of advertisements providing another demerit to an already struggling system of generating awareness and attention for new antibiotics entering the market.[828]

As the rising costs of defending a drug impact company decision making, one cannot ignore the concurrent rising costs of *developing* that drug.[829] While the exact amount of how much it costs to develop a drug is proprietary data that changes by drug and by complexity, the reported financial investment increased tenfold between 1991-2014. Ellen 't Hoen published an article in 2016 with a chart breaking down five estimates over this time frame offered by Joseph DiMasi, of the Tufts Center for Drug Development, the Office of Technology Assessment (OTA), and the Office of Health Economics in the United States. [830] These estimates started from 231 million USD in 1991 before rising to 2.5 billion in 2014, and while the methods and estimates (particularly of those by DiMasi), are relatively stable as to how the figures are arranged and thus comparable as far as what they assess and what their data reflects, the data itself remains both flawed and contested.[831] Estimates are based not only actual dollars spent in the research and development process, but a cumulative speculation of projected risk factors and expenditures that may have also influenced R&D

2000," Annual Report Pursuant to Section 13 Of the Securities Exchange Act of 1934. (New Brunswick, United States: Johnson & Johnson, March 2000).

[826] J&J Expenses consolidated from annual reports: Johnson & Johnson. "Johnson & Johnson Annual Report 2000."

[827] Johnson & Johnson. "Johnson & Johnson Annual Report 2021," Annual Report Pursuant to Section 13 Of the Securities Exchange Act of 1934, (New Brunswick, United States: Johnson & Johnson, March 2022).

[828] American Medical Association, "AMA Calls for Ban on DTC Ads of Prescription Drugs and Medical Devices," AMA Press Releases, November 17, 2015. https://www.ama-assn.org/press-center/press-releases/ama-calls-ban-dtc-ads-prescription-drugs-and-medical-devices.

[829] Developing here meaning both in-house development and the purchasing of licenses from universities, biotechs, or other alliances.

[830] Recreated from Hoen, Ellen 't. Private Patents and Public Health Changing Intellectual Property Rules for Access to Medicines. Amsterdam: Health Action International, 2016, 129.

[831] Hans Hogerzeil, Interview by Erin L. Paterson, 2 February 2023.

over an estimated length of time to hypothetical market launch.[832] It is not clear how much of the research and development costs are for which kind of drug and what is included in the estimate itself, and the cost of drugs that "failed" are mixed in with costs of drugs that did not fail to reach market. The publication of these estimates has an exceptionally long reach. DiMasi's "The Price of Innovation" alone has been cited over 6000 times.[833] This has an impact. For those reading these estimates, it creates an illusion of financial uncertainty and desperation within the pharmaceutical industry.

In 2013, Andrew Witty (then CEO of GlaxoSmithKline) called the "$1billion price tag 'one of the great myths of the industry,'" as it specifically included the cost of failed drugs.[834] The consideration here is somewhat convoluted. In small numbers, if someone were to invest $100 into a product and it was successful, and after sales etc., that product gave that individual $500 in return, they would experience a $400 profit. If that same person invested $100 into a product, and it went nowhere, then *physically* they only lost $100 on a bad investment. But they also lost $400 of potential profit, which could have been earned if another decision had been made. By factoring in the loss of potential value and potential return on investment, the estimated cost of developing a new drug rises higher and higher.[835]

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[832] DiMasi, Hansen, and Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22 (2003): 325-330.

[833] Elsevier, "The Price of Innovation: New Estimates of Drug Development Costs," Journal Article Database, Science Direct, Accessed January 24, 2025, https://www.sciencedirect.com/science/article/abs/pii/S0167629602001261.

[834] Ben Hirschler, "GlaxoSmithKline Boss says New Drugs Can Be Cheaper," *Reuters,* March 14, 2013, sec Healthcare, https://www.reuters.com/article/glaxosmithkline-prices/glaxosmithkline-boss-says-new-drugs-can-be-cheaper-idUSL6N0C6ART20130314.

[835] For more information on this financial concept and system, there have been several recent economic studies dedicated towards potential and real value in the drug development industry. Two can be found here:
Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," (Washington DC: Congressional Budget Office, April 2021), 9-10, https://www.cbo.gov/publication/57126.
Aylin Sertkaya, Trinidad Beleche, Amber Jessup, and Benjamin D. Sommers, "Costs of Drug Development and Research and Development Intensity in the US, 2000-2018," JAMA Network Open 7, no. 6 (June 28, 2024): e2415445, https://doi.org/10.1001/jamanetworkopen.2024.15445.
Olivier J. Wouters, Martin McKee, and Jeroen Luyten, "Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018," *JAMA* 323, no. 9 (March 3, 2020): 844, https://doi.org/10.1001/jama.2020.1166.
DiMasi himself discusses the impact of this value capital system in his 2016 publication: Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of

The billion-dollar price tag is a product of this type of value capitalization.

As a result of the intermingling of real money lost and potential profit to be gained on the balance sheet, public understanding of how much it costs to develop a drug is often blurry. It is not clear, particularly without public disclosures of these balance sheets, how much money is actually being spent, and how much a company needs to recoup in order to mitigate its investments in the production phase. However, these estimations, ever growing as they are, have led to an industry complication that is consistently incompatible with mitigating production costs: shareholder and cost expectations combined within internal models for overall profit and loss margins.

At its inception, the idea of a shareholder was someone who would invest a certain amount of money into a business or enterprise with the expectation that they would receive a return on investment (ROI) from the successful development and sale of that business's product or service. By "buying a share" of the prospective profits, they take an inherent gamble as to whether they will ever see a return on their investment.[836] Particularly risky investments which may see no return at all are provided by individuals considered "angel investors." Regardless of the level of investment risk, shareholders gamble on the probability of success when they invest money towards any enterprise, and they do so for the purpose of receiving not only an equal return for their initial investment, but for predictable and continued profits once the business proves profitable.

This is true for all enterprises, including pharmaceutical companies. As quoted earlier, Johnson and Johnson's credo since its inception has been both to create a good product that serves a public good, but *also* to ensure their shareholders earn a profit. The difference with Johnson and Johnson compared to the form of corporate management

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R&D Costs," *Journal of Health Economics* 47 (May 2016): 20–33, https://doi.org/10.1016/j.jhealeco.2016.01.012.

[836] Milton Friedman, *Capitalism and Freedom*, Fortieth Anniversary, (Chicago, United States: The University of Chicago Press, 2002), 103.

supported by Milton Friedman's neoliberal philosophy, is that J&J still acknowledges their overall intention to do good, where Friedman has been quoted as saying

> "A Corporation is the property of its stockholders…its interests are the interests of its stockholders. Now, beyond that should it spend the stockholders' money for purposes which it regards as socially responsible but which it cannot connect to its bottom line? The answer I would say is no."[837]

Those that adhere strongly to the general purpose of these neoliberal ideals, including J&J though it does attempt to strike some form of balance at least in its credo, the key purpose must be profit overall. For the stockholders, or shareholders, the fiduciary reward for investing is the profits that come as a result of their gamble, and anything that does not improve those profits or provide an adequate ROI is irrelevant to both the interests of the corporation and the shareholders themselves. Even if a pharmaceutical company's product *could* provide a social good (and often does), the goal for the *company* is to ensure that its shareholders are well compensated financially. To do this, pharmaceutical companies must ensure that the products they create generate enough revenue to be satisfactory to those shareholders.

Although this transition to prioritizing shareholder value has become more normalized in the past thirty years, J&J's attempts to continue with this *business as usual* behavior was met with increasingly furious public backlash with bedaquiline. When the first of bedaquiline's patents was about to expire in 2023, they attempted to extend its term. That summer, a fierce social media campaign led by tuberculosis advocate and author, John Green, called out Johnson & Johnson for their attempts at ever-greening. Green wrote an OpEd in the Washington Post in May 2023,[838] and in July had posted a Youtube video asking his followers and fans to make their displeasure known.[839] The condemnation was swift. Only a

[837] Joel Bakan, *The Corporation: The Pathological Pursuit of Profit and Power*, (New York, United States: Free Press, 2004), 34.
[838] John Green, "Opinion | Why Is a Curable Disease Still Allowed to Kill Millions?" *The Washington Post*, May 16, 2023, https://www.washingtonpost.com/opinions/2023/05/16/multidrug-resistant-tuberculosis-treatment/.
[839] John Green, "Advocating for J&J to Withdraw Their Patent on Bedaquiline," Accessed January 5, 2024,

few weeks later, J&J lowered the price of bedaquiline to $130 per treatment. By October, they announced it would no longer be seeking to extend its patents in low- and middle-income countries allowing for the generic market to proceed.[840]

Johnson and Johnson had already decided to remove itself from the antibiotic development field, and in late 2023: its decision from a financial perspective could only be seen as a logically sound one. There would be no standard rentier capitalism relationship with this product, at least not as things currently stand, and despite their efforts: they were not able to make a drug with a patient population in the hundreds of millions either profitable or accessible.

IV. Comparing Bedaquiline's launch to Hepatitis-C drug: Sofosbuvir: How effective medications and high patient populations does not mean broad access to those medications

Chapter One detailed the ways in which neo-liberal capitalism influences pharmaceutical outcomes. Because bedaquiline is a unique antibiotic to have made it through the Dry AP, there are few ways to understand if its existence on the market is unique or how its status can be fully understood. But, it is here that the comparison to Gilead's hepatitis C drug, sofosbuvir, is particularly illuminating. Sofosbuvir is to hepatitis C everything that bedaquiline is for tuberculosis. It is a safe, efficacious, drug that dramatically improves the health of patients with limited side effects or additional complications. Like bedaquiline, sofosbuvir received a large sum of public funding ($60.9 million) to bring it to market, [841] though sofosbuvir did maintain higher operating costs and secured more venture capital throughout its market journey. And finally, like bedaquiline, sofosbuvir also found its way

https://www.youtube.com/watch?v=Y_cT0nNMPNw.

[840] Talha Burki, "J&J Patent Decision to Enable Generic Tuberculosis Treatment," *The Lancet* 402, no. 10410 (October 2023): 1313, https://doi.org/10.1016/S0140-6736(23)02273-0.

[841] Rachel E, Barenie Jerry Avorn, Frazer A. Tessema, and Aaron S. Kesselheim, "Public Funding for Transformative Drugs: The Case of Sofosbuvir Author Links Open Overlay Panel," *Drug Discovery Today* 26, no. 1, January 2021: 273.

onto the EML relatively quickly, joining the list in 2015 – the same year as bedaquiline – with a tiered pricing model.[842] However, the antiviral sofosbuvir has precisely what bedaquiline lacks: a large high-income country pool of prospective patients. Where only 7860 United States citizens were reported to the CDC with tuberculosis in 2021, over two million were recorded as hepatitis C positive.[843] [844]

The price of sofosbuvir was always its key point of controversy. A twelve-week course was initially listed for $84,000 and $94,500 USD (when used in combination with additional drugs), with only Egypt negotiating a 99% price reduction in order to achieve a twelve-week course for only $900.[845] $900, as previously stated, being the same price provided for a six-month course of bedaquiline in J&J's initial tiered structure. Even with the extreme price differentials, the prevalence of health systems that could afford the treatment and individuals placed in the high-income country environment, has enabled upwards of 800,000 persons to be cured of hepatitis C.[846] First year returns for sofosbuvir were the highest of any drug launch in history reaching upwards of $10 *billion* in 2014.[847] The transfer to shareholders was astonishing, and over the next three years as much as 86% of Gilead's gross profits (or $65 billion) were translated into a "cash stockpile and distributions of capital aimed at shareholders."[848] It is the epitome of share profitability for an infectious disease drug.

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[842] WHO Expert Committee, "The Selection of Essential Medicines," World Health Organization Technical Report Series 994, 72.
[843] TD Filardo, P Feng, RH Pratt, SF Price, and JL Self, "Tuberculosis — United States, 2021," *Morbidity and Mortality Weekly Report* 71: 2022, 441-442, http://dx.doi.org/10.15585/mmwr.mm7112a1.
[844] H. Bradley, E.W. Hall, E.M. Rosenthall, P.S. Sullivan, A.B. Ryerson, and E.S. Rosenberg, "Hepatitis C Virus Prevalence in 50 U.S. States and D.C. by Sex, Birth Cohort, and Race: 2013-2016," *Hepatol Commun* 4, 2022: 355, https://doi.org/10.1002/hep4.1457
[845] WHO Expert Committee, "The Selection of Essential Medicines," World Health Organization Technical Report Series 994, 73.
[846] Michael J. Sofia, "Enter Sofosbuvir: The Path to Curing HCV," *Elsevier Inc. Cell* 167, September 22, 2016, 28, https://www.cell.com/cell/pdf/S0092-8674(16)31141-2.pdf.
[847] Andrew Pollack, "High Cost of Sovaldi Hepatitis C Drug Prompts a Call to Void Its Patents," New York Times, 20 May 2015, https://www.nytimes.com/2015/05/20/business/high-cost-of -hepatitis-c-drug-prompts-a-call-to-void-its-patents.html.
[848] Victor Roy, *Capitalizing a Cure: How Finance Controls the Price and Value of Medicines,* (Oakland, United States: University of California Press, 2023), 67, 154.

Wildly profitable, a high earner, and targeted at a large disease population in high income countries, sofosbuvir managed to avoid the complications that implicated bedaquiline's launch. Despite this, shareholders have been leaving Gilead and sofosbuvir, and the average share price has fallen as a result.[849] Success on the stock market requires year over year growth, and sofosbuvir could not sustain that status on its own with few equally impressive drugs in Gilead's portfolio that could replicate such effects. Regardless of all the profit that it has brought Gilead and its shareholders, physician and sociologist Victor Roy simplifies sofosbuvir's burdens as two key factors. First, as sofosbuvir's launch had been so wildly successful, there was no room for it to grow, and second: a drug that *cures* diminishes the target consumer pool that it sells to.[850] It is the curse that any antibiotic in the process of being developed at this time shares. New cures for infectious diseases, regardless of how profitable they are for a company, no matter how wildly successful their launch, will plateau in sales at some point, and eventually: the number of prospective consumers will diminish.

The sole market alternative that would provide the space for increased interest in this space, is if the need for a new antibiotic change dramatically and the patient population experiencing that need has the financial ability to pay for new medications. Bedaquiline and sofosbuvir both indicate progress in drug research and development against infectious diseases that impact high patient populations. Their use of public funds, and the high patient need, as well as the timing of their launch make them unique comparators. Although sofosbuvir targets a virus rather than a bacterial infection, a key difference in their launches is due to the fact that there is a large high-income patient population compared to those with tuberculosis. With the case of tuberculosis: too many low-income patients are being affected, but not enough high-income patients. Those that can afford the medication simply aren't

[849] Bret Jansen, "Gilead: Like Waiting For Godot," *Seeking Alpha,* 21 June 2016. https://seeking alpha.com/article/3983359-gilead-like-waiting-godot.
[850] Roy, *Capitalizing a Cure*, 67, 100.

providing a great enough return on investment to justify the cost of research, development, and distribution. If twenty-million high-income patients were suffering from M/XDR TB however, now the cost benefit analysis is entirely overturned. The need threshold has changed, and the potential for quick turn over on the stock market would justify the sudden investment portfolios involved. The cost of life until that point, however, remains catastrophic.

Conclusion

Chapter Three highlighted the ways in which the antibiotic pipeline of research and development is a component of the antibiotic infrastructure that supports global health, and how the development of new drugs assisted in achieving access to effective medications. This chapter, however, highlights the flaws in that pipeline by exploring the drug trajectory of bedaquiline from Johnson & Johnson and TB Alliance's corporate roots to its launch and the start of its post-patent stage. Despite successfully emerging through the antibiotic pipeline and achieving marketing approval in many countries worldwide, the only new class of antibiotic to emerge since the 1980s is not an accessible to those in need. It is neither affordable, nor even available to its largest patient populations, and sales for the drug have continued to not meet expectations. If the creation of new drugs within the antibiotic pipeline is meant to support the antimicrobial resistant threat and the need for access to new medications effective against resistant strains: it is flawed. The infrastructure that supports access to antibiotics and the ability for antibiotics to be considered a major part of health care infrastructure is crumbling.

Bedaquiline seems to have been a litmus test of sorts for Johnson & Johnson, and its status on the market may have been the final barrier to J&J's continued research within the antibiotic space. There are five patents associated with bedaquiline, each covering a specific aspect of the compound's use, chemical structure, process of manufacturing, and

preparation.[851] The first of these patents expired in 2023. The last will do so in 2027. At time of writing, no compulsory license has been enforced to force the generic production of bedaquiline prior to these patents expiring, but in July 2022, Indian company Macleods Pharmaceuticals successfully cleared the Global Fund's Expert Review Panel in the development of a generic and is prepared to place the drug into production as soon as it is able.[852] A little more than half a year after this announcement: J&J issued its declaration that it would cease its work in the antibiotic field.

With a rocky launch and persistent challenges of bedaquiline's pricing, along with an uncertain future for potential return on investments for future drugs of this or similar kinds, there is little J&J can offer to shareholders beyond the public good that its credo adheres to. While returns on investments for any antibiotic flux between highly successful and little to no return at all within the first 8 years of launch,[853] a 2019 study found that 99% of the cancer drugs brought to market could not only recoup the initial investment prior to patent expiry, but even the most expensive drug to market (costing $2.827 billion) was able to recoup all R&D expenses within five years.[854] For shareholders the decision to not invest in antibiotics is purely a matter of economics. Particularly as for any capitalistic market it is "anathema for capital to consider making a loss, unless it is potentially beneficial in the longer term," and antibiotics will not be potentially beneficial in the longer term.[855]

Although the development of PPPs was meant to be able to serve the function of

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[851] UNITAID Secretariat, "A Review of the Bedaquiline Patent Landscape: A Scoping Report," (Geneva, Switzerland: World Health Organization, January 2014), 7, https://unitaid.org/assets/TMC_207_Patent_Landscape.pdf.
[852] Global TB Community Advisory Board, "Activists across the World Demand Urgent Action to Improve Access to Lifesaving TB Medicine, Bedaquiline," TB Online, July 2022, https://www.tbonline.info/posts/2022/7/1/activists-across-world-demand-urgent-action-improv/.
[853] Sakib Rahman, Olof Lindahl, Chantal M. Morel, and Aidan Hollis, "Market Concentration of New Antibiotic Sales," *The Journal of Antibiotics*, 2021, 1, https://doi.org/https://doi.org/10.1038/s41429-021-00414-5.
[854] Kiu Tay-Teo, André Ilbawi, and Suzanne R. Hill, "Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies," *JAMA Network Open* 2, no. 1 (2019): 5-6, https://doi.org/doi:10.1001/jamanetworkopen.2018.6875.
[855] Kevin Walsh, *The Representation of the Past: Museums and Heritage in the Post-Modern World*, (New York, United States: Routledge, 1992), 116.

financially pushing or pulling a potential product through to marketing authorization and approval, once a drug actually enters the market its success is still overseen by the potential profit it can manage. Corrective maintenance meant to fix lags in private corporate research interest, such as the Orphan Tax Credit or Priority Review Voucher system, and even donation programs, have been put in place in an effort to assist drugs through the pipeline. But these measures are integrated too thoroughly within the pharmaceutical company financialized structure, and any outside investment is still considered a part of the funds that pharmaceutical companies yearn to recoup on the market. Despite not investing $500 million total themselves, J&J used that figure as the amount needed to be overcome with the development of bedaquiline,[856] and as it currently stands: the same philosophy will exist in other markets.

Determining what the exact amount that J&J (or indeed other pharmaceutical companies) invest, however, is a process mired in secrecy, but even if the number was fully understood: it would not change the end goal of the pharmaceutical company to make the most off of the product they have created. Some activists have called for the delinkage of the cost of innovation/development from the price of the drug. [857] However, as discussed in Chapter Three, pharmaceutical companies have no incentive to do so, indicating that while the cost of the drug and the sales point of the drug should be "delinked" from any kick pack to a pharmacist, doctor, etc., the value and profit of the drug should not be delinked from the manufacturing expenses of a drug. [858] As drug prices continue to rise, the concern of enabling access to those that need drugs the most will continue to rise with them.

Drug donation programs can be of use, but lack of regulatory transparency and

[856] Adrian Thomas, "Statement," 72 Session, Interactive Civil Society Hearing on the Fight Against Tuberculosis. (United Nations, New York, June 4, 2018). Video, minutes 21:48–22:03. https://webtv.un.org/en/asset/k1y/k1y7oh47cp . Accessed 14 December 2023.
[857] James Love, Interview with Erin L. Paterson, 30 April 2024.
[858] James Anderson, Interview with Erin L. Paterson 9 May 2024.

approval for the drugs involved in the programs create bottlenecks that further increase tensions on accessibility of new medications. New programs aimed at helping to smooth out the regulatory hurdles have been suggested by the WHO and low to middle income countries, but as of time of writing these implementations have not been put into effect on a broad scale. Bedaquiline, and indeed pretomanid and other new products developed to treat tuberculosis, continue to struggle because of these concerns. From an accessibility standpoint, these programs are often risky to depend on as they can be discontinued at any time (such as with Johnson & Johnson's eventual closing of their donation program).[859]

Concern over the dry antibiotic pipeline and a lack of new antibiotics capable of treating resistant strains of infection, overlap with concerns regarding accessibility. This is primarily due to the fact that access to safe and efficacious medications requires new medications to treat these new resistant strains. While the relationship between TB Alliance and J&J is very different from the PPPs/PDPs described in Chapter Three, and there was no clear accessibility amendment to the negotiating agreements between TB Alliance and J&J as discussed in the previous chapter, their relationship does carry with it a word of warning in the face of accessibility concerns. Even as an essential medicine, bedaquiline remains increasingly difficult to access. Worse, though, is that treatments for MDR TB are routinely considered too expensive to purchase and transport to countries and patients with the greatest need. If new drugs are to emerge from the pipeline, and be able to shore up the infrastructure that is crumbling due to a lack of effective medications – then access must be a component of those discussions. However, as Chapter Five will reveal, those access challenges continue beyond the scope of the originator developer as supply chains and API manufacturing agreements are becoming increasingly fragile.

[859] Rutta, Kambili, and Mukadi, "The Bedaquiline Donation Program: Progress and Lessons Learned after 4 Years of Implementation," 1039.

Chapter Five: Accessing that Which is Short: Antibiotics Old and New

"When there's no shop, there's nothing." – Dr. Kathleen Holloway.[860]

"Because we don't know…we could have a very false sense of security where it looks like there are multiple suppliers but at the end of the day it could come down to just one thing." – Dr. Erin Fox.[861]

"Why are you putting so much effort in developing new ones, when we cannot provide access to the ones that are already recommended?" – Martijn Van Gerven.[862]

The final component of the antibiotic infrastructure that will be discussed in this dissertation is that of the antibiotic supply chain. In order to have effective access to antibiotics, and a functioning antibiotic infrastructure, the antibiotics that are eventually developed must be able to make it from the point of manufacturing to the consumer. However, over the past thirty years, the frequency and rate of antibiotic shortages as a result of supply chain failures has increased not only in LMICs but in HICs as well.[863] This chapter argues that not only has the supply chain infrastructure that allows for both the physical production of antibiotics, and their transport has been compromised for low-income countries due to increasing financial strain, but that high-income countries are also suffering from this lack of supply chain "maintenance" (see Chapter One).

These shortages may be due to lack of raw materials, facility shut down (due to maintenance, environmental disasters, or business decisions among other factors), and actual transportation disruptions (again, due to environmental concern, but also including political or regulatory decisions and state of countries themselves [e.g.: war zones can limit the transportation of goods to those in need]). As Belma Skender and Mingyuan Zhang have pointed out in their 2024 article on antibiotic shortages, they could also be due to an over

[860] Kathleen Holloway, Interview by Erin L. Paterson, 20 April 2023.
[861] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.
[862] Martijn Van Gerven, Interview by Erin L. Paterson, 23 August 2023.
[863] Consult Appendix 4 for more detail on the state of shortages in the United States as one example of HICs struggling to maintain a stable antibiotic supply.

reliance on a limited number of API manufacturers who cannot keep up with supply and demand needs for multiple reasons.[864]

As an example of the impact these shortages can have in HIC settings: since 2001 there have been 345 shortages of antibiotics in the United States accumulating a total of 163,278 days of a product being short. Of this number, thirty drugs account for 72% of this time (117,875 days out of 163,278 days), and 70 drugs, as seen specifically in Appendix 5, were those that were included on the WHO's Essential Medicines List. These numbers are just for one HIC, but they stand as a testament to the experience of others within the same economic domain, and cast a warning where it can be assumed that those with less means are experiencing an even greater scarcity of available medicaments.

Tracking this data *with* greater specificity, however, is complex as there is no standard (global) definition for "drug shortage." There are similarities, of course, among the various definitions used, but each variation comes with its own unique caveats which prohibit a perfect one to one comparison between different nation states. In the Unites States Food and Drug Administration, "drug shortage" can refer to "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug."[865] For the European Medicines Agency, shortages are defined and reported at the national level. France, for example, uses two phrases: "tension d'approvisionnement" (supply tension) and "la rupture de stock" (out of stock).[866] Tension occurs when supplies are available at the moment, but may not be available to meet community needs.[867] Out of stock occurs when "a

[864] Belma Skender and Mingyuan Zhang, "From Local Issue to Global Challenge: A Brief Overview of Antibiotic Shortages since the 1970s," *Humanities and Social Sciences Communications* 11, no. 1 (September 18, 2024): 2, 5. https://doi.org/10.1057/s41599-024-03759-y.
[865] United States FDA, "Frequently Asked Questions about Drug Shortages," Government, Food and Drug Administration, October 11, 2023. https://www.fda.gov/drugs/drug-shortages/frequently-asked-questions-about-drug-shortages.
[866] Agence nationale de sécurité du médicament et des produits de santé, "Disponibilité Des Produits de Santé," Gouvernement, https://ansm.sante.fr/disponibilites-des-produits-de-sante/medicaments.
[867] Santé Publique France, "Ruptures de Stock et Tensions d'approvisionnement Des Vaccins," Gouvernement, https://vaccination-info-service.fr/Generalites-sur-les-vaccinations/Qualite-securite-et-efficacite-des-vaccins/Gestion-des-stocks-des-vaccins/Ruptures-de-stock-et-tensions-d-approvisionnement-des-vaccins.

community pharmacy or a pharmacy for internal use in an establishment (health or medico-social) [is unable] to dispense a drug to a patient within 72 hours."[868] Both forms are reported on the Agence nationale de sécurité du médicament et des produits de santé (ANSM) registry for public awareness.[869] Canada, similarly, refers to drug shortages by a case by case formulary code level which can make it seem like there are hundreds of shortages for a product that the United States would only consider as one shortage.[870] Within all of the above definitions is an additional caveat that a patient may not even be aware there is a shortage because an alternative exists and is supplied without comment, though doing so is not without its own risks regarding the potential increase of AMR.[871] This can be done for any number of reasons, but mainly the point is that a patient is requesting treatment and has a prescription for treatment and likely: the patient does not care which specific drug they get so long as they get a drug that alleviates the symptoms they originally went to the doctor/pharmacist for in the first place.

Consistency among the definitions of shortages is more or less on the same general lines, but the nuances make pure country to country comparisons more challenging. The most consistent verbiage tends to veer towards any combination of supply not meeting present (or expected) demand.[872] The causes of that supply failure, however, can be summarized into seven key areas, that pharmacy administrator and medical shortages expert, Sundus Shukar (et. al) referred to as supply issues (including: manufacturing issues, unavailability of raw

[868] Ministère du travail de la santé et des solidatirtés, "Rupture d'approvisionnement d'un médicamanet," Gouvernement, https://sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/prescription-et-dispensation/article/rupture-d-approvisionnement-d-un-medicament.
[869] ANSM only tracks French shortages, and so these reports are only for those experiencing shortages within France.
[870] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.
[871] Mingyuan Zhang, "In Shortage: Understanding Global Antibiotic Supply Chains Through Pharmaceutical Trade Fairs," *Anthropologica* 65, no. 1 (September 28, 2023), 2-3, https://doi.org/10.18357/anthropologica65120232605.
[872] S Shukar, F Zahoor, K Hayat, A Saeed, AH Gillani, S Omer, S Hu, ZUD Babar, Y Fang, and C Yang, "Drug Shortage: Causes, Impact, and Mitigation Strategies," *Frontiers in Pharmacology,* 12 no. 693426, (2021), 3, https://doi.org/10.3389/fphar.2021.693426

materials, business issues, and logistics issues), demand issues (such as just-in-time inventory, increased marketing, or tendering systems) or regulatory issues.[873]All three of these main bracket issues can be folded into overarching issue of policy oversight and management. Drug shortages, therefore, are representative of this conflict as they indicate a failure of policy, management, and product delivery.

In order to successfully maintain these supply chains and ensure that there are no breaks, the infrastructure must be looked at as a collective whole. Knowing which Active Pharmaceutical Ingredient (API) manufacturers are producing which drugs, and use which shipping rates is often a matter hidden behind non-disclosure agreements, and following the shipping lanes and transportation requirements is equally obstructed. The only country in the world that does publicly reveal this information, is New Zealand,[874] for the rest of the world: the supply chain infrastructure is forcibly invisible.

In order to make sense of the antibiotic access concerns stemming from fragility within the supply chain infrastructure, three case studies were developed. The first, and largest, is set in the United States, where thanks to a unique dataset provided by Dr. Fox at the University of Utah, I was able to review thirty years of antibiotic shortages effecting the United States and provide a clear statistical analysis as to their causes and impacts. This work does not make a final argument on *what* is causing these shortages, as many times that answered is not entirely evident, but it does show a trajectory of increasing fragility as more shortages have occurred within the United States since tracking began in the 1990s. The second two case studies follow a similar methodology (see the Introduction for more details), and depend on the development of a corpus of literature from the Web of Science Database detailing shortages in both Europe and in LMICs around the world. The purpose of these case

[873] S Shukar, F Zahoor, K Hayat, A Saeed, AH Gillani, S Omer, S Hu, ZUD Babar, Y Fang, and C Yang, "Drug Shortage: Causes, Impact, and Mitigation Strategies," Frontiers in Pharmacology, 12 no. 693426 (2021), 6-9, doi: https://doi.org/10.3389/fphar.2021.693426.
[874] Martijn Van Gerven, Interview with Erin L. Paterson, 23 August 2023.

studies is to highlight the growing fears and concerns that are related to antibiotic shortages, comparing them to the known data collected from the United States, and highlighting these instances as symptoms of the crumbling infrastructure that supports antibiotic access worldwide. As this infrastructure becomes increasingly more visible due to its "breakdowns,"[875] identifying how and why these breakdowns occur may be the only way to implement policy that can address the bottom up maintenance required to fix it.

I. Analyzing the data provided by Erin Fox and University of Utah on the United States Drug Shortages

In 1999 while serving as a pharmacy resident on the drug information service team, Erin Fox became involved in internal drug shortage tracking and management at her place of work, the University of Utah. Initially, she only tracked shortages that her university's hospital system was implicated by. However, this was an unsatisfactory system of understanding the overall progression of shortages on a national scale, and it was difficult to see when or where shortages might occur within the University hospital system without knowing the larger context of the national problems. With this in mind, the University of Utah joined with the American Society of Health System Pharmacists (ASHP) to begin tracking and keeping note of all drug shortages for all classifications of medications within the United States.[876]

Shortages in the United States were not discussed with a great deal of concern or consideration at that time, a distinct lack of interest that can be tracked in the Food and Drug Administration's yearly Center for Drug Evaluation and Research (CDER). These reports, often proforma, rarely changed terminology from year to year. No mention of antibiotics shortages occurred on the CDER prior to 1999, and its first mention during that time merely

[875] Susan Leigh Star, "The Ethnography of Infrastructure," *American Behavioral Scientist* 43, no. 3 (1999): 381-82, https://doi.org/10.1177/00027649921955326.
[876] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.

discussed the concept of shortages as something CDER would "attempt to prevent or alleviate" as it "coordinated responses to 10" known shortages within that year for medications that included tuberculosis and AIDS.[877] In 2000, the verbiage repeated much of the 1999 format, but also provided an indication for cause:

> Drug shortages occur for a variety of reasons including manufacturing difficulties, bulk supplier problems and corporate decisions to discontinue drugs. Because drug shortages can have significant public health consequences, we work with all parties involved to make sure all medically necessary products are available within the United States.[878]

These two sentences are repeated verbatim in every succeeding iteration of this report, but it was a consistency not fated to last.

In 2001, anthrax was put in the mail and sent to various news and government agencies. The letters led to 22 individuals contracting anthrax infections and the stockpiling of the on-patent antibiotic, ciprofloxacin, to treat anthrax.[879] This stockpiling led to one of the first shortages that drew national concern and attention as access to ciprofloxacin became increasingly difficult to manage. Fortuitously, the University of Utah's tracing system was already up and running and was able to accurately track the extent of this initial shortage and its influence. Although relatively short lasting, spanning only from October through November 2001, the heightened concern for not having an antibiotic when it was of most need transformed the concept of a drug shortage from a market event to a national security – or even "counterterrorism" concern.[880] [881] From that point forward, until the end of CEDR's yearly reporting in 2007, all remaining reports included one extra line with regards to

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[877] Food and Drug Administration, "CDER 1999 Report to the Nation: Improving Public Health Through Human Drugs," 28.
[878] Food and Drug Administration, "CDER 2000 Report to the Nation: Improving Public Health Through Human Drugs," 35.
[879] Jackson Landers, "The Anthrax Letters That Terrorized a Nation Are Now Decontaminated and on Public View," *The Smithsonian Magazine,* September 12, 2016. https://www.smithsonianmag.com/smithsonian-institution/anthrax-letters-terrorized-nation-now-decontaminated-public-view-180960407/.
[880] Erin Fox, Small File Data Shortage Through 2022, Received March 31, 2023, distributed by Erin Fox at University of Utah.
[881] Food and Drug Administration, "CDER 2001 Report to the Nation: Improving Public Health Through Human Drugs," Report to the Nation, Rockville, Maryland: Food and Drug Administration, 2002.

shortages: "Utilizing data obtained from manufacturers and distributors, our drug shortage program provides supply and production information in response to federal government requests in relation *to counterterrorism efforts*" (emphasis mine).[882] It is a threat, and a perspective that seemed to inextricably link the notion of drug shortages (antibiotic specifically to some extent) directly with a national security concern.

Five years later, then president George Bush signed the 2006 Pandemic and All-Hazards Preparedness Act which led to the creation of BARDA (mentioned in Chapter Three as a funding apparatus for PPPs developing antibiotics). Their remit, again couched in militaristic terminology, indicated that BARDA was responsible for working

> with both public and private sector partners to support innovative solutions, advanced research and development, regulatory approval, and procurement of life-saving medical products—drugs, vaccines, therapeutics, diagnostics, and medical devices – that are known collectively as medical countermeasures (MCMs)[883]

BARDA would immediately begin getting to work on managing not only innovative responses, but in sourcing and supporting additional research into mitigating drug concerns in the future.

At the same time, Fox and fellows of the University of Utah published the results of their observations in a series of journal articles highlighting repeating concerns found in their data. Most alarming to them was the signs that between 2010 and 2011 a distinct increase of drug shortages could be observed within their data sets. In Matthieu Beuvelet's dissertation analyzing the impact of piperacillin/tazobactam shortages on a specific Montreal Hospital, he provided the a graph to highlight just how extreme the shortage crisis had become, showing a distinct spike post 2010, easing somewhat during 2014 before rising once more in 2017.[884]

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[882] Food and Drug Administration, "CDER 2001 Report to the Nation: Improving Public Health Through Human Drugs," 29.

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[884] Matthieu Beuvelet, "Impact d'une Rupture d'approvisionnement de Piperacilline-Tazobactam Sur La Consommation Des Antibactériens et La Prise En Charge Des Pneumonies Au Centre Hospitalier de l'université de Montréal," (Doctoral Dissertation, Université Grenoble Alpes, 2019), 20, https://dumas.ccsd.cnrs.fr/dumas-02301893v1/file/2019GREA7044_beuvelet_matthieu%281%29%28D%29_version_diffusion.pdf.

Not long the total scale and impact of these shortages started to become known, then President Barack Obama requested the FDA to issue a report on correcting and mitigating shortage concerns.[885] The FDA tapped into the resource base that Fox had been developing, and the report they generated provided "pivotal trial data" on the concept of drug shortages and their impact on the United States.[886] Sterile injectable medications, stood out in particular as one of the most frequent kinds of shortages within the United States between 2011 and 2012, something that was also marked by Janet Woodcock and Marta Wosinska in their 2013 analysis on the "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages."[887] [888]

By 2012 Obama's executive order became law as the *21 USC 356c: Discontinuance or interruption in the production of life-saving drugs was updated to specify* required reporting on any changes or potential delays in medicaments. This order remains the only United States governmental oversight relating to drug shortages, and though it has occasionally been updated (as in 2020 during the Covid-19 pandemic), there is limited transparency as to the specific reasons or causes of these shortages.

Nine years later, on 22 March 2023, the United States Senate Committee on Homeland Security & Governmental Affairs held a hearing hosted by Chairman Gary Peters on how drug shortages could be perceived as, again, a national security concern. At this hearing, four experts on drug shortages, including Fox, provided testimony on the causes and effects of recent shortages, long term problem solving, and their concerns for the impact of shortages as a whole.[889] Overriding fears that were expressed during the hearing was the

[885] Food and Drug Administration, "Strategic Plan for Preventing and Mitigating Drug Shortages," (Washington DC, United States: Food and Drug Administration, October 2013), 3.
[886] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.
[887] Food and Drug Administration, "Strategic Plan for Preventing and Mitigating Drug Shortages," 9.
[888] Janet Woodcock and Marta Wosinkska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages," *State of the Art* 93, no. 2 (2013): 170–76.
[889] Expert witnesses at this hearing included: Dr. Andrew Shuman (Associate Professor of Otolaryngology-Head and Neck Surgery and Chief of the Clinical Ethics Service Center for Bioethics and Social Sciences in Medicine, University of Michigan Medical School), Vimala Raghavendran (Vice President of Informatics

potential impact on an embargo or failure to transmit medical products between China and the United States, and the concern that should a trade (or other kind of) dispute begin between the two nations, the United States' dependency on Chinese production of medical supplies could lead to unacceptable drug shortages and delays for individuals in need.[890]

In both 2001 and 2023 the concern over drug shortages was amplified due to existing geopolitical threats that added pressure to market systems on the availability and deliverability of essential products. But even without these factors, the supply chain for antibiotics is not stable on its own, and the increasing frequency of drug shortages in the United States will likely continue should they not be addressed.

Following an interview, I had with Fox in March 2023, I was given access to her private data collection on her national shortage tracking since 2001. I separated all antibiotics from the rest of her data and generated a new set of statistics from her data to directly target the degree of antibiotic shortages in the United States and the trends that manifested within them. As some of the antibiotics were still in shortage when I received the data on 31 March 2023, the numbers are only reflective of figures through that date.

Of the 345 antibiotic shortages that have taken place since 2001, 146 shortages were for oral/topical antibiotics (42% of all shortages); whereas 199 shortages since 2001 were for injection/infusion antibiotics (58% of all shortages). The average shortage lasted for 474 days, though this includes strong outliers of shortages which were marked as 0 days (the drug had gone out of business and therefore would not have been continued regardless), and drugs that were short for upwards of ten years continuously. Ampicillin sulbactam, cefotaxime injection, ceftazidime, clindamycin injection, and vancomycin injection have all been listed

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Product Development at US Pharmacopeia), Dr. Erin Fox (Associate Chief Pharmacy Officer of Shared Services and Adjunct Professor, College of Pharmacy University of Utah), and Dr. John Goodman (President of the Goodman Institute for Public Policy Research).

[890] United States Congress, Senate, Committee on Homeland Security and Governmental Affairs, *Drug Shortage Health and National Security Risks: Underlying causes and Needed Reforms,* 118th Cong., 2023.

as short for 10-14 years, a fact that earned particular notation on the 2023 Homeland Security and Government Affairs Majority Staff Report that accompanied the senate hearing.[891]

21 antibiotics that had a shortage were confirmed to have been the only source of that antibiotic, where 64 antibiotics that had a shortage were confirmed to have alternative sources available for that antibiotic, leaving 260 antibiotics where it was not clear if they were the only source or not. 129 unique antibiotics accounted for the 345 listed shortages that the United States experienced. 53 antibiotics only experienced one shortage, leaving 76 drugs that experienced two or more shortages per drug, and 70 that were specifically on the EML.[892] To ensure that I reported carefully, I specifically reviewed Fox's data to identify which drugs were not only on the list, but which exact formulation was recommended on the EML and which shortage was in effect at that time. I recorded the quantity of the drug, where it intersected with the EML, and the dates of the shortage in specific. From there, I investigated known marketers of the drug, and any known corporations that had previously been given authorization but were now no longer in the field to clearly identify which companies were associated with shortages that occurred.

Due to the extreme nature of date ranges between shortages and to provide a more accurate understanding of where the greatest complicating factors lay with which antibiotics, I separated the thirty antibiotics that experienced a shortage for the longest period of time from the dataset and organized them based on the length of their shortage and known factors that contributed to their longevity. As it is an extensive chart despite these restrictions, this edited portion of Fox's research can be consulted in full in Appendix 4. However, what this chart reveals is that there were only a few stated reasons for shortages to have occurred. Accounting for overlap as different shortages may have had more than one listed cause,

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[891] Gary Peters, "Short Supply: The Health and National Security Risks of Drug Shortages," Majority Report, Washington DC: Homeland Security and Government Affairs, March 2023, 9.
[892] Erin Fox, Small File Data Shortage Through 2022, Received March 31, 2023, distributed by Erin Fox at University of Utah.

Manufacturing Delays/Raw Material Shortages accounted for fourteen shortages, with Unknown Reasons (10), Business Decisions (7), and Supply & Demand (6) accounting for the rest. Manufacturing delays would indicate a problem specifically with the API manufacturer, and as far as the infrastructure is concerned, it would highlight that fragility is overwhelmingly occurring at the point of production. This does not, of course, account for the other reasons downstream, and there: Business Decisions and Supply & Demand overlap most significantly as corporate choice on the quantity of drugs to produce vs the amount required suffer from poor estimations and a need to ramp up service.

Perhaps most strikingly about these thirty drugs, however, *is* precisely how much time these drugs have been considered short. The shortest length of time on the list accounted for 4.7 years, while the longest (ciprofloxacin) extended for *twenty-four years.*[893] These treatments are meant to be essential medicines, capable of addressing the concerns of the populace, but their continued lack of availability in this setting provides a target as to where structured maintenance can be applied to this antibiotic infrastructure. If raw materials and manufacturing concerns are causing the most extreme delays – it is there where targeted assistance should be implemented. As of yet, however, such targeted attempts have not been put into practice.

Expanding beyond the specifics of which drugs are short, however does not provide a full picture of what is happening on individual treatment levels. Examining how these drugs are used and in which capacity was the next step of this analysis. To do so, I reviewed each antibiotic that had been traced and assigned an additional level of indication depending on their drug data. I categorized the drugs into nine categories based on what their particular efficacy was against which type of bacteria. These groups included: Gram Positive only or

[893] These shortages were not continuous, the average length of a ciprofloxacin shortage in the United States was between 1-6 years in term, however, this shows a startling consistency that this particular formulation is not stable or dependable. In ciprofloxacin's case – lack of raw materials, and supply & demand issues following the Anthrax scare, were largely the cause of its continued delays.

"GP," Gram Negative only or "GN," "GP & GN," "Mycobacteria," "GP & Mycobacteria," "GP & Anaerobes" "GP, GN, & Anaerobes," "GP, GN, Mycobacteria," and "GP & GN, Anaerobes, Mycobacteria." Of these groups, the following were the total calculated unique shortages that occurred:

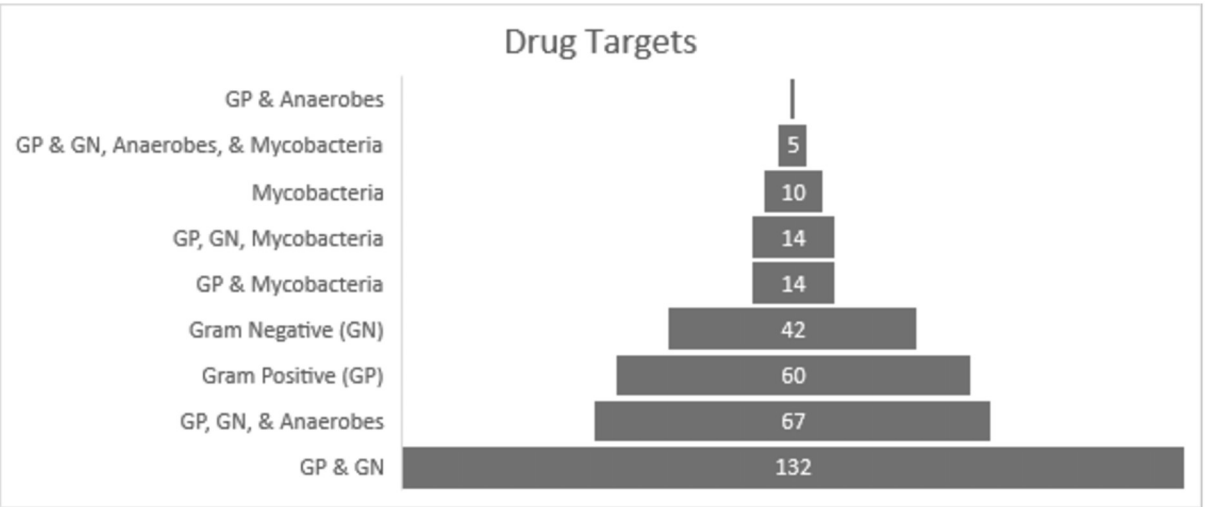

Figure 5 Drug Targets of short ABs in the United States

Only one drug, ceftolozane/tazobactam (Zerbaxa), specifically targeted Gram-Positive Anaerobic Bacteria exclusively. All other targets had multiple drugs that were targeting bacteria in those classes.

Although mycobacterium is a form of Gram-Positive bacteria, I chose to split it as a separate and unique category as not all Gram-Positive drugs can work on mycobacteria. In this way, the efficacy and clarity of which drugs are capable of being used in which circumstances are clearer. Continually, drugs that target mycobacteria and are used against tuberculosis made up 9% of all days a drug was short in the United States (and 12% of all drugs that were short).

Fox determined if a shortage should be included in her database if any formulation – a drug and its associated dosage amount – was unavailable for any period of time, it was resolved when that drug was available back on the market.[894] For instance, as of March 2023,

[894] If a company went out of business and ceased making a drug it was marked as short for "0 days" as the company had no intentions of returning that product to the market. However, this number does blur matters of

isoniazid has been in an active shortage in the United States since 2022. However, this is specific to the supply of 300mg Isoniazid tablets which is only supplied by three authorized vendors, two of which are unable to do so at this time.[895] The third can, but as two are incapable it is still listed as short. Depending on the third supplier's availability the increased demand on their available supply could lead to an even more extensive shortage in the future. However, there are several 100mg formulations available and it could be possible for a patient to take three 100mg tablets to compensate for not having one 300mg tablet if they had to. Thus, for patients in need of isoniazid, there are options available. This is not the case for Sanofi Aventis's rifapentine which has been short since 2021 and is the only approved formulation on the FDA's orange book.[896] Meaning that no patient in the United States can access this drug in any form.

What I have been able to uncover reviewing this data is that the large majority of antibiotics that are affected by drug shortages tend to be broad spectrum in nature. While there are many shortages affecting antibiotics that treat gram positive bacteria, there is a statistically significant amount that influence antibiotics for gram negative bacteria as well. As there are less antibiotics that target gram negative bacteria – this is extremely concerning. Overall, though, what can be clearly understood is that there is no avenue within the antibiotics spectrum of delivery that is unaffected. From hyper specific treatments, such as with Tuberculosis medications, to more generalized yet common treatments in the case of

access and accessibility. The greatest way to measure if that drug's removal had an impact would to be to look to see if other drugs of that formulation experienced shortages as a result of the first company's dissolution. In the case of Sulfacetamide ophthalmic ointment, for instance, small shortages had been marked prior to one company's discontinuation of the product, with extended shortages being reported after the discontinuation occurred.

[895] ASHP, "Isoniazid Tablets," Database, Drug Shortage Detail: Isoniazid Tablets, March 22, 2023. https://www.ashp.org/drug-shortages/current-shortages/drug-shortage-detail.aspx?id=865&loginreturnUrl=SSOCheckOnly.

[896] Information procured by consulting FDA online Orange Book Database consulting any approvals listed for Rifapentine: United States Food and Drug Administration, "Search Results for Proprietary Name, Active Ingredient or Application Number: Rifapentine," Database, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, May 4, 2023.

amoxicillin – shortages are occurring for extended periods of time across the United States and in many cases: are not being appropriately or adequately addressed. Resolutions for these shortages are often slow to take shape, something that is particularly shocking considering the frequency of use.

The bulk of the research into the antibiotic shortages affecting the United States comes from data that ends with an artificial stopping point of March 2023. Naturally, these shortages have continued and the dates and durations discussed above have fluctuated as a result. In late 2022 and continuing through 2023, an amoxicillin shortage occurring concurrently with a Tamiflu antiviral medication led to worsening health outcomes of children in the United States experiencing respiratory infections in particular. Overprescribing, in this case doctors advising patients take amoxicillin when the cause is viral rather than bacterial, was blamed in part, but so too was the changing in general anticipation of when a disease would strike.[897] Just-in-time manufacturing had scheduled the drugs to be delivered at a later date than the diseases actually presented in reality.

The amoxicillin shortage would eventually have later consequences in 2023, as Pfizer's Bicillin L-A (a penicillin G benzathine) was used as an alternative to treat the bacterial infections that amoxicillin wasn't available to treat. By July 2023, Pfizer announced a Bicillin shortage due to the unexpected increase of demand.[898] In ordinary circumstances, Bicillin is a drug used for the treatment of syphilis, and its sudden lack was now exerting additional pressure on doctors and patients when it came to managing the sexually transmitted disease.

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[897] Andrew Jacobs and Roni Caryn Rabin, "Flu and R.S.V. Hit the Holidays, Heightening Demand for Antibiotics and Antivirals," *The New York Times*, November 26, 2022, Online edition, https://www.nytimes.com/2022/11/23/health/drug-shortages-flu-holidays.html.

[898] Benjamin Ryan, "Antibiotic Shortage Could Worsen Syphilis Epidemic," *The New York Times*, July 7, 2023, Online edition, https://www.nytimes.com/2023/07/07/health/syphilis-epidemic-antibiotic-shortage-pfizer.html.

This analysis elucidates the impact of an infrastructure that is increasingly showing its cracks. It highlights where illnesses are likely to become more exasperated, and it marks a trend in the kind of health metrics that have been collected over the past twenty years. It is a trend, that eventually became too egregious for the government to ignore, and in March 2023 – the previously mentioned senate hearing was officially held.

II. An invisible infrastructure: API manufacturers and the obscurity provided by their NDAs

China, and national security concerns were highlighted as key points of potential peril for those involved in the senate meeting.[899] However, nestled within those concerns were continuous calls by the witnesses that the consolidation of API manufacturers and the lack of transparency when it came to identifying statistics of active API businesses, were greatly important as well.[900] As Fox's data has already shown, manufacturing delays and raw material shortages were a consistent reason for delays with essential antibiotics. The opacity surrounding API manufacturers, however, make it so that it is impossible to truly assess the full scale of potential issues. Susan Leigh Star argued that infrastructure should largely be invisible, and only visible when it is broken.[901] However, in this case: the infrastructure itself has forcibly retained its invisibility despite its breakage. If one cannot see it, one cannot accurately assess its damage.

To understand this matter in practice, one must assess what information is actively provided to researchers (such as Dr. Fox) that are responsible for tracking national shortage information. The FDA maintains a complete list of all approved drugs formulations and their associated manufacturers in a database called the Orange Book.[902] This Orange Book

[899] United States Congress, *Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms.*
[900] United States Congress, *Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms.*
[901] Star, "The Ethnography of Infrastructure," 381-82.
[902] A complete list of approved pharmaceutical companies that provide antibiotics on the WHO's Essential Medicines List within the United States can be found in Appendix 2.

provides data such as the Active Ingredient, Proprietary Name, Application Number, Dosage Form, Route, Strength, and Applicant Holder. Regrettably, the Orange Book does *not* clearly state when a company chooses to discontinue its product line. It will state that it has been discontinued, but not the date. This information can be found in quarterly reporting, and a future study investigating similarities of companies entering or leaving the market at set periods of time would help more clearly establish similarities, differences, or patterns amongst the temporalities involved in leaving the antibiotic market. Of most importance to this study at this time, however, is that the Orange Book and FDA reports do not provide the identity of the pharmaceutical company's API manufacturers.

API manufacturers are responsible for generating the end medicinal product in a formulation that can be used to treat a patient. Separate from labeling, boxing, and packaging concerns, these manufacturers are solely responsible for ensuring the medicine they make is efficacious and up to the standards approved by regulatory authorities. While some major pharmaceutical companies do maintain their own API manufacturing facilities, such as Teva Pharmaceuticals and Novartis, many hire outside companies to produce the final formulation on the pharmaceutical company's behalf. The business relationship between an API manufacturer and a pharmaceutical company (whether that company is generating patented medications or generics) is then considered "proprietary information" that the FDA is prohibited from disclosing it in its Orange Book or in other reporting methods.[903] When the FDA records which company is permitted to market a drug within the United States, it only lists the name of the pharmaceutical company that "owns" the drug that will be sold.

The only country in the world that currently releases information regarding API manufacturers (and all other aspects of the supply chain) in addition to the pharmaceutical company that is marketing a drug, is New Zealand.[904] Although my research into the New

[903] United States Congress, *Drug Shortage Health and National Security Risks.*
[904] Martijn Van Gerven, Interview with Erin L. Paterson, 23 August 2023.

Zealand supply chain does not fit into the confines of this dissertation, I was able to generate a comprehensive database exploring the extent of essential antibiotics within this supply chain and the frailty of its system.[905] As one very specific example, Multichem's amoxicillin/clavulanic Acid (brand name: Amoxiclav) relies on four separate API manufacturers: Zhuhai United Laboratories Co Ltd (China), Sandoz Industrial Products SA (Spain), Lek Pharmaceuticals d.d. (Slovenia), and Suanfarma Italia SPA (Italy). It then goes through finished product testing and final dose manufacturing at Reig Jofre SA (Spain), before undergoing 'manufacturing of intermediate product/over labelling)' at Sandoz Industrial Products SA and/or Zhuhai United Laboratories. It has final packing back at Reig Jofre before being sent to New Zealand where it is released by Multichem.[906] Bottlenecks in production and/or delivery can happen at any one of these locations. And should there be simultaneous delays for any reason, those bottlenecks would then compound to elongate expected drug wait times. All of these designations appear on the New Zealand MedSafe database with full and complete references to composition, ingredients, manufacturers and so on.[907]

The FDA Orange Book's online database, by contrast is far more sparse.[908] Its details include only the name of the applicant (the pharmaceutical company that is registered to

[905] I intend to continue working on the database I developed on the New Zealand supply chain, and publish the results of those findings in the future. These results would indicate specifically what the current status of the New Zealand antibiotic supply chain is, what key marks of tension or frailty there exists, and provide a risk assessment on "should the worst happen, what event would see the eradication of access to the most antibiotics at one time." This work is beyond the scope of my current dissertation and would require more time and funding to proceed adequately, as well as collaboration with those with far more specific data visualization training. I look forward to the opportunity to work on this in a more comprehensive fashion at a later date.
[906] Medsafe, "Amoxicillin/Clavulanic Acid," Government, Medsafe Product Detail, Accessed August 27, 2024. https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=11652.
[907] Medsafe, "Amoxicillin Clauvinate," Government, Medsafe Product Detail, Accessed August 27, 2024, https://www.medsafe.govt.nz/regulatory/ProductDetail.asp?ID=11652.
[908] For the purposes of this example I chose the nearest approved equivalent in the FDA Orange Book. Although there are differences in the route and the application of the drug, and the formulation, these alterations should not distract from the revealed manufacturing information differences on both sites.

market the product within the United States), and general drug form and dosing permissions.[909]

This lack of information regarding APIs provides a false sense of security regarding the antibiotic supply chain, as it is unclear how many applicant holders are utilizing the same API in order to develop their product. It is forcibly obscuring the infrastructure, and keeping it perpetually invisible, thus rendering maintenance attempts: largely ad hoc and moot. In my preliminary analysis of New Zealand's database (see Appendix 6) I found that the ten companies with market authorization to sell in New Zealand use between 4-18 manufacturers to develop their products. For the API manufacturers that receive those contracts, each company creates between 3-18 unique doses that only *they* are responsible for creating. In one specific example, seven "applicant holders" all relied on Sandoz GmbH (Austria) for their products to come to market. In the US FDA Orange Book, this would appear as seven independent companies with seemingly no relationship to one another all stating that they are providing their own unique generic version of a product. In reality, they all rely on one company for that product. Therefore, should Sandoz GmbH experience any strain or difficulty, seven companies will simultaneously lose the ability to provide access to the range of antibiotics that are emerging from that plant.

Because New Zealand does not have the same shortage tracking history as Erin Fox's research team has been able to put together in the United States, it is not possible to wholly compare the two effectively. Only current, or active, shortages and delays are listed on the New Zealand Pharmac website which publicly lists such data.

On 9 September 2024, I reviewed their shortage website and compared it to the United States' current shortage reporting. There were few similarities, but understanding why

[909] Food and Drug Administration, "Product Details for NDA 050575," Government. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Accessed August 27, 2024, https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=050575#24522.

that is the case is complicated. In 2021, for example, gentamicin injections were marked as short in the United States due to Baxter and Hikma Pharmaceuticals reporting "increased demand" overburdening their supply.[910] It is unclear if this report was listed in New Zealand at that time, but in the United States Pfizer is (at time of writing) considered to be capable of supplying gentamicin injections in 2024, but Pfizer is *not* capable of doing the same for New Zealand due to "regulatory changes planned for late 2024 which will lead to an out of stock of their brand of gentamicin from November 2024."[911] If this is because the shortage is being pre-emptively reported in New Zealand where it has not yet occurred in the United States is unclear. As is the ripple effect this will cause for the few manufacturers that do still produce gentamicin at this time. More research, beyond the scope of this project, that can adequately compare and contrast shortage data collection of multiple countries simultaneously would be very beneficial as it would provide clarity to what the impact of these shortages are on a global scale.

The overwhelming majority of drug shortages occur in generic formulations,[912] but lacking more information on these APIs and how these APIs are capable of maintaining a global supply chain has enabled undue risk throughout the antibiotic infrastructure landscape.[913] Without knowing where support needs to be given, it is impossible for regulators or politicians to create legislation to adequately support the supply chain. As such, despite the actions that have been discussed already in this dissertation, there has been limited progress in addressing these supply chain issues beyond the surveillance efforts already in place. From a research perspective, investigating the cause and understanding of shortages of

[910] ASHP, "Drug Shortage Detail: Gentamicin Injection," Accessed September 9, 2024, https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortage-Detail.aspx?id=718.
[911] Pharmac | Te Pātaka Whaioranga | NZ, "Gentamicin Sulphate (Pfizer) Inj 40 Mg per Ml, 2 Ml Ampoule: Supply Issue," Pharmac | Te Pātaka Whaioranga | NZ Government, (July 11, 2024), https://pharmac.govt.nz/medicine-funding-and-supply/medicine-notices/gentamicin-inj.
[912] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.
[913] Martijn Van Gerven, Interview by Erin L. Paterson, 23 August 2023.

antibiotics in the United States is often a guessing game and an attempt at applying reason to firm data points.

Another example from the FDA's Orange Book is that of amikacin. As of 2021, Amikacin was authorized for sale by five companies: Avet Lifesciences LTD, Fresenius Kabi USA LLC, Hikma Pharmacueticals USA Inc, Sagent Pharmacueticals INC, and Teva Pharmaceuticals USA. Currently, six companies, (Abbot Laboratories, Abbot Laboratories Hosp Products Div, Apothecon Inc Div Bristol Myers Squibb, Hospira Inc, Igi Laboratories Inc) have discontinued development of this formulation. A shortage for this formulation spanned from 2009-2017. "Manufacturing Delays" was the stated reason for the shortage, but what did this mean on the API side? During the amikacin shortage, three new companies joined the business, did they have a different API? Do those three companies share the same API, and therefore is the supply chain still at risk? Due to the privacy policies in place between the corporations and the FDA, this information is not available and cannot be analyzed.

If a consumer, or regulatory authority, is only given names of companies who have authorization to market a product, a long list of approvals can create a sense of security and the belief of a stable supply chain. However, if all or most of these companies share the same API manufacturer: then that supply of antibiotics is one fire away from being disrupted. When put into a geopolitical context, the US Homeland Security report clearly indicated that "between 2010 and 2015, the number of Chinese based API manufacturers that registered with the FDA more than doubled," and as of 2019 – 80% of all API manufacturing takes place outside of the United States.[914]

Vimala Raghavendran of USP, provided context for these statistics during the Senate Hearing, arguing that geographic concentration, anywhere, including the United States can

[914] Gary Peters, "Short Supply: The Health and National Security Risks of Drug Shortages," Majority Report, Washington DC: Homeland Security and Government Affairs, March 2023, 3-4.

lead to drug shortages.[915] She called for the establishment of an early warning system and research center of excellence that could help assess risks in the supply chain and predict drug shortages giving stakeholders in the public and private sector enough notice to react, as well as driving the importance of global API manufacturing rather than hyper focused localization of product development.[916]

In 2022 the National Academies of Science, Engineering, and Medicine compiled their own report that analyzed the FDA's response to the medical supply shortages and the policy landscape affecting shortage mitigation. They identified key legislative gaps such as: the undue focus on disruptions solely to manufacturing that ignore transportation or distribution errors, a lack of fiscal penalty associated to failing to adequately notify the FDA of potential drug shortages, no present requirement for "risk mitigation management plans" to either be available on inspection or submitted to the FDA for review. [917] However, as of 2014, the FDA does have the "authority to initiate administrative, judicial, or other punitive actions when a firm refuses to provide access to records."[918] While these current policies have been effective in responding to and preventing shortages, they have not fully been able to mitigate shortages or indicate precisely where the problems are arising from.[919]

At the time of writing, antibiotic shortages in the United States have not yet reached a critical point where total stockouts have been reported on key formulations. However, it is clear that a trend is beginning to form, and that the tools to properly assess the magnitude of a potential crisis have not yet been established. The infrastructure is crumbling, and its crumbling is happening at a faster and more consistent rate as time goes on. The consistency

[915] United States Congress, Senate, Committee on Homeland Security and Governmental Affairs, *Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms*, 118th Cong., 2023.
[916] United States Congress, *Drug Shortage Health and National Security Risks*.
[917] Wallace J. Hopp, Lisa Brown, and Carolyn Shore, *Building Resilience into the Nation's Product Supply Chains*, (Washington DC: National Academies Press, 2022), 60.
[918] Hopp, Brown, and Shore, *Building Resilience into the Nation's Product Supply Chains*, 60.
[919] Food and Drug Administration, "Drug Shortages CY 2022," Required by Section 506C–1 of the Federal Food, Drug, and Cosmetic Act. (Washington DC, United States: Food and Drug Administration, 2022), 3

in the type of drugs and the type of illnesses they treat shows where additional support needs to be implemented into the supply chain as it stands, and that API manufacturers are a particularly weak point in this extended chain, however lack of opacity in this space continues to obstruct exactly how bad and how extensive the potential frailty is. Worse, these shortages are not unique to the United States, and they are experienced in varying degrees around the world. Without the same type of tracking and monitoring infrastructure that enabled this analysis to be conducted on the United States, though, alternative assessments had to be conducted in order to track the history of the antibiotic access infrastructure as it exists beyond US boarders.

III. Lack of reporting infrastructure leading to a generalized assessment of the striations between the shortages experienced by High and Low-Middle Income Countries (i.e.: Availability vs Affordability).

The European Medicine's Agency does not have the same centralized system of drug approvals or shortage tracking databases as seen in the United States' FDA. There is no consolidated Orange Book or shortage tracking institution in Europe. Rather, each individual country – like the United States – reports its own experiences. Therefore, tracking antibiotic shortages in Europe requires understanding each individual country's definition of what a shortage is and individually tracking how those countries report their data.

Extant and historical data beyond present day shortage possibilities is limited as an exhaustive research study- like the one prepared by Erin Fox and ASHP- has not yet been generated. Some scholars, such as Belma Skender and Mingyuan Zhang have worked to try to offer broader information regarding the impact of modern antibiotic shortages.[920] Zhang in particular has analyzed and assessed the way Chinese and Indian pharmaceutical manufacturing practices affect supply chains, and how pharmaceutical trade fairs impact this

[920] Skender and Zhang, "From Local Issue to Global Challenge."

same chain.[921] Additional, and deeper analysis into the global impact relies primarily on a consolidation of reports, journal articles, conference session discussions, and contemporary data of European countries that have actively discussed antibiotic shortages, their causes, and effects.[922] This opacity echoes the similar problems facing the supply chain infrastructure discussed in the previous section, and how despite the fact infrastructures are meant to be invisible until a breakdown occurs, lack of uniform tracking methods ensure that correcting the breakdown is harder than it could be.

Identifying these breakdowns requires individual and small-scale reporting that can then be made more generalized when combined with other reports around the same time/within the same compound. An example of this kind of reporting can be found in the Elderly Medicine Unit at the General Infirmary in Leeds, United Kingdom. In 1998, medical practitioners there began a study to determine which antibiotics in their ward were more likely to lead to patients acquiring *Clostridium difficile* diarrhea (CDD) following antibiotic treatment.[923] They determined that between cefotaxime and piperacillin-tazobactam their patients were less likely to acquire CDD after a course of piperacillin-tazobactam.[924] As a result of this study, this Infirmary transitioned its treatment protocols to prescribe piperacillin-tazobactam as a first line treatment as opposed to cefotaxime.

Pip-Tazo, as it has been colloquially referred to,[925] first received marketing authorization in 1993. Seventeen years younger than cefotaxime, it was a fresh face on the

[921] Mingyuan Zhang, "In Shortage: Understanding Global Antibiotic Supply Chains Through Pharmaceutical Trade Fairs," *Anthropologica* 65, no. 1 (September 28, 2023). https://doi.org/10.18357/anthropologica65120232605. Mingyuan Zhang and Lise Bjerke, "Antibiotics 'Dumped': Negotiating Pharmaceutical Identities, Properties, and Interests in China–India Trade Disputes," *Medical Anthropology Quarterly* 37, no. 2 (2023): 148–63. https://doi.org/10.1111/maq.12757.

[922] A full detailed analysis of the corpus of data that I used can be found in Appendix 3.

[923] C. D Settle, M.H. Wilcox, W.N. Fawley, O.J. Corrado, and P.M. Hawkey, "Prospective Study of the Risk of Clostridium Difficile Diarrhoea in Elderly Patients Following Treatment with Cefotaxime or Piperacillin-Tazobactam." *Alimentary Pharmacology & Therapeutics* 12, no. 12 (December 1998): 1217–23, https://doi.org/10.1046/j.1365-2036.1998.00428.x.

[924] Settle, et al., "Prospective Study of the Risk of Clostridium Difficile Diarrhoea in Elderly Patients Following Treatment with Cefotaxime or Piperacillin-Tazobactam," 1221–23.

[925] James Anderson, Interview by Erin L. Paterson, 9 May 2024.

antibiotic market. Its two main ingredients: piperacillin (first patented in 1974) and tazobactam (1982) were combined in an effort for the beta-lactamase qualities of tazobactam to amplify the effects of piperacillin. It worked, and it has circulated in the years since becoming a front-line antibiotic in complex cases. Though it should be noted that while piperacillin first joined the WHO's Essential Medicines List in 1988, the combination therapy was only listed on the EML's Watch group in 2017.

In the late nineties, while hospitals were trying to work out their own usage concerns, finding that Pip-Tazo provided better health outcomes to patients was obviously a boon. However, it was a boon that would come with its own kind of unique complications. Three years after the Leeds hospital ran its study, reports of (what would be the first) piperacillin-tazobactam shortage began.[926] This shortage was also found to affect the United States, and was due to alleged manufacturing problems according to Fox's database.[927] While initial Pip-Tazo shortages lasted around two and a half years, various formulations of this drug continued to be in short supply between 2001 and September 2020 – often for manufacturing delays or other manufacturing related issues.

Because the Elderly Medicine Unit at the General Infirmary had started tracing the efficacy of the recently released piperacillin-tazobactam combination to see if it provided better health effects in their patient population compared to the previously used cefotaxime, when the antibiotic fell short they were uniquely suited to observe the health effects of transitioning back to cefotaxime. They were, also, able to show the impact of this particular shortage on the health of their afflicted patient population. Between 2000 and 2001 (prior to the shortage), expected outcomes were observed: piperacillin-tazobactam use increased,

[926] M. H. Wilcox, "Long-Term Surveillance of Cefotaxime and Piperacillin-Tazobactam Prescribing and Incidence of Clostridium Difficile Diarrhoea," *Journal of Antimicrobial Chemotherapy* 54, no. 1, June 16, 2004: 170, https://doi.org/10.1093/jac/dkh285.
[927] Erin Fox, Small File Data Shortage Through 2022, Received March 31, 2023, distributed by Erin Fox at University of Utah.

cefotaxime use decreased, and rates of CDD dropped (up to 54% lower).[928] However, after the shortage: cefotaxime usage increased 370% in 2002 and rates of CDD increased 232%.[929]

This data indicates that shortages may have an additional adverse effect on health outcomes as the rates of drug use increased beyond previously stated levels, as well as the spread of infection. This does not mean that the shortage directly caused an increase in actual infection, however it is possible that cefotaxime was not being used as appropriately as it could have been as habits on appropriate prescription rates of Pip-Tazo may have influenced usage. Additional comparator studies could help elucidate precisely why these rates occurred the way they did, and what was happening in the hospital setting specifically that led to these choices.

Another method of tracking these shortages beyond individual institution reporting, are mass surveys. In 2006, the European Society of Clinical Microbiology and Infectious Diseases Study Group on Antibiotic Policies sent a total of 384 surveys out to hospitals throughout Europe to determine if antibiotic shortages were affecting pharmacy output. They received 83 responses from 28 countries.[930] [931]

The most frequently affected agent was cefepime, though piperacillin-tazobactam was fourth on the list – a problem considering one of cefepime's primary alternatives *is* piperacillin-tazobactam. As previously shown within this chapter, when one antibiotic becomes short, its alternative is at an increased risk for also experiencing a shortage due to increased demand. (If we follow the chain of events from the Leeds study, the next drug that could potentially face strain is Cefotaxime as it was Pip-Tazo's replacement, and on and on).

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[928] Wilcox, "Long-Term Surveillance of Cefotaxime and Piperacillin-Tazobactam Prescribing and Incidence of Clostridium Difficile Diarrhoea," 169.
[929] Wilcox, "Long-Term Surveillance of Cefotaxime and Piperacillin-Tazobactam Prescribing and Incidence of Clostridium Difficile Diarrhoea," 170.
[930] S. Harbarth, P. M. Filius, S. Natsch, F. M. MacKenzie, and I. C. Gyssens, "#P1105 Shortage of Antimicrobial Agents in Europe: Results of an International Survey," In 17th ECCMID, Munich Germany, 2007.
[931] Harbarth, Filius, Natsch, MacKenzie, and Gyssens, "#P1105 Shortage of Antimicrobial Agents in Europe: Results of an International Survey."

This domino effect of shortages, not only leads to worsening health outcomes for the initial infection a patient experiences, but also rises the chances that antimicrobial resistance may form as a result.

The final determination by the research group concluded that of the hospitals who responded, 71% had experienced an antibiotic shortage at some point in the preceding year. These shortages ranged from 1 week to 18 months (some ongoing at time of reporting). Only four countries of the 28 respondents did not experience any shortage at all, though the poster does not specify which ones.[932] Additional shortages that were noted by the participants included those which were also found on Fox's data set, including: cephalosporins, colistin, doxycycline, rifampicin, vancomycin, nitrofurantoin, Fosfomycin, amphotericin B, amikacin, and tobramycin.[933] All of these antibiotics, with the exception of amphotericin B, are on the WHO EML depicting a great concern for accessibility and availability of essential antibiotics. One evident bias in this data is the fact that these antibiotics were specifically for hospital use, and they do not necessarily indicate larger country wide or out-patient experiences. Without greater specificity on which kind of drugs were short (intravenous or not, for example), it is difficult to make any broad ranging conclusions juts from this data set alone. By itself, however, it displays that there is concern, and a large amount of it, within hospital settings and additional research in non-hospital settings would be of use to see how the two compare.

One example of nonhospital distribution comes in the form of a 2007 Fosfomycin shortage in France. The stockout came about as prescription limitations in France led Sanofi-

[932] Participant countries were designated on a map of Europe that appears to have been outdated by the 2007 publication. The countries included: Portugal, Spain, France, Ireland, United Kingdom, Switzerland, Italy, Belgium, Netherlands, Germany, Denmark, Poland, Czech Republic, Slovakia, Austria, Hungary, Slovenia, Croatia, Yugoslavia, Bulgaria, Greece, Turkey, Finland, USSR. As Yugoslavia and the USSR did not exist in 2007 it is unclear where the participants were actually located. Furthermore, the map only designates 24 "participating countries", however the poster says there were 28 respondents, and 4 did not report a shortage. Therefore, I presume their map is actually only depicting where hospitals which reported a shortage existed.
[933] Harbarth, et al., "#P1105 Shortage of Antimicrobial Agents in Europe: Results of an International Survey.".

Aventis to undergo a stock quota management period, lowering rates of production.[934] A research group reporting on the impact of the Fosfomycin shortage found that in 36% of cases where Fosfomycin would have been used: there was no effective alternative. As Fosfomycin was the ideal treatment against the gram-negative bacteria: *pseudomonas aeruginosa, Klebsiella, Enterobacter* and *Serratia,* without it: those patients could not find efficient relief.[935]

These results were discussed again in a 2008 shortage review by pediatrician and infectious disease specialist Robert Cohen of the former Groupe de Travail Anti-Infectieux de l'agence française de sécurité sanitaire des produits de santé (AFSSAPS). He tracked five antibiotic shortages and one anti-tuberculosis shortage in France that year (translated to English): cefepime (specifically brand name Axépim®), fosfomycin (Fosfocine®), liquid forms of penicillin V(Oracilline®), oral forms of colistin (Colimycine®), injectable forms of cloxacillin (Orbenine®), and isoniazid (no brand name associated with report).[936] He tracked the reasoning for three of these drug shortages as well, making a point to mention that there were additional problems with using alternatives that could cause clinical concerns for both physician and patient.[937]

Cohen drew attention to the lack of interest in pharmaceutical companies to invest in "old products" due to their limited profitability, but that the manufacturing and raw supplier provider were equally problematic due to continued failures of quality control and timely production. He called for the AFSSAPS to assess the urgency of antibiotic usage, and new

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[934] Aurélien Dinh, Jean-Pierre Bru, Isabelle Dresco, Catherine Janus, and Louis Bernard, "Prescription de la fosfomycine en situation critique," *Médecine et Maladies Infectieuses* 38, no. 7 (July 2008) : 383. https://doi.org/10.1016/j.medmal.2008.03.002.

[935] Aurélien Dinh, Jean-Pierre Bru, Isabelle Dresco, Catherine Janus, and Louis Bernard, "Prescriptions Justifiées Par Un Référent: Exemple de La Fosfomycine," Powerpoint presented at the 8th Journées Nationales d'Infectiologie, Dijon, 2007, https://www.infectiologie.com/UserFiles/File/medias/JNI/JNI07/COL/COL1-04-dinh.pdf.

[936] Robert Cohen, "Pénurie Transitoire d'Anti-infectieux," Powerpoint, 2007, http://www.infectiologie.com/UserFiles/File/medias/JNI/JNI08/Com/penurieATB-afssaps2008-cohen.pdf.

[937] Robert Cohen, "Pénurie Transitoire d'Anti-infectieux," Powerpoint, 2008, http://www.infectiologie.com/UserFiles/File/medias/JNI/JNI08/Com/penurieATB-afssaps2008-cohen.pdf..

practices on how best to manage stockouts should they occur- including alternatives or transitions to manufacturers from other countries.[938] For a time, the AFSSAPS did just that, and additional presentations and reports came out in the years that followed tracking the impact and usage of antibiotics until it was closed down and replaced by the Agence nationale de sécurité du médicament et des produits de santé in 2012.

In 2011, Europe was still struggling to maintain its supply of cefepime, with reports coming this time from Switzerland. Prior to the shortage occurring, cefepime had been a main prescription in the hospitals that participated in the postmortem survey. The alternatives though, were not ideal. The main alternative was piperacillin-tazobactam, which still had shortage problems of its own, followed by imipenem-cilastatin, ceftazidime, meropenem, or ciprofloxacin.[939] The patient cost as a result of this transition came in the form of increased resistance in pseudomonas aeruginosa as treatment options failed to resolve quickly and efficiently.[940] As a gram-negative bacteria, pseudomonas aeruginosa is difficult to treat in the first place, but added resistance creates greater uncertainty in future treatment outcomes. The Swiss research group responsible for tracking this shortage continued to call for more research into the increase of antibiotic shortages that had been noticed since 2000, but attention to such a thing remained sparse.

Their call would be answered two years later when a Teva Pharmaceuticals funded study surveyed the subscribers of *Hospital Pharmacy Europe* regarding their individual hospital's drug shortage experiences.[941] The four-person research group, Kim Pauwels, Steven Simoens, Minne Casteels, and Isabelle Huys, created a lengthy survey that they sent

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[938] Cohen, "Pénurie Transitoire d'Anti-infectieux."
[939] C. Plüss-Suard, A. Pannatier, C. Ruffieux, A. Kronenberg, K. Mühlemann, and G. Zanetti, "Changes in the Use of Broad-Spectrum Antibiotics after Cefepime Shortage: A Time Series Analysis," *Antimicrobial Agents and Chemotherapy* 56, no. 2 (February 2012): 990, https://doi.org/10.1128/AAC.05560-11.
[940] Plüss-Suard, et al., "Changes in the Use of Broad-Spectrum Antibiotics after Cefepime Shortage: A Time Series Analysis," 993.
[941] Kim Pauwels, Steven Simoens, Minne Casteels, and Isabelle Huys, "Insights into European Drug Shortages: A Survey of Hospital Pharmacists," Edited by John Conly, *PLOS ONE* 10, no. 3 (March 16, 2015): e0119322, https://doi.org/10.1371/journal.pone.0119322.

to across the European continent. They received 160 responses from various hospital representatives across 27 countries in Europe (though primarily western Europe), the highest amount from the United Kingdom. Their collected data was published in a dataset separate from their published article, and their article focused primarily on geographic regions to indicate percentage of impact and care. As their article looked at the overall impact of all drug shortages, not just their antibiotic concerns, I used their published dataset to create more specific figures and tables most relevant to this dissertation.

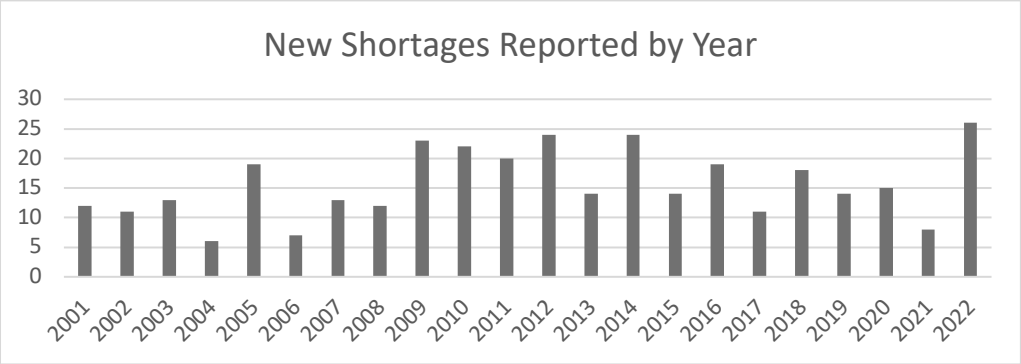

Figure 6 New shortages reported by year 2001-2022[942]

Somewhat hidden in the original article, is the prevalence of UK responses. Due to the hospital respondents self-reporting their country of origin, there were split responses for the United Kingdom: 10 from England, 6 from Scotland, and 24 from the UK. For the generation of this figure, and for consistency as it is not clear where in the United Kingdom the 24 respondents originated from, I included all these responses under the United Kingdom heading. The difference when seen in a comparative scale is evident and may reveal an implicit bias for English language reporting and responses and subscription participation. There is also, potentially, a reporting bias as well integrated within the survey itself. At the time that the Teva study was in progress, the United Kingdom was already in the process of reviewing and analyzing AMR and the impact of antibiotic research. (Only one year later,

[942] Data taken and organized from supplementary data set within: Kim Pauwels, Steven Simoens, Minne Casteels, and Isabelle Huys, "Insights into European Drug Shortages: A Survey of Hospital Pharmacists," Edited by John Conly, *PLOS ONE* 10, no. 3 (March 16, 2015): e0119322, https://doi.org/10.1371/journal.pone.0119322.

Jim O'Neill's research team would publish its report, discussed earlier in this dissertation). While there is an overwhelming number of responses in the UK to Teva's study, they may simply have already had the tools to analytically respond to the survey in a more detailed fashion than other respondents.

One of the many questions asked on the survey was if they had "the impression that certain types of medicine suffer more frequent drug shortages than others?" and the answers given varied drastically not only across national borders but within countries themselves, showing a lack of consistency within territorial borders as well. While 36 respondents either did not answer or did not believe that any medication had a more frequent shortage over another, 24 hospitals in particular stated that "treatment of an acute but short-term illness (e.g. an antibiotic) was most likely to have a shortage.[943]

However, even though the majority of countries did not choose antibiotics as the *most* frequently short medication, 69 hospitals from 21 (out of 27) countries agreed that antibiotics were affected by shortages.[944] When asked to specify which kinds of drugs, what the pricing profile of the drugs were, and what formulation was most short, the responses given matched the thorough studies conducted by the United States on the same issue. Generic, cheap, injectable drugs were the most likely antibiotics to fall short.[945]

Respondents also reported that they believed that the acquisition process of drug purchasing is one of the factors that led to shortages across all sectors. They foreshadowed the same concerns that were discussed in the United States as they reviewed causes and considerations of their own national shortages. Due to the selection of drug procurement via governmental or hospital tender, competing manufacturers engage in a race to the bottom to

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[943] Data taken and organized from supplementary data set within: Pauwels, Simoens, Casteels, and Huys, "Insights into European Drug Shortages," e0119322.
[944] Pauwels, et al., "Insights into European Drug Shortages: A Survey of Hospital Pharmacists," Supporting Information S1 Dataset.
[945] Data taken and organized from supplementary data set within: Pauwels, et al., "Insights into European Drug Shortages," e0119322.

offer the lowest possible financial cost for the sale of their stock in order to be selected for tender.[946] As a result of losing long term contracts or tenders, competitor companies need to leave the manufacturing of one antibiotic and transition to the development of another in order to remain in business. If anything should happen to the approved manufacturer – there are no alternatives to shore up supply.

Following the publication of the European Drug Shortages survey, shortages continued to occur throughout Europe. In 2017, researchers from the Goethe-Universität tracked the impact of another piperacillin-tazobactam shortage. Their research identified this new shortage to be the responsibility of Qilu Pharmaceutical Co. Ltd plant in Jinan (East China).[947] And later, it would be revealed that the cause of the shortage had come about due to an ethanol boiler eruption in October 2016.[948] By December 2016 though, supplies were already starting to run short and researchers were once again tracking impact and replacement methods on patient populations.

Frustration at both the persistence shortages, beyond that of just antibiotics, led a well-known German radio broadcaster, Deutschlandfunk Kultur to create a report on drug shortages and monopolies that expanded past the boundaries of antibiotics alone. Their detailed analysis of a series of drug shortages from large name companies such as Bristol Myers-Squibb, Aspen-Pharma, and Teva led them to specifically draw attention to the fact that: "It is all the more astonishing that in Germany - unlike in the USA, for example - there is no legal obligation for manufacturers to report bottlenecks, but only a voluntary obligation" (translated into English).[949]

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[946] Pauwels, et al., "Insights into European Drug Shortages," e0119322.
[947] Johanna Kessel, Barbara Dolff, Thomas Wichelhaus, Nils Keiner, Michael Hogardt, Claudia Reinheimer, Imke Wieters, et al, "Piperacillin/Tazobactam-Lieferengpass: Zentrale Restriktion und Alternativempfehlungen als effektive Antibiotic-Stewardship-Maßnahme an einem Klinikum der Maximalversorgung," *DMW - Deutsche Medizinische Wochenschrift* 143, no. 08 (April 2018): e59–60. https://doi.org/10.1055/s-0043-122706.
[948] Anja Schrum and Ernst-Ludwig Aster, "When essential medicines become scarce," Radio Broadcast Archive, *Drug Monopolies*, March 12, 2018, https://www.deutschlandfunkkultur.de/arzneimittel-monopole-wenn-lebenswichtige-medikamente-knapp-100.html.
[949] Schrum and Aster, "When essential medicines become scarce."

The short supply of piperacillin-tazobactam in 2017 Germany did not see an increased rate of CDD, but did show an increased risk of vancomycin resistant enterococci septicemia.[950] One of the key concerns noted was that even if adverse effects and infection rates can be appropriately controlled by effective prescription and alternative treatment methods, antibiotic stewardship program guidelines are put at risk as a result of transferring care. As identified in pervious sections, concerns relating to "dosing errors, over- or under-therapy and the cause of secondary bottlenecks in alternative substances and prioritize the care of particularly sensitive areas."[951]

In the years leading up to the Covid-19 pandemic these issues continued to put strain on manufacturers, supply chains, and distributors. A 2018 survey conducted by European Association for Hospital Pharmacists found that of the 1666 total responding hospitals, 90% found that shortages were a current problem in delivering care to patients; 77% states antimicrobial shortages were the most common.[952] This survey spanned 38 European countries and compared data to an earlier survey conducted in 2014. The majority of respondents reported experiencing daily and weekly shortages, which led to delays or cancellations of care/treatment, medication errors, sub-optimal treatment, and other complications up to and including death.[953] With the absence of intensive records on the extent of these shortages, it is unclear which antibiotics specifically were short, or what the specific impact of antibiotic shortages were beyond the sense of understanding that antibiotic shortages were happening and were causing "an effect" of some kind.

It is likely that some of the short or restricted supply antibiotics were meant to target resistant bacteria as consistently: the supply chain for antibiotics targeting gram-negative

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[950] Kessel, et al., "Piperacillin/Tazobactam-Lieferengpass," e65.
[951] Kessel, et al., "Piperacillin/Tazobactam-Lieferengpass," e65-66.
[952]Nenad Miljković, Nicholas Gibbons, Aida Batista, Raymond William Fitzpatrick, Jonathan Underhill, and Petr Horák, "Results of EAHP's 2018 Survey on Medicines Shortages," *European Journal of Hospital Pharmacy*, February 4, 2019, 60, https://doi.org/10.1136/ejhpharm-2018-001835.
[953] Miljković, et al., "Results of EAHP's 2018 Survey on Medicines Shortages," 61-2.

bacteria faced global complications during this time period (see above). However, even the most basic antibiotics: penicillins, experienced shortages which naturally put strain on other antibiotic supply chains as prescriptions shifted to accommodate patient demand. For example, between 2013 and 2017 France increased its use of doxycycline to treat syphilis due to a benzathine penicillin G shortage, requiring studies on potential effects of resistance after the fact.[954]

These continued and mounting experiences, though haphazard in their data collection and often sparked by local concerns that need to be examined in their overall totality, has led to increased attention by the European Commission and national governments in how to respond to and track drug shortages. On 17 June 2023, the European Commission published a press release stating they were working on ways to ensure there is no repeat of 2022's antibiotic crisis in the fall of 2023.[955] One month later on 4 July 2023, the French senate met to discuss the shortage of medicines and the choices of the French pharmaceutical industry.[956] The senate report indicated multiple antibiotic shortages between 2019 and 2022 and a need for improved reporting and response systems.[957] At time of writing there has been no specific action put into place to address these concerns. It is possible, due to the continued opacity as to what is actually causing the shortages (is it a raw material issue, manufacturing problem, business decision, transportation concern etc.?), that finding a unique solution will be challenging.

[954] A. Sanchez, C. Mayslich, I. Malet, P. Grange, M. Janier, J. Saule, P. Martinet, et al, "Surveillance of Antibiotic Resistance Genes in Treponema Pallidum Subspecies Pallidum from Patients with Early Syphilis in France," *Acta Dermato Venereologica* 100, no. 14 (2020): adv00221, https://doi.org/10.2340/00015555-3589.
[955] Célia Dejond, "European Health Union: EU Steps up Action to Prevent Shortages of Antibiotics for next Winter." Press Release. European Commission, July 17, 2023, https://ec.europa.eu/commission/presscorner/detail/en/ip_23_3890.
[956] Sonia De La Provôté and Laurence Cohen, "Pénurie de médicaments : Trouver d'urgence le bon remède – Rapport," Rapports de commission d'enquête, Sénat Session Extraordinaire de 2022-2023, (Paris, France: Sénat, July 4, 2023), https://www.senat.fr/notice-rapport/2022/r22-828-1-notice.html.
[957] De La Provôté and Cohen, "Pénurie de médicaments : Trouver d'urgence le bon remède – Rapport," 15, 52, 274.

In conjunction with a need for action, as Young and Coeklebergh mentioned in their 2024 book on Maintenance: communication is key.[958] The continued invisibility surrounding the supply chain has led to ad hoc reporting of European sources, and increased frustration as action to correct supply chain issues are perceptibly limited. Without using the same terminology, the same way of referencing, nor even the same reporting mechanisms: shortages are not effectively tracked or traced. The black box, on how a product even arrives in a patient's hand, becomes ever more obscured as a result.

The concerns discussed so far in this section are largely concerns of availability. Something in the supply chain, often marked as a manufacturing disturbance, is prohibiting the product from reaching its end point. As far as antibiotic accessibility is concerned: the infrastructure here is showing its breaks at the root. However, for LMICs, this poses an additional problem as *affordability* is often a component for accessing medications.

In 2014, the Utrecht University Institute for Pharmaceutical Sciences and Health Action International analyzed the impact of the availability of medicines on the WHO's EML in 23 countries across the LMIC spectrum, including nations in the WHO regions of Africa, Americas, Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific.[959] They found that in all cases, the median availability for *any* drug type – including antibiotics – was less than 50%.[960] Private sector availability did provide more access to antibiotics but GDP factor did not play a role in accessibility as Upper Middle Income Countries were less likely to have essential medicines compared to Lower Income Countries in both the public or private sector. This is possibly due to funding initiatives and donor programs that ensured availability to LICs unable to purchase drugs on their own. MICs are more expected to

[958] Young and Coeckelbergh, eds., *Maintenance and Philosophy of Technology: Keeping Things Going,* 10-11.
[959] Yaser T. Bazargani, Margaret Ewen, Anthonius De Boer, Hubert G. M. Leufkens, and Aukje K. Mantel-Teeuwisse, "Essential Medicines Are More Available than Other Medicines around the Globe," Edited by Imti Choonara, *PLoS ONE* 9, no. 2 (February 12, 2014): 1-2, https://doi.org/10.1371/journal.pone.0087576.
[960] Bazargani, et al., "Essential Medicines Are More Available than Other Medicines around the Globe,"4.

manage such purchases without outside help and therefore do not have access to such programs. (Specific examples of this regarding Tuberculosis treatment programs will be discussed later in this chapter). Overall, the average availability of antibiotics among the respondents was 78.4%, a far from satisfactory result – particularly as lack of adequate antibiotics can lead to increased use of second line drugs and antimicrobial resistance.

Of the articles collected for the corpus used in this dissertation, 57% of them referred specifically to HIC countries when using the word "shortage," however searching for "accessibility" or "availability" flipped the priority with 62% of articles using these terms referring to countries from Low to Middle Income Countries across Africa, Asia, and South America.[961] These reflect a sense of temporality involved in both terms, with "shortage" being considered a short-term, expected to be resolved, scenario, whereas "access" or "availability" concerns were those that were longer in length and may have additional complicating factors leading to the inhibition. Despite this, financial impact is not taken into consideration, nor are the general status of medical stock and supply. If a country never had access to a cephalosporin in the first place, would it ever be considered short? Or is it merely unavailable? If it did have access to cephalosporin, but lost that access due to a factory mishap: would it be recorded as a shortage then, or not? Again, this lack of consistency with definitions and experiences made the tracking and tracing of the history of off-patent antibiotic accessibility a particular challenge whose successful resolution would be beyond the scope of this dissertation.

Some outlier reports stand out from this corpus, however. One, from Bangladesh in 1994 which suggested that despite efforts made to adhere to the EML program, only an average 54% of the 12 marker essential drugs they screened for were in stock at time of

[961] See Appendix Five for more detail

survey.[962] No explanation is given to what caused the lack of availability nor were the marker drugs identified. As far as a one to one direct comparison, understanding the depth and totality of these shortages is once more obfuscated by the lack of visibility within this infrastructure.

Other reports made, from Ghana, for instance, discussed the utility of the drugs in use in conjunction with a specific disease. In 1996, a study for suggested treatments of pelvic inflammatory disease (PID) found that of formulations capable of addressing this problem, available medications ranged from 0%-94.1% available (indicating that there was never a time when accessibility was guaranteed).[963] [964] [965] Furthermore, after additional review, the affordability of these treatments was a major concern. The table below, generated from the data regarding PID in Ghana at this time, reveals the number of days a minimum wage worker would need to work in order to purchase *one dose* of a prescribed antibiotic capable of addressing PID with minimum wage calculated at ¢2000.[966]

Drug Name	% Availability	Median Cost (cedi)	Number of days needed to work in order to afford ONE dose of medication
Ceftriaxone (250mg - injection)	23.50%	¢20000	10
Ciprofloxacin (500mg - tablets)	23.50%	¢1850	0.925
Doxycycline (100mg - capsule)	41.20%	¢250	0.125
Erythromycin (250mg - tablets)	58.80%	¢200	0.1
Metronidazole (200mg - tablets)	47.10%	¢22.5	0.01125
Metronidazole (500mg - injection)	91.40%	¢2750	1.375
Tetracycline (250mg - capsule)	94.10%	¢40	0.02

Table 8 Number of days needed to work in order to afford one medication in Ghana[967]

[962] A.B. Guyon, A. Barman, J.U. Ahmed, A.U. Ahmed, and M.S. Alam, "A Baseline Survey on Use of Drugs at the Primary Health Care Level in Bangladesh," *Bulletin of the World Health Organization* 72, no. 2 (1994): 269
[963] William K. Bosu and David Mabey, "The Availability and Cost of Antibiotics for Treating PID in the Central Region of Ghana and Implications for Compliance with National Treatment Guidelines," *International Journal of STD & AIDS* 9 (1998): 551.
[964] Bosu and Mabey, "The Availability and Cost of Antibiotics for Treating PID in the Central Region of Ghana and Implications for Compliance with National Treatment Guidelines," 552.
[965] The average percent availability for these drugs was 49.5%, the median was 44.4%, the mode was 23.5%.
[966] WageIndicator 2023, "Minimum Wage in Ghana (1963 -2012)," Archive. Accessed August 3, 2023. https://africapay.org/ghana/salary/minimum-wages/minimum-wage-timeline.
[967] Data organized and represented based on documentation in Bosu and Mabey, "The Availability and Cost of Antibiotics for Treating PID in the Central Region of Ghana and Implications for Compliance with National Treatment Guidelines," 552.

In the cases of ceftriaxone and metronidazole (500mg), more than a full day's work would be required to have access to *one* injection. Treatment course guidelines vary, but public health consultant and physician, William K. Bosu and David Mabey calculated one such treatment course based on the WHO's recommended regimen 14-day mixed dose regimens costing between ¢22,160 and ¢167,000 with particularly severe cases needing treatment that cost upwards of ¢549,800.[968] For someone to receive a correct course for pelvic inflammatory disease, they would need to work between 11.8 and 274.9 days to afford their treatment course. Furthermore, the chances of them acquiring all of the recommended drugs for the entire course varies dramatically depending on the drug regimen chosen and availability of supplies. Bosu and Mabey both concluded at the end of their research that only 9% compliance existed when it came to treading PID, something that could be very easily explained by both the affordability and availability concerns (with tobramycin and oxytetracycline having availability rates as low as 0%).[969]

While incidences with lack of accessibility due to affordability concerns continued to abound, but the simple fact that sometimes the drug never even appeared in stores – despite the potential for a sale, was an equally present factor within this corpus. Injectable forms of metronidazole, along with twenty-two other essential antibiotics were short in Iran for an average of 6.5 months each in the early 2000s.[970] [971] In Brazil, researchers conducting surveys on their local populations found that "antibiotics were reported as the main inaccessible treatments," with 14% of individuals in Manaus, Brazil specifically unable to

[968] Bosu and Mabey, "The Availability and Cost of Antibiotics for Treating PID in the Central Region of Ghana and Implications for Compliance with National Treatment Guidelines," 553.
[969] Bosu and Mabey, "The Availability and Cost of Antibiotics for Treating PID in the Central Region of Ghana and Implications for Compliance with National Treatment Guidelines," 552-3.
[970] A Manafi, MR Panjehshahin, M Ghorbanpour Saravi, SA Emami, and SK Forootan, "Reduced Bioavailability of Oral Metronidazole in Postoperative Ileus," *Iranian Red Crescent Journal* 9, no. 3 (2007): 130.
[971] Kheirollah Gholamia, Golnaz Kamaliniab, Mohammad Mahdi Ahmadian Attaric, and Jamshid Salamzadehd, "Three Years Evaluation of Drug Shortages From Educational Pharmacies in Tehran," *Iranian Journal of Pharmaceutical Research* 11, no. 2 (2012): 567.

access appropriate drug therapies.[972] High cost, and a lack of availability in local pharmacies were *both* considered causes.[973]

During the Covid years, articles relating to accessibility and drug shortages increased significantly in LMICs.[974] The increased attention to drug supply chains capable of moving Covid vaccinations equally affected the uncertain supply chains of antibiotics in rural and hard to reach places. These articles focused on the need for pharmacies to switch an unavailable drug for an available drug (such as in India),[975] the availability of key drugs on the essential medicines list (India),[976] availability and cost affordability (China, Pakistan),[977] [978] and patterns of use due to availability concerns (Ethiopia).[979] Each of these articles repeated the same information already seen in each of the preceding decades. Antibiotic use is high, but variability and guarantee of antibiotic accessibility is low. More complex antibiotics that can treat resistant strains were expensive and often not available, and cost remains a problem in these cases.

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[972] Gustavo Magno Baldin Tiguman, Marcus Tolentino Silva, and Taís Freire Galvão, "Consumption and Lack of Access to Medicines and Associated Factors in the Brazilian Amazon: A Cross-Sectional Study, 2019," *Frontiers in Pharmacology* 11 (October 6, 2020): 5; 7, https://doi.org/10.3389/fphar.2020.586559.
[973] Baldin Tiguman, Tolentino Silva, and Galvão, "Consumption and Lack of Access to Medicines and Associated Factors in the Brazilian Amazon," 6.
[974] Consult Appendix 3 for more detail
[975] Fatima Khan, Bhanu Chaudhary, Asfia Sultan, Manzoor Ahmad, Yasir Alvi, Mohammad Salman Shah, and Haris M. Khan, "Qualitative Thematic Analysis of Knowledge and Practices of Surgical Antimicrobial Prophylaxis at a Tertiary Care Teaching Hospital," *Surgical Infections* 22, no. 4 (May 1, 2021): 3-4, https://doi.org/10.1089/sur.2020.181.
[976] Amrita Aryal, Asmita Dahal, and Rajeev Shrestha, "Study on Drug Use Pattern in Primary Healthcare Centers of Kathmandu Valley," *SAGE Open Medicine* 8 (January 2020): 3, https://doi.org/10.1177/2050312120926437.
[977] Yulei Zhu, Xinglu Xu, Wenqing Fang, Ying Wang, Huizhen Dai, and Xin Li, "Availability, Cost and Affordability of Selected Antibiotics and Antiviral Medicines against Infectious Diseases from 2013 to 2019 in Nanjing, China," Tropical Medicine & International Health 26, no. 5 (May 2021): 519, https://doi.org/10.1111/tmi.13559.
[978] Zikria Saleem, Hamid Saeed, Zunaira Akbar, Amna Saeed, Saleha Khalid, Laiba Farrukh, Aleena Irfan, et al., "WHO Key Access Antibiotics Prices, Availability and Affordability in Private Sector Pharmacies in Pakistan," *Cost Effectiveness and Resource Allocation* 19, no. 1 (December 2021): 4, https://doi.org/10.1186/s12962-021-00263-x.
[979]Solomon Ahmed Mohammed and Abebe Getie Faris, "The Pattern of Medicine Use in Ethiopia Using the WHO Core Drug Use Indicators," Edited by Mihajlo Jakovljevic. *BioMed Research International* 2021 (December 24, 2021): 1–11, https://doi.org/10.1155/2021/7041926.

In an April 2023 interview with Kathleen Holloway, she affirmed that one of the factors relating to drug shortages was the clash between the public sector and private sector funding. The devaluation of the public sector's health care infrastructure naturally led to a lack of support when it came to drug management and control. Drug shortages in the public sector, therefore, were common.[980] The global non-profit Management Sciences for Health attempted to rectify some of these shortage concerns in 2003 with the development of the Accredited Drug Dispensing Outlets in Tanzania, Kenya and Uganda. The goal was to train and support pharmacies and drug sellers so they were able to appropriately manage and distribute medications. However, without guaranteed sources of funding beyond the scope of many national governments on their own, initiatives like this struggle to adequately support publicly owned facilities. Trained individuals will often transition into private sector resellers that expand into progressively more remote areas and selling drugs without proper supervision in order to generate a profit.[981] The only two countries that Holloway determined did not have this private sector problem was Bhutan and North Korea, due to the absence of *any* private sector pharmaceutical service.[982] As she bluntly stated in an interview: "When there's no shop, there's nothing,"[983] and the problems that they have instead are of a wholly different sort as a result.

The Web of Science corpus is unable to provide a fully reasoned and balanced understanding of the effect of antibiotic shortages in either Europe or LMICs. These are specific results that highlight a targeted moment in time. These results are comparable to one another, and reveal consistent similarities: whether a drug is affordable or not, the availability of that drug is still in question. The manufacturing of that drug at the API level may be the largest source of concern, and transportation and delivery following fluctuations in demand

[980] Kathleen Holloway, Interview by Erin L. Paterson, 20 April 2023.
[981] Kathleen Holloway, Interview by Erin L. Paterson, 20 April 2023.
[982] Kathleen Holloway, Interview by Erin L. Paterson, 20 April 2023.
[983] Kathleen Holloway, Interview by Erin L. Paterson, 20 April 2023.

would make up the second most prevalent issue. When set aside the more specific and measurable data that Fox developed for the United States, these trends become amplified even more.

The infrastructure that they are a part of, is clearly in the process of breaking down, and for all cases: an enforced lack of clarity either by the purposefully obfuscation of information on how the supply chain works has been prohibiting successful efforts to correct or address shortage needs.

IV. Contextualizing shortages and the spectrum of antibiotic shortage tracking

As early as 1999, 82% of respondents to an Infectious Disease Society of America Emerging Infections Network survey reported that they needed to change out an anti-infective they had prescribed due to a shortage.[984] However, the sheer quantity of new shortages and their durations have increased since that point, suggesting more practitioners would face such problems in their practices today. Antibiotic shortages since 2001 have been relatively consistent in number per year, though certain spikes can be observed over certain groupings of time. 2010 is often denoted as a particularly bad year for drug shortages in the United States, with one calculation stating that between 2010 and 2011 antibiotics alone made up 13% of the *total* drug shortages within the United States including all forms of medication.[985] Beyond 2010, though the average number of new shortages between 2009-2014 remained high at 21, and though the new shortages reported dropped in 2021 the highest

[984] Milena M. Griffith, Alan E. Gross, Sarah H. Sutton, Maureen K. Bolon, John S. Esterly, Jean A. Patel, Michael J. Postelnick, Teresa R. Zembower, and Marc H. Scheetz, "The Impact of Anti-Infective Drug Shortages on Hospitals in the United States: Trends and Causes," *Clinical Infectious Diseases* 54 (2012): 685.
[985] Milena M. Griffith, Zachary Pentoney, and Marc H. Scheetz, "Antimicrobial Drug Shortages: A Crisis Amidst the Epidemic and the Need for Antimicrobial Stewardship Efforts to Lessen the Effects," *Pharmacotherapy* 32, no. 8 (2012): 665.

reported number of shortages in the United States was experienced in 2022 at 26 new shortages—exceeding the 2012/2014 high of 24.

As we have seen, drug shortages today largely affect off-patent, generic, medications. Earlier in this dissertation, DRIVE-AB's "Revitalizing the antibiotic pipeline," info-graphic was used to reveal how there was an expectation for drugs to make it through the antibiotic pipeline and reach a generic form on the market.[986] The purpose of this Innovative Medicines Initiative funded project was to re-evaluate and re-invigorate the push/pull financial incentives previously discussed in this dissertation with the purpose of encouraging sustainable antibiotic use and distribution. DRIVE-AB's pipeline extends past the registration and market and continues through the production and dissemination of generic formulations.[987]

This "continuity," as DRIVE-AB calls it, marks the political understanding of an eventual post-patented drug supply chain, and an implicit expectation of accessibility as a result. This supply chain would lead from a producer to a distributor, to a transporter, then to pharmacies and patients for as long as there is need of that drug. Generic drugs as a whole, currently take up 80% of the drug market and are a key part of the drug ecosystem and economy, especially for low income communities.[988] But as Chapter One has discussed, their existence is a result of geopolitical machinations. [989]

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[986] Christine Årdal, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John Rex, "Revitalizing the Antibiotic Pipeline:
Stimulating Innovation While Driving Sustainable Use and Global Access," Final Report, DRIVE-AB. Innovative Medicines Initiative, 2018,
https://www.imi.europa.eu/sites/default/files/projects/documents/DriveAB_Report_FINAL.pdf.

[987] Christine Årdal, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John Rex, "Revitalizing the Antibiotic Pipeline: Stimulating Innovation While Driving Sustainable Use and Global Access," Final Report, DRIVE-AB. Innovative Medicines Initiative, 2018, 5.
https://www.imi.europa.eu/sites/default/files/projects/documents/DriveAB_Report_FINAL.pdf.

[988] Jeremy A Greene, *Generic: The Unbranding of Modern Medicine*, (Baltimore, United States: John Hopkins University Press, 2014), 1.

[989] Hayden, *The Spectacular Generic,* 52.

Pharmaceutical patent law provides limited-time monopolies to drug innovators so that they may sell their product and recoup the cost of investment (ideally making a profit) prior to the introduction of competition. The argument behind permitting these monopolies is that, without patent protection, a company could sink millions of dollars in research and development costs, overcome the hurdles of market registration, and enter a product onto the market, only to have a different company copy the design and sell the same product without any of the sunken investment. Arguments or suggestions that royalties be paid rather than the implementation of monopolies were soundly rejected, [990] and alternatives (such as market entry rewards) have been met with equally tepid responses by governments and regulatory bodies. There is no argument that on-patent medications cost more than their future generic counterparts, but there is an expectation that when a patent expires, the new generic drugs will enter the market and broaden access to medications that were priced out of reach for those in need.[991] Johnson & Johnson's attempts at ever-greening bedaquiline and the fierce public outcry resulting from this practice was discussed in Chapter Four. However, bedaquiline is a newer antibiotic. Old antibiotics, free from the recent trappings of patent oversight, now exist firmly in the generic domain, and access to these medications is not necessarily guaranteed. Maintaining and ensuring continued production of a generic drug means that the manufacturing company must offer the lowest price possible, and in a game of race-to-the-bottom pricing: eventually problems do arise.

The concept of generic medications is something that emerged primarily after the 1970s when the United States began to exert its internal patent law requirements on other countries at a global scale. Kaushik Sunder Rajan's, *Pharmocracy: Value, Politics, and*

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[990] Kaushik Sunder Rajan, *Pharmocracy: Value, Politics, and Knowledge in Global Medicine,* Edited by Michael MJ Fischer and Joseph Dumit, Experimental Futures: Technological Lives, Scientific Arts, Anthropological Voices, (Durham, United States: Duke University Press, 2017), 196.

[991] For more information on generic medications, their uses, their stereotypes, and the ways generic medications are perceived, see: Jeremy A Greene, *Generic: The Unbranding of Modern Medicine*, (Baltimore, United States: John Hopkins University Press, 2014).

Knowledge in Global Medicine, highlights how "much of the industrialized world (bar the United States) in fact had thriving economies in pharmaceutical copies for much of the twentieth century" and that the push to standardizing patents on a global scale was a purely American mechanism.[992] Cori Hayden's 2023 book, *The Spectacular Generic,* equally discusses the ways in which the generic manufacturing market, prior to the pressure of United States trade negotiations, was not something that relied on patent law negotiations in order to exist. Drugs would be reversed engineered and sold regardless of the current state of patent regulations beyond Mexico's borders. When concerns regarding quality concern were brought to the fore, neoliberal arguments regarding efficacy and consumer choice were issued in retaliation. If a drug proved to be efficacious: then the consumer would continue to purchase it. Therefore, it was in the generic manufacturer's best interest to continue making the most efficacious drug it could to win consumer confidence.

Naturally, this brings up the concern of equivalencies.[993] Chapter One discussed the ways in which drugs themselves could chemically be very similar to one another, but still have different mechanisms of action based on one subtle shift or change in cell structure. When a generic formulation is made, that does not mean that the originator company handed the recipe to another company, but rather that another company created a product with enough bio-equivalence that it seemingly matches that of the originator's company and that the new product is capable of providing the same effect as a result. The differentiation between a patented drug and a generic formulation can be entirely minuscule or non-existent, with only the legal/bureaucratic precedent of originating/branded product with an intact monopoly vs. alternative product without such protections serving as a difference.

[992] Sunder Rajan, *Pharmocracy,* 291.
[993] Cori Hayden, *The Spectacular Generic: Pharmaceuticals and the Simipolitical in Mexico*, Edited by Vincanne Adams and João Biehl, Critical Global Health: Evidence, Efficacy, Ethnography. (Durham, United States: Duke University Press, 2003), 33-35).

However, generic medications are often beset with a series of questions, such as: is the generic formulation *really* the same as the originator/branded medication? Or is it just similar? And even if it is similar…is being similar just as good? Chemical, and later bioequivalence and good manufacturing practice became the gold standard for proving that yes: it is the same. [994] But as Hayden states, "bioequivalence is geopolitics." [995] National standards of drug development in Mexico, as an example, were raised to meet the same requirements as those in the United States, as United States manufacturers feared that without such requirements implemented the Mexican market could undercut their own production capacities. [996] This created a barrier for manufacturers to enter the generics market as well as raised the expectation of what needed to be a part of the production cycle. But meeting these standards do not necessarily mean that the chemical formulation created by the manufacturer in the first place was any less *equivalent,* and thus the status of any of these drugs and what they may or may not be called or used as, often comes down to a political ideology, rather than a chemical makeup.

Between 10-11 December 2018, the World Health Organization met with the Norwegian Directorate of Health, various European and American health service representatives, members of the NGOs like ReAct and GARDP, as well as other experts and interested parties to discuss the reasons behind antibiotic shortages. Their report, published in 2019, offered a concise overview of antibiotic shortages and possible solutions. It mentioned the 2017 piperacillin/tazobactam shortage caused by a fire at a manufacturing facility, yet the specific methodology on how to circumvent future shortages was neither precise nor definitive. Fifteen recommendations, split between short term and long-term options were

[994] Hayden, *The Spectacular Generic,* 36.
[995] Hayden, *The Spectacular Generic,* 52.
[996] Hayden, *The Spectacular Generic,* 51-2.

recommended by the group, but with no actionable or enforceable power, the report remained a list of suggestions with no requisite or determined resolution.

Not long after, in 2021, Guillaume Beraud (an infectious disease specialist and expert in mathematical modeling) analyzed a series of reports coming from low, middle, and high-income countries all stating that they were experiencing antibiotic (or vaccine) shortages.[997] Beraud attributed two primary causes of the shortages that both derived from the same root: the frailty of a system that relies on only a few companies to supply products.[998] Regardless on if a company is affected by a lack of ingredients or if there is a sudden increased demand, if there are only relatively few corporations responsible for manufacturing a product there is an increased risk of a supply chain shortage as a result. This is a theme that is echoed time and again, throughout the articles and reports discussed within this chapter, and yet an action to address these concerns remains lacking.

While drug shortages in low-middle-income countries (LMICs) are not considered "new," shortages in high-income countries (HICs) have begun to appear with more frequency.[999] One reason is that there are simply fewer active pharmaceutical ingredient (API) manufacturers actively producing antibiotics than there were prior.[1000] APIs are the backbone of the pharmaceutical industry and the geolocation and production capabilities of these APIs are essential to stable supply chains. If they are implicated in any way, the distribution channels of not just one API vendor/client relation – but any other API who generates the same formulation – could be implicated.

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[997] Guillaume Beraud, "Shortages Without Frontiers: Antimicrobial Drug and Vaccine Shortages Impact Far Beyond the Individual," *Frontiers in Medicine* 8, no. 593712 (2021): 1–2, https://doi.org/doi:10.3389/fmed.2021.593712.
[998] Beraud, "Shortages Without Frontiers," 2.
[999] Kim Pauwels, Isabelle Huys, Minne Casteels, and Steven Simoens, "Drug Shortages in European Countries: A Trade-off between Market Attractiveness and Cost Containment?" *BMC Health Services Research* 14, no. 1 (September 26, 2014): 438. https://doi.org/10.1186/1472-6963-14-438.
[1000] Erin Fox. Interview by Erin L. Paterson. 31 March 2023.

As shortages continue to be marked and referenced in various articles and journals, on a governmental level: there appears to be no coordinated action to address antibiotic shortages or their growing impact either in independent European countries or in the Union as a whole. What references that could be found, usually came in the form of concern over rising rates of AMR. The European Center for Disease Prevention and Control released a policy briefing in 2016 stating that the consumption of last-line antibiotic, colistin, had doubled between 2010 and 2014 as a result of carbapenem resistance.[1001] Increased demand without adequate increase of supply leads is one of the key reasons shortages occur. The documentation regarding the rise of AMR refers consistently to a "shortage" or "lack" of "effective drugs" while drawing attention to how few antibiotics are presently in development to resolve this issue.[1002] The use of this terminology to indicate there is a "lack of effective drugs" ignores the existence of drugs that do exist but whose lack is not a matter of future scientific achievement or production, but a present matter of supply chain delivery and demand.

Conclusion

This chapter highlights the role of antibiotic shortages as a symptom of a crumbling antibiotic access infrastructure meant to support global health needs. It uses Fox's data in the United States to lay the groundwork as a comparator case study to a corpus of data collected and analyzed from the Web of Science to provide a global outlook on the historical evolution

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[1001] European CDC, "Last-Line Antibiotics Are Failing: Options to Address This Urgent Threat to Patients and Healthcare Systems," ECDC Policy Briefing. (Stockholm, Sweden: ECDC, 2016).

[1002] This is an observed trend following a review of the 102 innovation related articles found in web of science and other reviewed literature within this domain. Three examples of this verbiage can be found in: Marianne Frieri, Krishan Kumar, and Anthony Boutin, "Antibiotic Resistance," *Journal of Infection and Public Health* 10, no. 4 (July 2017): 369–78, https://doi.org/10.1016/j.jiph.2016.08.007 ;
Laura Freire-Moran, Bo Aronsson, Chris Manz, Inge C. Gyssens, Anthony D. So, Dominique L. Monnet, and Otto Cars, "Critical Shortage of New Antibiotics in Development against Multidrug-Resistant Bacteria—Time to React Is Now," *Drug Resistance Updates* 14, no. 2 (April 2011): 118–24, https://doi.org/10.1016/j.drup.2011.02.003.;
Suzanne Edwards, Chantal Morel, Reinhard Busse, and Stephan Harbarth, "Combatting Antibiotic Resistance Together: How Can We Enlist the Help of Industry?" *Antibiotics* 7, no. 4 (December 18, 2018): 111, https://doi.org/10.3390/antibiotics7040111.

of antibiotic shortages worldwide. As a result of limited data points from non-American countries, the invisibility of the infrastructure and the frailty of that invisibility is most prominently featured. Many shortages can be tracked to simultaneous experiences, where one nation reports individually on an event and another nation is experiencing the same thing – indicating the interrelations between these supply chains and the frailty a lack of diverse corporate options to choose from presents. However, the *whys* of these scenarios is not frequently a matter of discussion, rather only: how is it currently impacting communities in the moment themselves.

In order to successfully support an infrastructure where patients have access to antibiotics when they are in need, the physical production and dissemination of those antibiotics is essential. API manufacturers, thus, play an enormously important role in ensuring that antibiotics are in circulation. The infrastructure, as such, depends on them.

In 2013, Janet Woodcock and Marta Woskina wrote an article indicating that while "not every production disruption turns into a shortage…virtually all shortages are preceded by disruptions in production…Drug shortages are first and foremost driven by the inability of various firms to maintain production because of the failure of quality management in facilities that produce the finished dosage form of the drug."[1003] In asking why these corporations have poor quality management, and are shut down by regulators due to either glass shards in the products they create or to contamination concerns (birds flying inside sterile areas),[1004] we must also ask: with what revenue are these supply chains being supported by.

The key component of a generic drug is its low cost. It is essential to have a low cost so that hospitals, governments, individuals etc. can purchase them despite economic strains.

[1003] Janet Woodcock and Marta Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages," *Clinical Pharmacology & Therapeutics*, November 7, 2012, 170-171, https://doi.org/10.1038/clpt.2012.220.
[1004] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.

Race to the bottom tenders that offer the lowest of the low are fiscally satisfactory on their face, but they come with increased risk due to the *reasons* those companies can seemingly afford to produce products at such low levels. Chapter Two discussed the evolution of the Essential Medicines List and the ways in which the attention to antibiotics as essential medicines has fluctuated in the face of the rise in AMR. Key to this discussion, was the fact that these antibiotics were, and are, largely generic in form and formulation. The factories that developed these companies were often built long ago, with many originally developed in the 1960s. A government review of United States factories that manufacture sterile injectables (the most common antibiotic affected by drug shortages worldwide), discovered that these facilities have "undergone only limited upgrades…while running 24 hours a day, 7 days per week." [1005] Failing to undergo upgrades, or even stopping to clean a facility that is operating at capacity inevitably leads to problems. When purchasers increasingly only target the lowest price on a tender agreement, however, these budgets do not take into consideration any ability for the manufacturer to address quality and supply concerns. And, as has been historically evident through this research, once a company becomes confronted with a quality crisis: their absence from the market can create a global shortage scenario that has no quick fix.

Good manufacturing practices, and new legislation revolving environmental concerns, are not bad regulations. They ensure that the products that are developed in these factories can reach patients and treat them in a way that has been tested and proven to work, without creating potentially more devastating side effects down the road. However, as regulators increasingly investigate factories to ensure they are up to code, there is an understanding that if a factory needs to shut down: it will impact the supply chain.[1006]

[1005] Woodcock and Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages,"173.
[1006] Erin Fox, Interview by Erin L. Paterson, 31 March 2023.

The corpus of documents used within this dissertation indicate consistent antibiotic shortages that are increasing in frequency worldwide. Where initially, access challenges are those that are stereotypically applied to the experiences of low-middle-income countries, the increased frequency of reporting involving high-income countries reveals that there is a root systemic issue in the global antibiotic supply chain. If access equals availability and affordability: historically affordability was the most likely barrier to lack of access. However, availability is now clearly showing that it too is at risk.

Essential medicines, especially those that come in injectable formulations, are at particular risk due to the specialized needs of their production and the demands from seriously ill patients. Despite the essential nature of the antibiotics discussed within this chapter, and the actions taken by the WHO and others in efforts to improve access to these medications, shortages and lack of access has often been taken for granted as a low-middle income country problem.[1007] However these concerns can be viewed as pre-warnings for high income countries as well, due to the continual diminishing returns that generics manufacturers receive when producing antibiotics. Shortages that have often been seen in LMICs, are increasingly found in HICs as the supply infrastructure struggles with maintaining its global supply.

Multiple articles reviewed in this chapter have indicated that replacing one antibiotic for another during a time of shortage led to worsening patient outcomes or higher rates of antimicrobial resistance. Higher rates of AMR necessarily increase the pressure on companies to produce a new antibiotic that can address resistant strains of bacteria. But failing to address accessibility concerns, makes it unclear if that new product would ever reach the patients in need. Patients who, if they are waiting for a product they need due to a lack of access initially – may no longer be alive once the drug reaches the market.

[1007] See Chapters One, Two and Four

This corpus additionally shows a series of instances from across the economic spectrum, where a failure to diversify tenders and this reliance on race-to-the bottom purchasing agreements has created an ecosystem where the global antibiotic supply chain can no longer be relied upon to provide access to needed medications on a global scale regardless of a country's income status.

There are three key takeaways from this analysis. First: access challenges that have faced low-middle-income countries (LMICs) served as a kind of canary in the coal mine, an early alert that there was something unbalanced with the antibiotic supply chain that could speak to worsening health outcomes; second, lack of suitable antibiotic diversity in terms of distribution has led to a worsening of antimicrobial resistance globally as the most appropriate antibiotic was not always available during treatment; and finally, the failure to diversify tenders and a reliance on race-to-the bottom purchasing agreements has led to a frail supply chain that can no longer be relied upon to provide access to needed medications on a global scale regardless of a country's income status.

For AMR, what becomes apparent in this circumstance, is a phrase coined by Salla Sariola and her research associates: "a stacking of lacks."[1008] When health infrastructures are limited to the point where drugs are the only way to manage survival, drugs must be used.[1009] Lack of regulation ensuring that supply chains provide quality goods, ensures a lack of access.[1010] But lack of investment into these supply chains to ensure they have the time and capacity to upgrade to release quality materials is equally a factor. Lack of alternatives leads to the overuse of the drugs that are available. More expensive drugs are inaccessible, and so their existence is inconsequential. In so far as the infrastructure is concerned: this stacking of

[1008] Salla Sariola, Andrea Butcher, Jose A. Cañada, Mariette Aïkpé, and Adélaïde Compaore, "Closing the GAP in Antimicrobial Resistance Policy in Benin and Burkina Faso," Edited by Li Cui. *mSystems* 7, no. 4 (August 30, 2022): e00150-22, https://doi.org/10.1128/msystems.00150-22.
[1009] Sariola, et al., "Closing the GAP in Antimicrobial Resistance Policy in Benin and Burkina Faso," 6.
[1010] Sariola, et al., "Closing the GAP in Antimicrobial Resistance Policy in Benin and Burkina Faso," 3.

multifaceted lacks is reflective of multiple points of breakdown that have (over time) not received proper maintenance or care to ensure the system works effectively. And, because the supply chain has struggled, it has begun to cause additional strain on the innovation side. A need for new drugs is thus amplified at the same time as the delivery of old drugs has been increasingly ignored.

Kevin Outterson of CARB-X defines this circumstance as a three-legged stool comprised of antibiotic innovation, stewardship, and access.[1011] His designs with his PPP is to ensure and support these different components as they arise.[1012] His work, and the work of others involved in ensuring that access remains a key component of new drug innovation, is paramount, as the increasing stacking of lacks and failure of antibiotic access challenges continues to spread.

Antibiotics are an infrastructure investment to ensure the stability and sustainability of global production and productivity. But for them to be able to do that, the infrastructure that upholds antibiotics must be addressed. Access to those antibiotics must be established for them to be effective as a lack of antibiotics leads to high rates of morbidity and mortality. This chapter highlighted the key causes and concerns relating to access challenges in different income settings, and how, despite innovation and global rise of GDP, those concerns have only become more dire over the past forty years. The increased rate of antibiotic shortages in High-Income countries reveals that the systemic flaw of Just-In Time manufacturing, and an over reliance on APIs that are increasingly distanced from one another and operating on race-to-the-bottom tenures with relatively little safeguards in case of medical necessity or natural disaster, and how these "high level" flaws have naturally trickle down to LMICs who continue to experience the burden of supply chain mismanagement in addition to local financial, regulatory, and practical concerns.

[1011] Kevin Outterson, Interview with Erin L. Paterson, 12 April 2024.
[1012] See Chapter Four for more detail.

Finally, as this data and this analysis is particularly nascent in its form and formulation, this chapter serves as a way to help draw attention to the lack of currently available data in this space. This inquiry, using scant resources and linguistically limited, reveals the burgeoning of a trend regarding antibiotic shortages. It also problematizes the notion of antibiotic shortages as a part of a problem that is often left ignored. As a component of the antibiotic infrastructure in practice, the effectiveness of the supply chain is one that reveals whether the infrastructure is working appropriately or not. With increased failings, these breakdowns should be assessed in greater detail. And it is an area worth continued, more specific, study in the future.

Conclusion

"Either the countries are poor, or the patients are poor, or both are poor. That's why nobody is investing because you will never earn any money with that." – Peter Beyer.[1013]

"Attention to antibiotics as material infrastructure, and the inversion posed by AMR if these substances were to be removed, prompts further questioning of how materials are currently arranged and entangled with antibiotics. Bringing to the fore antibiotics as affective infrastructure allows for analyses of the ways in which these substances enable and define relations—between people, organisations, countries and so on." – Clare Chandler.[1014]

The original premise of this dissertation was developed by Christoph Gradmann, Jørgen Leisner, Claas Kirchhelle, Maria Jesús Santesmases, and Frédéric Vagneron. As it was originally conceived, my work was set to study:

> history of antibiotic regulation at the international level between circa 1980 and 2010…[With the] aim to understand how the narrative of a decline in innovation, research and development of new antibiotics, along with a growing concern about antimicrobial resistance, has arisen internationally…By regulation we mean—broadly speaking—the setting of international requirements for production, registration, quality control, etc., and the multiple international expert bodies working to facilitate the production, marketing and circulation of antibiotics on a global scale.[1015]

My dissertation has diverted from this original premise. It has looked at the infrastructure needed to support antibiotics as a key component of global health care. It does review international regulations and the external bodies that influence key areas, but it does so from a far more broad perspective. It argues that in order for antibiotics to be an effective part of global health care they must be accessible (i.e.: available and affordable), and if the drugs are neither available or affordable they are unable to meet that goal. I used the World Health Organization's Essential Medicines List, the antibiotic pipeline, and the antibiotic supply

[1013] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 39.
[1014] Clare I. R. Chandler, "Current Accounts of Antimicrobial Resistance: Stabilisation, Individualisation and Antibiotics as Infrastructure," *Palgrave Communications* 5, no. 1 (May 21, 2019): 9. https://doi.org/10.1057/s41599-019-0263-4.
[1015] Armacad, "Three-Year PhD Fellowship 2021 - The Dry Antibiotic Pipeline and the Global Policy Laboratory (1980-2010), France," Scholarships, Research and Study Opportunities Database, June 27, 2021, https://armacad.info/2021-06-27--three-year-phd-fellowship-2021-the-dry-antibiotic-pipeline-and-the-global-policy-laboratory-1980-2010-france.

chain as examples of this infrastructure, and through them highlighted how this infrastructure has evolved and struggled since 1977.

The core premise of this work was to look at the contemporary history of antibiotics and the ways in which this history has evolved from the known histories of antibiotic drug development that came before. To this extent, this dissertation has advanced the understanding of what the contemporary playing field is for antibiotics including their development pipeline (and how that metaphor has been utilized), as well as their accessibility. However, the drafting of this dissertation and the methodology used in the conceptualization of this work does ask additional questions beyond this narrow scope in how historians can respond to and develop histories of "big-c" Contemporary histories of medicine.[1016]

During my MA research, I familiarized myself with archival research, reviewing letters, transcriptions, practitioner notebooks, hospital records etc. in order to draft a cohesive narrative around the events at the focus of my studies. This tradition is a long-established part of historical research, and is a key component to providing understanding of historical subject matter. Primary sources, regardless of form and format, are the backbone of a historian's methodology. Without these sources, speculation and presumption take the place of analytical assessment. While secondary sources can inform readers as to a particular narrative, lack of evidence from the period in question that can speak for itself is problematic.

In attempting to write a dissertation devoted to Contemporary history, however, lack of primary sources was a non-starter. Corporate records prohibit the public sharing of data, government archives institute a privacy ban on anything up to a certain point, and as I moved from one archive to the next searching for a link or avenue to find appropriate material to

[1016] While contemporary history is often used to discuss histories post 1945, here the utilization of the capital highlights its existence as *the most* contemporary times under discussion. For the purposes of this discussion, and this dissertation, I would argue this would entail any histories that are written on time periods too recent for public dissemination of archival records…roughly 1980 to present day.

cite: I was faced with one (sometimes arbitrarily determined) time restriction after another. How, then, should I create a corpus of primary sources to facilitate an argument that could answer the questions I sought to address?

The answer I came to was not limited to form, but rather one that was dependent on variants. Wherever possible, I spoke directly to individuals that were involved in the histories I was investigating. I made liberal use of the internet crawler, Internet Archive, to review documents and websites that are no longer presently in existence – comparing data that was once reported to what is presently accessible. I was able to retrieve 'lost' PDFs this way, tracking down dead URLs from sites no longer hosted or maintained. I depended on open sourced publications of corporate records, and those that were filed publicly due to government requirements (such as with corporate returns). And I sought out opportunities to access private collections when possible, and to create corpora that I could divine impressions from disparate locations.

Oral testimony is its own form of primary source, and discussions on how oral testimony should and should not be used are common place within a historian's education. No primary source is ever perfect, but there is an additional degree of caution applied to oral testimony as so many extenuating circumstances impact the data collection process. Questions answered are dependent on questions asked. Perspective and personal interest vary depending on the transient emotional situation of both interviewer and interviewee. Technological problems (such as the internet failing during an interview) can interrupt the flow of thought and artificially highlight or subdue moments of importance. Furthermore, the status of the interviewee in relation to the topic being discussed can alter the ways in which responses are provided. Two of my interviewees declined to be publicly identified, several questioned the public nature of their comments and how those comments would be used. All interviewees needed to sign an agreement stating that I could use their comments for this

work, but I also provided them all with the opportunity to review the transcription and make edits should they feel their words did not appropriately convey their intentions or if they said something that they felt legally should not be shared due to confidentiality agreements signed with other parties.

For the witness seminar that I conducted with the help of Mirza Alas Portillo, Nadya Wells, Frédéric Vagneron, and Claas Kirchhelle, the oral testimonies collected were developed as a form of shared memory. Each participants' recollection of events fed into and supported the next statement to be made. This provides both validity to the statements as multiple individuals can testify to the events within the memory having happened, but it also provides a confirmation bias. If ten people in a room say something happened, and one person disagrees but chooses not to speak because they fear disagreeing with the majority: it hides the dissent and the alternative reflection. Although I followed up with several witness seminar participants after the fact and supplied citations throughout the seminar's transcript: it is impossible to determine with 100% accuracy that things happened *exactly* as it was said.

All primary sources contain these biases. But in a Contemporary history where there is a dearth of additional sources to support claims this becomes a trickier playing field to navigate. I used my additional methods to generate primary sources and perspectives as ways of specifically addressing these concerns, and melded these with secondary literature where I could to support both the historical tradition that surrounds this field as well as the narrative that I interpreting.

This kind of Contemporary history rests at a particular nexus point where the veil between it, sociology, and political science is increasingly thin. Journalism, too, lurks within these wings. Even as I was writing chapters for this dissertation, new events would be reported on in the media leaving me to question what was too recent to include and how to respond. But these events cannot wholly be ignored, as even while gathering my oral

testimonies did these events provide a retrospective analysis to the interviewees themselves. On several occasions, interviewees would mention a new publication that helped them contextualize their own thought processes, how then could I not include these mentions when discussing these histories?

In this increasingly digital age where the speed of events, and knowledge of those events, is manifesting at an alarming rate: pinning down a cohesive historical narrative is important. It provides perspective and assistance to those with decision making powers. It provides understanding to those simply curious about how things have come to be. It provides wholistic context where short and pithy newspaper articles may not be capable. The time frame of what should be included within a Contemporary history feels ever shorter, though, as the need for this information rises. My methodology, while incapable of addressing everything within this space, was dedicated to finding ways to ensure that those involved within this space could share their perspectives and their work outside of the traditional archives that are a historian's usual bread and butter.

I was not able to address all aspects of antibiotic infrastructure, development, or accessibility. Most glaring throughout this work is the lack of discussion regarding animal/agricultural uses of antibiotics. Though mentioned in passing, animal/agricultural use was not my intended focus. By choosing to highlight human health alone, I leave the door open for future work relating to agricultural access and accessibility, the concerns that increasing calls for antibiotic stewardship may have on farming industries, and how the pipeline of drug innovation for agricultural use may differ from that of human innovation. These domains, human vs animal, are very different, and to compound them both into this dissertation would have materially changed both the argument and the methodology I was depending on, especially in regards to the differences of use within HIC and LMICs. Although this work was deemed, early on, to be outside of the scope of what I would review,

it is an area that is ripe for further investigation. Claas Kirchhelle and Nicolas Fortané are two researchers, among many, who have published extensively on this topic, and discussions of a One Health approach to antibiotics would be a natural extension of this research moving forward.

Other points of consideration moving forward would be how the notion of an infrastructure and maintenance can be applied to other history of medicine narratives or drug trajectories. Questions that arise in this field could be on how do these histories differ? How have other drugs managed the intersection between drug development and accessibility? How has accessibility in HICs differed compared to LMICs? One pathway in particular that deserves greater attention is the history of chronic disease medication, long hailed as a profitable venture for pharmaceutical companies in HICs, but which is inaccessible for many LMICs to this day.[1017]

In my analysis regarding PPPs, the same historical review and analysis could be applied to other drug PPPs such as the Medicines for Malaria Venture (MMV) which predates many of the PPPs discussed here. The methodology I used to gather data would be easily transferrable to other PPP studies, and a comparison of how these drug developing PPPs operate and produce outputs would be of particular interest.

While classified as a Contemporary history, this work is solidly within the field of history of medicine and it combines and makes liberal use of philosophy of science and technology studies as well. The table below indicates how my three areas of exploration (the Essential Medicines List, the antibiotic pipeline, and the antibiotic supply chain) relate to Susan Leigh Star's nine components of infrastructure, as well as which chapter to turn to for more information on these components.

[1017] United Nations, "Lifestyle Diseases: Access to Chronic Disease Care in Low- and Middle-Income Countries," United Nations, https://www.un.org/en/chronicle/article/lifestyle-diseases-access-chronic-disease-care-low-and-middle-income-countries.

	WHO's EML (Antibacterial section)	Antibiotic Pipeline	Antibiotic Supply Chain
Embeddedness	Built upon WHO's existing infrastructure, and depends on the international communications and support networks of the WHO.	Built upon the standard pharmaceutical drug pipeline that has been in effect in all fields of medicine since the 20th century.	Built upon preexisting standards of shipping and control, as well as notions of manufacturer agreements and transportation.
Transparency	A simple task that is updated every two years and as such doesn't require much additional attention by the country using it.	Attention to the antibiotic pipeline only began after there was concern that new antibiotics were not emerging from it, and that AMR could not be successfully countered.	The manufacturing and shipment of a product is often discounted as long as the product successfully reaches its end destination.
Reach or scope	Has a global reach, though it does recommend (and has led to) the creation of national essential medicines lists that can be managed on the individual country level, however its recommendations and its work as far as encouraging broader access to antibiotics remains a global initiative regardless.	All companies producing antibiotics are adding to the access infrastructure by providing new products for consumption.	A global supply chain that ensures products reach those at need regardless of income level or location, however – challenged by this scope at the same time as different countries and income levels have different abilities to procure and support the supply chain effectively.
Learned as a part of membership	It is taken for granted as a component of the WHO's support for countries, and it equally is taken for granted as something that is efficacious	All companies that are in the field of antibiotic development, are aware of the steps that it takes to bring a drug through the antibiotic pipeline.	Those that are involved in procurement, are actively aware of the supply chain needs and requirements, but those outside of this group may not be aware or understand its complexities.
Links with conventions of practice	Its recommendations and follow through are strongly associated with WHO guidelines and rules. As well as contemporary thoughts and beliefs as conventions change over time.	All companies that are developing antibiotics are using the antibiotic pipeline in the same way as each other, following the same steps and conventions of practice as their peers.	The supply chain is supported by similar supply chains and industry standards across a vast spectrum, not solely dedicated to antibiotics and not unique in its functioning as a result.
Embodiment of standards	Standardized based on previous WHO settings and requirements, and updates to follow new standards as they arise.	Good Manufacturing Practices (GMP) and regulatory standards are applied to all companies producing antibiotics that hope to successfully bring their drug to market.	The supply chain must follow standards of conditions to ensure that the product reaches its end destination in optimal condition.
Built on an installed base	Originated out of other departments of the WHO and its recommendations are followed as a result of the work that came before.	The antibiotic pipeline follows the same steps as other drug development pipelines, and when additional components (such as the development of PPPs are introduced: these models are similarly shared among the other companies engaging in this work).	The supply chain operates using the same base as other supply chains, using similar shipping routes, and manufacturing installations in similar formats to ensure successful operations.
Becomes visible upon breakdown	Attention is focused on it once it becomes clear that the drugs on the list are not capable of addressing problems they are meant to address (example: rise of AMR) See Chapter Two	Lack of effective antibiotics has drawn specific attention to the "Dry Antibiotic Pipeline" and as such, it has become visible. See Chapter Three and Four	When products fail to reach patients in time, attention is focused now on the supply chain, and its breakdowns in both manufacturing and transportation. See Chapter Five.
Is fixed in modular increments	List updates every two years regardless, but when major adjustments are required it takes time to fix, and the schedule may change as a result.	Fixing the pipeline has received a large amount of attention, particularly in where funding needs to be applied, where incentives need to be implemented, and how to best address the most evident concerns. These are all modular and incremental fixes.	Fixing the supply chain, because of its global impact and effort, must be done incrementally. Individual plants or individual areas of occupation, travel routes, etc., are adjusted first rather that top down broad-spectrum changes.

Table 9 Comparing Susan Leigh Star's understanding of infrastructure to three components of antibiotic infrastructure

Each chapter of this dissertation has shown how this infrastructure works, can be conceived, and can be put into practice. The Essential Medicines List, pipeline, and supply chain are all

working in service of increasing access to antibiotics which ensures that antibiotics themselves can help uphold global health care. While those directly involved in the pipeline from a pharmaceutical manufacturing perspective may not be keen on considering accessibility as a part of their pipeline: by creating a new drug they are providing a product that they want to be purchase. Making it available to purchasing audiences, and ensuring the price point is one in which that product *can be bought* all tie into the notion of what accessibility is. The developers of the drug may not call it "access," but this facilitation is a part of the access narrative and as such: a part of the antibiotic infrastructure as a whole.

Prior to this work, there has been no cohesive history of the infrastructure of antibiotics, nor how antibiotics became *an* infrastructure in the way that Clare Chandler describes in her 2019 article.[1018] This dissertation therefore offers an opportunity to see how antibiotics are able to become that indispensable part of the global health care ecosystem, and what – beyond the antibiotic pipeline – may be imperiling them on this world stage.

While this dissertation only focused on three components of the antibiotic infrastructure, the methodology I used can easily be applied to other components to help strengthen an overall understanding of what contributes to antibiotic success. Embeddedness, and the way multiple infrastructures intersect and are entangled with one another, is key here, and there have been several examples throughout this work of where additional study could be applied. While this dissertation analyzes the EML, the antibiotic pipeline, and antibiotic supply chain specifically as what hold up antibiotics at this time: it is wholly cognizant of the fact that influences from exterior infrastructures play a role.

While originally this work was meant to be dedicated wholly to the antibiotic pipeline, the pipeline is only one component of this larger infrastructure, and detailing the

[1018] Clare I. R. Chandler, "Current Accounts of Antimicrobial Resistance: Stabilisation, Individualisation and Antibiotics as Infrastructure," *Palgrave Communications* 5, no. 1 (May 21, 2019): 2, 6-7, 9. https://doi.org/10.1057/s41599-019-0263-4.

various branches that needed support, and understanding the ways in which this infrastructure was used in practice was essential.

A great deal of attention of course, though, has been laid at the feet of the antibiotic pipeline. The dry antibiotic pipeline narrative is often used to indicate that there are few, if any, new antibiotics in the process of being developed. As a metaphor that is used in order to develop products specifically to address AMR, in its traditional form: it fails to do. The traditional pipeline is not interested in disease management. However, the actors that have shown increasing concern about the pipeline, including the WHO, ReAct, MSF, several Public-Private Partnerships, and government entities, utilize the pipeline in order to help generate financial resources to motivate innovation for this goal. The presumption is once the product is created it will be available for use against AMR, but the current antibiotic infrastructure does not offer a smooth pathway for this goal to take place.

Public investment in this space is important, but the consolidation of API manufacturers due to a race to the bottom in tender agreements, as well as the abandonment of antibiotic production from larger and more stabilized pharmaceutical companies, has led to a circumstance where the products themselves are simply unavailable in the quantities needed to meet global supply demands.[1019] Continually, regulatory complications make it so that even if a drug is approved in one country – that does not guarantee it will be able to be sold and made accessible in another. Wait times and inconsistent oversight or requirements delays appropriate care.

If the pipeline is framed solely as a development issue, it does not take into account the post-market situation of antibiotics, nor does it address the access concerns that a new antibiotic would face once it is ready for sale. Failure to apply preventative or corrective

[1019] Kim Pauwels, Steven Simoens, Minne Casteels, and Isabelle Huys, "Insights into European Drug Shortages: A Survey of Hospital Pharmacists," Edited by John Conly, *PLOS ONE* 10, no. 3 (March 16, 2015): e0119322. https://doi.org/10.1371/journal.pone.0119322.

maintenance to these access concerns ensure that even if a new drug is produced, for patients in need of appropriate medications the infrastructure meant to facilitate that access is not sufficient.

To this end, I suggest an additional structure to the one-track linear pipeline described in both the Introduction and Chapter One of this dissertation. Rather than conceive of the antibiotic pipeline as a mechanism from innovation to marketing approval, the pipeline (and its success) can be more accurately measured if accessibility is taken into account from the start. The pipeline metaphor on its own is a convenient and understandable image that is easy to recall. Doctoring this image slightly, adding emphasis in different areas, helps to keep the metaphor relatable while expanding new knowledge. New antibiotics, once they are developed, must be able to find their way to a patient in order for that pipeline (and the antibiotic infrastructure that it's a part of) to be effective. Therefore, by including accessibility from the start, programs designed to address "Dry Pipeline" concerns can more accurately assess the feasibility of their projects. The diagram below highlights how this two "pipe" approach would work, but also where this dissertation has shown that infrastructure is struggling.

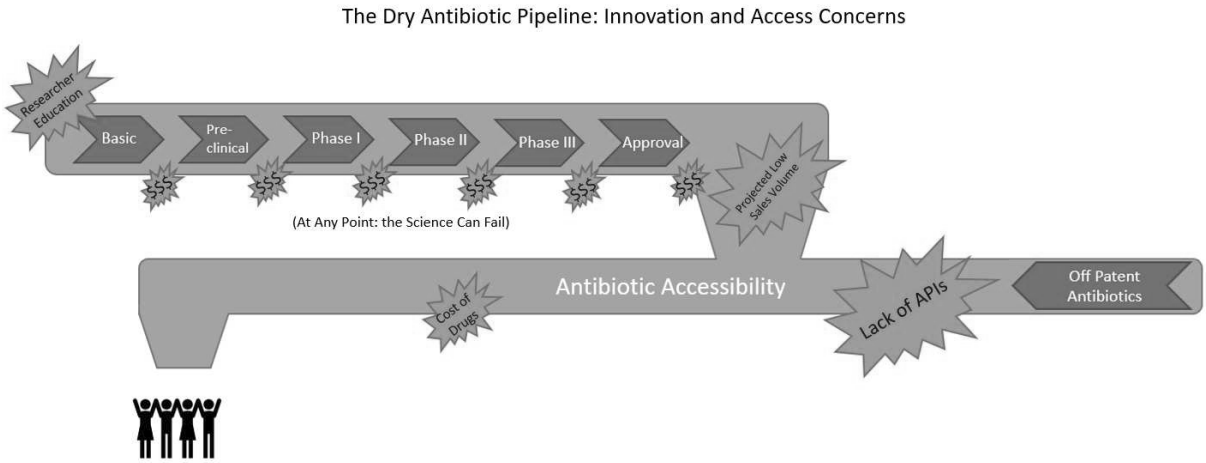

Figure 7 Reconceived Dry Antibiotic Pipeline addressing access needs

A lack of education, unstable (or uncertain) funding apparatuses that eventually may be at odds with the expected returns on investment, lack of API manufacturers or regulations to ensure API supply chain stability, and the cost of drugs are all components of this particular infrastructure issue. Access to old antibiotics, and new antibiotics, are both affected by these areas of concern, and thus these "blast points" indicate locations where potential maintenance specific to addressing those issues could be applied. This maintenance could take the form of new innovation, such as new methods of addressing the lack of APIs (unique rotating tender deals, or additional payment incentives that ensure little to no downtime for factory support - ensuring consistent supply rather than sudden closures due to unexpected breakdowns or failure to meet good manufacturing practice standards) for instance.

This dissertation has shown how access to antibiotics has long been seen as a low to middle-income country dilemma. These countries inability to afford medications led to their inaccessibility of those medications. However, this dilemma is one that is increasingly becoming a problem for high income countries where money is not the issue: but actual production and delivery of efficacious antibiotics. Unfortunately, understanding the depth of this supply chain frailty is incredibly complicated. The only country in the world that publicly discloses each step of their drug supply chain is New Zealand.[1020] Beyond this one nation's borders, the decision to withhold information for a proper fragility analysis is one made under the auspices of proprietary information. Agreements with pharmaceutical companies at the government level, ensure that information is made secret. Worse, there are no global monitoring or tracking system regarding antibiotic shortages so that short supply, delays, or total stock outs can be forecast, mitigated, or circumvented efficiently and effectively.[1021]

For high-income countries, alternative medications are often available to avoid major health disasters. However, even in these countries: allergies, co-infections, and other health

[1020] Martijn Van Gerven, Interview with Erin L. Paterson, 23 August 2023.
[1021] United States Congress, *Drug Shortage Health and National Security Risks*.

concerns can mean worsening health outcomes when those alternative medications are used. For low to middle-income countries, there may be no alternative medications at all. Financial matters mean that a smaller dispensary is made available to prospective patients.

If the infrastructure, which may not have been perfectly put in place to begin with, is to succeed: these would be the areas that need to be updated or "maintained." Knowledge pathways and increased communication, and the dissemination of data between one party to another (for instance, to improve clarity on which APIs are doing business where, how their goods are transported, and along which shipping streams at which price points), are key.

In 1977 the WHO created the first iteration of the Essential Medicines List with the hope of narrowing a large field of drugs that had a wide and expansive array of iterations and formulations to the strict necessities that any hospital or formulary would need to treat the medical needs of the world. National lists, which modified the EML in the attempt to strictly focus and target on the individual health needs of a particular nation, extended this concept from the WHO so as to create a lowest bar of commitment.[1022] These lists were very important, as they ensured that all the necessary medications were included, but excluded those that targeted diseases, disorders, or other ailments that were not prevalent within a national context. This reduced the overall expenditure on unneeded drugs, and enhanced the power of the formulary. Antibiotics, whether on the WHO's EML or on the national EMLs evolved on these lists from drugs that needed to be narrowed down to avoid over purchasing, to drugs that needed to be tracked and monitored for AMR purposes. These lists highlighted the growing fear and tension of a lack of new antibiotics, and calls for action were made for new antibiotics to be developed to fill in gaps that were being made in treatment pathways.

The early 2000s showed the evolution of the WHO's position regarding essential medicines to allow for drugs that were still on patent to join the EML. Their argumentation

[1022] Hans Hogerzeil, Interview with Erin L. Paterson, 2 February 2023.

was that it was for individual countries to decide and determine their disease burdens and decide the quantity of the drugs they needed to treat their patients – even if the drugs they needed came at a higher cost. [1023] Despite newer antibiotics being added to the list, the concern over how much of that antibiotic to purchase in lieu of the cheaper medications that could generally still treat non-resistant strains, proliferated. In the case of bedaquiline, it is far easier to treat non-resistant tuberculosis than MDR or XDR TB. [1024] Even with bedaquiline added to the Essential Medicines List, access to this needed medication has stayed low as the price has been too high to justify its purchase in the quantities needed, particularly in LMICs such as India.[1025]

The high cost of drugs limits the purchasing of those drugs from the majority of the world's population. This drug price is primarily influenced by the pricing escalator that has been built into the pharmaceutical company's dogma since the 1980s.[1026] In order to continue to grow their shareholder value and to ensure that the company displays ever greater returns, rather than corporate stability and surety, the price of all drugs developed is artificially inflated to provide the greatest return on investment. These actions have had a detrimental effect on LMICs who are continually priced out of medications, and it is increasingly having a detrimental effect on HICs (particularly the United States where there are no set price caps on medications) who are also faced with ever increasing price tags in order to access needed medication.

The death toll of antimicrobial resistance has not yet reached a critical mass where pharmaceutical companies are pressured into developing an effective antibiotic at the same

[1023] Jonathan Quick, Interview by Erin L. Paterson, 11 November 2022.
[1024] Jamie Rudman, Yaw Adusi Poku, Saleema Razvi, Brad Wong, and Rein Houben. "Preliminary Findings: Cost Benefit Analysis of Interventions to Reduce Tuberculosis Burden in Ghana," In Ghana Priorities: Tuberculosis. Accra, 2020. https://copenhagenconsensus.com/publication/ghana-priorities-tuberculosis.
[1025] Médecins Sans Frontières, "Lifesaving TB Medicines Still out of Reach for Children in High-Burden Countries | MSF," Press Release, September 3, 2021, https://www.msf.org/lifesaving-tb-medicines-still-out-reach-children-high-burden-countries.
[1026] Victor Roy, Capitalizing a Cure: How Finance Controls the Price and Value of Medicines, Oakland: University of California Press, 2023, 46-47.

break neck speed as they did with Covid-19 vaccines. Currently, for most individuals, there are sufficient antibiotics that will treat patient illnesses. If and when a new antibiotic does enter the market, due to the expected high price of its sale: prescribers will likely still recommend a cheap and off patent drug. Stewardship guidelines that reserve certain antibiotics in order to ensure low resistance rates, would also require that the new antibiotic only be used in the most at-need cases. Between the high sales price, and stewardship restrictions: the needed antibiotic will not be able to sell well. The current expected return on investment for any new drug developed is between $1-2 billion.[1027] This will not happen under the current market system, and it serves as a key reason many pharmaceutical companies have abandoned the notion of developing a new antibiotic in the first place. Should the death toll rise, and should flexibility around purchasing and the *need* for a new drug that can specifically target an AMR strain be called for: production will almost certainly increase. But to what end? And what would be the sustainable outcome of such a thing?

Antibiotic access has been historically side-lined in the discussions of antibiotic development, because it was never seen as a financially lucrative problem to address. High income countries rarely have discussions regarding access since access is largely seen as a LMIC issue. If a product is made and someone in a HIC can pay for it- access is not an industry concern. Availability, perhaps to some industry professionals, may be a concern. Keeping the supply chain active or ensuring that their products reach the population who is largely responsible for purchasing them, certainly. But *access* as a whole is often a neglected topic.

But even when it comes to addressing *availability* doing so is not easily managed within the current framework of the market system. Pharmaceutical companies are largely not in control of the active pharmaceutical ingredient manufacturers that produce drugs directly.

[1027] Mike Dunne, Interview with Erin L. Paterson, 2 February 2024.

Purchasers (government or otherwise) place tenders under the presumption that the manufacturers that offer their proposals will honor those proposals. Therefore, blame cannot be wholly placed on these purchasers. API manufacturers are, however, under no obligation to continue making a specific drug if it is no longer in their financial business interests. And so, if an API chooses to cease development for any reason: then it is not their responsibility to maintain a supply chain even if their loss could impact global availability.

Affordability, added on to this complicated framework, only adds increasing burdens to low to middle income countries which are already struggling to pay for high cost drugs.

This evaluation of the history and trajectory of the antibiotic infrastructure and how it works in practice, reveals that it is not simple matter of adding money into the pipeline to develop a new drug in order to solve AMR or access to efficacious antibiotics. Searching for one solution to this problem is idealistic and simplistic of the overall crisis as a whole. The infrastructure which allows for the spread of antibiotics has become too limited over the past forty years, and thus, it needs maintenance.

The works by Mark Thomas Young, Mark Coeckelbergh, Jérôme Denis, and David Pontille all discuss how maintenance as a philosophy can be applied. Infrastructures do break down, and they do have issues that need correcting. Preventative maintenance seeks to address these concerns before they become actual problems, and corrective maintenance is applied after the fact.[1028] Continual, and ongoing maintenance though – is a requirement to keep any infrastructure or investment ongoing.[1029] For this antibiotic infrastructure, that maintenance takes many forms. The EML's continual updates ensure that attention is diverted towards the most efficacious medications, and access to those medications is encouraged. The pipeline's financial concerns have been offset by the maintenance effets of new PPP/PDP strategies working to improve business interest in the field. For the supply

[1028] Young and Coeckelbergh, *Maintenance and Philosophy of Technology*, 19-20.
[1029] Denis and Pontille, *Le Soin de Choses,* 56.

chain, opening up the Latourian black box of how drugs move from place to place, adjusting just-in-time manufacturing, rotating tenders, and improving the diversity of manufacturers and how they're paid may increase supply chain reliability in the first place. These efforts are acts of both continued maintenance and acts of corrective maintenance to issues that have continued to manifest over time. And the need for this maintenance is only increasing.

As Clare Chandler made clear when she first discussed the notion of antibiotics as an infrastructure: these drugs are ones in which the modern-day age cannot live without.[1030] Every surgery, every cancer treatment, every risky intervention is done so with the understanding that antibiotics are on hand. Global access to antibiotics are, as the United States have put it: a security threat. [1031] Not just to the United States, but to every country in the world. But it is one, as many low to middle income countries can attest: a fate that millions of those in need of care are currently living through today.

As this dissertation comes to a close, though, it is cognizant that the history that has been discussed is one that is still very much unfolding. While the PPPs/PDPs analyzed in this dissertation are still working on developing new antibiotics for their pipeline – what happens after they make it through that pipeline is still uncertain. CARB-X's model may be one pathway forward that manages to marry both development and deliverability together, as it does include a requirement to ensure all partners have a plan regarding accessibility.[1032] Time will tell if that will be successful.

Furthermore, GARDP's interest in access, and its inspiration through MSF's moral values is something that should also be watched and monitored over the coming years. However, in a deep blow to MSF and all its business partners, the dissolution of the MSF

[1030] Chandler, "Current Accounts of Antimicrobial Resistance," 9.
[1031] United States Congress, Senate, Committee on Homeland Security and Governmental Affairs, *Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms*, 118th Cong., 2023.
[1032] Kevin Outterson, Interview with Erin L. Paterson, 12 April 2024.

Access Campaign was announced on 20 June 2024.[1033] Although there has been global outcry about this decision, it closed its doors on 31 December 2024. Theoretically, there will be some kind of combination where the Access Campaign members will find new roles and positions in MSF and continue their work of attempting to expand access to medications around the world. Groups such as GARDP who are only tangentially related to MSF at this point in time, are on the surface unaffected. However, this shift in policy, and this dissolution of access works could indicate differing priorities that GARDP may need to address moving forwards. This announcement, as recent as it is, and its impact cannot be analyzed or assessed within this dissertation, but the actions of MSF towards its Access Campaign cannot be idly ignored. While MSF, in response to public outcry, has stated it will continue access work in a new form: what that form is, is still uncertain.[1034] And their choices here, including all the impacts that it may have, shows a distinct lack of prioritizing access concerns continue to be on the rise.

There are other alternatives that can assist in managing an AMR threat and support the antibiotic infrastructure by reducing strain on the *need* for antibiotics. A thorough discussion of these alternatives is beyond the scope of this dissertation, but they should not be neglected entirely. Diagnostic innovation, which would help physicians understand precisely which medication to apply to which disease and improve the efficacy of treatment outcomes, is a severely lacking field.[1035] Increased efforts into infection prevention and control such as in improved water, sanitation, and hygiene (WASH) methods, improved primary health care structures that can address illnesses prior to the point of needing antibiotic intervention,

[1033] Medicines Law and Policy, "MSF's Access Campaign Is an Invaluable Actor in Global Health; Shutting It down Is Short-Sighted," *Medicines Law & Policy*, June 25, 2024, https://medicineslawandpolicy.org/2024/06/msfs-access-campaign-is-an-invaluable-actor-in-global-health-shutting-it-down-is-short-sighted/.
[1034] Médecins Sans Frontières, "MSF Strengthening Commitment to Access to Products for Healthcare," MSF Press Release, Accessed August 2, 2024, https://www.msf.org/msf-strengthening-commitment-access-products-healthcare.
[1035] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 70, 92.

improved diagnostics that can more accurately determine which bacteria is causing infection so future prescriptions are done more accurately and with less waste or risk of resistance, improved nutrition and food security which in turn bolsters a body's natural ability to combat mild infections without the need for drugs, and of course: vaccine development that would enable someone to become wholly protected from infection rather than reliant on a treatment after the fact.

But infection prevention and control, like addressing access to medicines, is not a linear pathway. Last year, an issue of Frontiers of Sanitation, Innovations & Insights dedicated an entire issue to Learning From and Preventing Failure in WASH. This research group underwent a comprehensive review of interventions that have been implemented, and analyzed for where and how things went wrong. Their research found: lack of holistic approaches, inadequate community engagement, unrealistic funder expectations, idealistic planning, poor coordination & communication, politics & bureaucracy, insufficient capacity, and project mentality to be the main causes for these failures. [1036] And, they highlighted this quote from an NGO working in Zimbabwe: "I tell people nothing works first time. Do not expect anything to work first time. So, you've got to experiment. You've got to try. You've got to go back. You've got to research and yeah, learn from experience."[1037] This thought process, this understanding of a rate of attrition when it comes to not only the development of drugs, but also in the implementation of interventions such as infection prevention and control must also be applied to notions of access to medicines. Each of the scenarios mentioned as factors influencing the poor implementation of WASH methods, could be applied to the errors that have plagued the access to medicines conversation. And each highlights a need for a holistic approach to mitigating future work in these fields.

[1036] Rebecca C. Sindall, Dani J. Barrington, and Esther Shaylor, "Learning From and Preventing Failure in WASH," *Institute of Development Studies*, February 2, 2023, 8-9, https://doi.org/10.19088/SLH.2022.025.
[1037] Sindall, et al., "Learning From and Preventing Failure in WASH," 8-9.

A rate of attrition must be accepted. Actions taken to address access to antibiotics must be considered in full. And perhaps most importantly: they must be implemented with continuous long-term management and planning in mind. There is already an infrastructure that supports these methods, but it too must be analyzed, assessed, and maintained to ensure that it is working the way it was intended – and can continue to provide its support for years to come.

In December 2023, the WHO released a report stating that in the past year "1.05 million deaths were associated with AMR, and 250,000 deaths were attributable to AMR," with a quarter of that figure taking place in Africa alone, and 7% of all deaths related to tuberculosis alone.[1038] But at various points during the witness seminar that I helped manage in January 2024, it was brought up that it was the wrong people dying, and that only if "enough" people began to die would it make a difference.

Peter Beyer:	When Germany had the G7 presidency starting in 2015, and also 2014, I went to the chancellery for WHO to see the German Sherpa [personal representative of a head of state who prepares an international summit], and we pitched the idea of doing a global R&D fund for antibiotic research. And it was funny because we gave this data, so many people are dying, and then the reaction was: 'we just had the climate-change guys, and they said more people would even die. And then there's the ocean-protection people, they also told us we could all die by I don't know when.' So, they were absolutely not impressed by how many people would die, because everybody is actually saying that everybody…
Marie-Paule Kieny:	We will all die.
Peter Beyer:	We all die…in the end the people die in Africa and not in high-income areas, and when it comes to money, there is none.[1039]

The perception that it will take the deaths of people living in high income country to draw increased attention, funding, and response, was near universal among the experts that I spoke with during this work. And while there is some middling attention and concern for the rise of

[1038]Benn Sartorius, et al., "The Burden of Bacterial Antimicrobial Resistance in the WHO African Region in 2019: A Cross-Country Systematic Analysis," *The Lancet Global Health* 12, no. 2 (February 2024): e201.
[1039]Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 53.

superbugs and the need for general response, we have not yet reached a point where the governments with the greatest influence can agree there is a big enough problem to be addressed. [1040] Nor, are economists entirely convinced that the market cannot be used to solve the problem. [1041] Once enough people start dying who can *pay* for new treatment, then the market will develop a product. Until then, for those involved in this field: finding financial solutions that address the development of new drugs and their accessibility to those in need has been an uphill challenge.

During that same witness seminar, the mere suggestion of an alternative pathway was equally seen as a dangerous thing. While some nations jockey for the chance to put their name on major publications, such as with the case of the O'Neill report, others are concerned about the potential fallout of investing in areas that may not yield the greatest level of success (a metric that is intangible and therefore difficult to define from one country to the next.) Marie-Paule Kieny, a French virologist and chair DNDi described the situation almost as a game of uncertainty: "Many of those who are the funders want to be seen as driving it, but at the same time they don't want to be alone, because if you are alone it means that maybe it is an error. So, they want to have others joining in, and co-fund." [1042] It turns into a matter of convincing enough people, simultaneously, of moving forward. But doing so, as I have shown throughout this work: is not an easy task.

It is a task that is growing harder, too, as the leaders in this field are slowly reaching the age of retirement or are transitioning into other fields altogether. In the final moments of our Witness Seminar, the collected participants: from industry, public private partnerships, academia, and NGOs, mused on who would come next.[1043] Who would carry the torch of this work through the next generations, and what would that future look like from there? The lack

[1040] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 87.
[1041] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 74.
[1042] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 53.
[1043] Alas Portillo, et al., "Emerging Financial Models for Antibiotic Development (2000-2016)," 91-104.

of a certain answer left a final, stinging, silence, as the participants closed down their work stations and left at the end of a long and intensive day of contemplation.

Access to antibiotics, just as with infection prevention and control methods, is an infrastructure problem. Its interventions are often without profit or fiscal reward, and the impact of each intervention can be difficult to assess in the short term. Infrastructure would need to be developed and maintained here too, because in both access to medicines and infection prevention and control: there is no end date. The point in both interventions is sustainable and continuous impact. Access to medicines now, and in the future. Infection prevention and control for diseases now, and those that will come in the future. Product development can be a piece of that infrastructure framework. But it needs to be modified in a way that makes that infrastructure less opaque. There has to be a plan for continued and sustained development, which includes an understanding that the financial return on investment will not be a pricing escalator: but rather a long-lasting sure bet of sustained income.

The infrastructure that existed prior to the 1980s does not exist any longer. The pharmaceutical companies creating one new antibiotic after another is gone. The finances that made the work of these scientists and corporate magnates possible, has been reallocated to other ventures. The supply chains are at risk. Essential Medicines Lists are facing more strain to be filled. Throughout the work that I have done on the history of access to medicines through the lens of the dry antibiotic pipeline, that infrastructure has only become more imperiled. And, as Johnson & Johnson's departure from the antibiotic development space in 2023, and MSF Access Campaign's dissolution in 2024 has shown: it is crumbling infrastructure that must be fixed.

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Due to the very modern nature of many of the sources used in this dissertation, there is some intermingling of documentation as to whether it qualifies as a primary or secondary source. Although it is standard to delineate between such source usage in the bibliography, I have chosen not to do this due to the nebulous nature of the sources I use. At any given moment, a source could very easily transform from a document to be analyzed as a statement in the time period it had been published, to analyzed as a reflection on matters after the fact thus serving both roles as primary and secondary source in one. To avoid confusion, and to provide ease and clarity to those reviewing the bibliography for sources used, I have chosen to compile all sources in alphabetical order and without any further specification.

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Appendix 1: The antibiotics section of the collected 1977-2023 World Health Organization Essential Medicines List (EML), set side by side for easy visual comparison and reflection.

1977-1990

L.1 1977	L.2 1979	L.3 1983	L.4 1985	L.5 1988	L.6 1990
Antibacterial Drugs	**Antibacterial Drugs**	**[No Category name]**	**Penicillins**	**Penicillins**	**Penicillins**
ampicillin	ampicillin	ampicillin []	ampicillin []	ampicillin []	Amoxicillin []
benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	ampicillin
benzylpenicillin	benzylpenicillin	benzylpenicillin	benzylpenicillin	benzylpenicillin	benzathine benzylpenicillin
chloramphenicol	chloramphenicol	phenoxymethylpenicillin	cloxacillin []	cloxacillin []	benzylpenicillin
cloxacillin (penicillinase-resistant)	cloxacillin	procaine benzylpenicillin	phenoxymethylpenicillin	phenoxymethylpenicillin	cloxacillin []
erythromycin	erythromycin	**Other Antibacterials**	procaine benzylpenicillin	piperacillin []	phenoxymethylpenicillin
gentamicin	gentamicin	chloramphenicol []	**Other Antibacterials**	procaine benzylpenicillin	piperacillin []
phenoxymethylpenicillin	metronidazole	cloxacillin []	chloramphenicol []	**Other Antibacterials**	procaine benzylpenicillin
salazosulfapyridine	phenoxymethylpenicillin	erythromycin	erythromycin	chloramphenicol []	**Other Antibacterials**
sulfadimidine	salazosulfapyridine	gentamicin []	gentamicin []	erythromycin []	chloramphenicol []
sulfamethoxazole +trimethorprim	sulfadimidine	metronidazole []	metronidazole []	gentamicin []	erythromycin []

tetracycline	sulfamethoxazole +trimethorprim	salazosulfapyridine	salazosulfapyridine	metronidazole []	gentamicin []
Complementary List	tetracycline	spectinomycin	spectinomycin	spectinomycin	metronidazole []
amikacin	**Complementary List**	sulfadimine []	sulfadimine []	sulfadimine []	spectinomycin
doxycycline	amikacin	sulfamethoxazole + trimethorprim []	sulfamethoxazole + trimethorprim []	sulfamethoxazole + trimethorprim []	sulfadiazine []
procaine benzylpenicillin	doxycycline	tetracycline []	tetracycline []	tetracycline []	sulfamethoxazole + trimethorprim []
sulfadiazine	nitrofurantoin	**Complementary List**	**Complementary List**	**Complementary List**	tetracycline []
	procaine benzylpenicillin	amikacin []	doxycycline	doxycycline	**Complementary List**
		doxycycline	nitrofurantoin	nitrofurantoin	doxycycline
		nitrofurantoin		trimethoprim	nitrofurantoin
					trimethoprim

1992-2002

L.7 1992	L.8 1995	L.9 1997	L.10 1998	L.11 2000	L.12 2002
Penicillins	**Penicillins**	**Penicillins**	**B-Lactam drugs**	**B-Lactam drugs**	**Beta Lactam medicines**
Amoxicillin []	Amoxicillin []	Amoxicillin []	Amoxicillin []	Amoxicillin []	Amoxicillin
ampicillin	ampicillin	ampicillin	ampicillin	ampicillin	Ampicillin
benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin
benzylpenicillin	benzylpenicillin	benzylpenicillin	benzylpenicillin	benzylpenicillin	benzylpenicillin
cloxacillin []	cloxacillin []	cloxacillin []	cloxacillin []	cloxacillin []	cloxacillin []
phenoxymethylpenicillin	phenoxymethylpenicillin	phenoxymethylpenicillin	phenoxymethylpenicillin	phenoxymethylpenicillin	phenoxymethylpenicillin
piperacillin []	piperacillin []	procaine benzylpenicillin	procaine benzylpenicillin	procaine benzylpenicillin	procaine benzylpenicillin
procaine benzylpenicillin	procaine benzylpenicillin	**Other Antibacterials**	**Restricted indications**	**Restricted indications**	**Other Antibacterials**
Other Antibacterials	**Other Antibacterials**	chloramphenicol []	amoxicillin + clavulanic acid []	amoxicillin + clavulanic acid []	chloramphenicol []
chloramphenicol []	chloramphenicol []	ciprofloxacin []	ceftazidime	ceftazidime	ciprofloxacin []
erythromycin []	doxycycline []	doxycycline []	ceftriaxone []	ceftriaxone []	doxycycline []
gentamicin []	erythromycin []	erythromycin []	imipenem + cilastatin	imipenem + cilastatin	erythromycin []
metronidazole []	gentamicin []	gentamicin []	**Other Antibacterials**	**Other Antibacterials**	gentamicin []
spectinomycin	metronidazole []	metronidazole []	chloramphenicol []	chloramphenicol []	metronidazole
sulfadiazine []	spectinomycin	nalidixic acid	ciprofloxacin []	ciprofloxacin []	nalidixic acid
sulfamethoxazole + trimethorprim []	sulfadimidine	nitrofurantoin	doxycycline []	doxycycline []	Nitrofurantoin
tetracycline []	sulfamethoxazole + trimethorprim []	spectinomycin	erythromycin []	erythromycin []	spectinomycin

Complementary List	trimethoprim	sulfadiazine []	gentamicin []	gentamicin []	sulfadiazine []
ciprofloxacin	**Complementary List**	sulfamethoxazole + trimethorprim []	metronidazole []	metronidazole []	sulfamethoxazole + trimethoprim []
clindamycin	chloramphenicol	trimethoprim	nalidixic acid	nalidixic acid	Trimethoprim
doxycycline	clindamycin	**Complementary List**	nitrofurantoin	nitrofurantoin	
nitrofurantoin	nalidixic acid	chloramphenicol	spectinomycin	spectinomycin	
trimethoprim	nitrofurantoin	clindamycin	sulfadiazine []	sulfadiazine []	
	trimethoprim	**Restricted indications**	sulfamethoxazole + trimethorprim []	sulfamethoxazole + trimethorprim []	
		ceftazidime	trimethoprim	trimethoprim	
		ceftriaxone	**Complementary List**	**Complementary List**	
		vancomycin	chloramphenicol	chloramphenicol	
			clindamycin	clindamycin	
			Restricted indications	**Restricted indications**	
			vancomycin	vancomycin	

2003-2013

L.13 2003	L.14 2005	L.15 2007	L.16 2009	L.17 2011	L.18 2013
Beta Lactam medicines	**Beta Lactam medicines**	**Beta Lactam medicines**	**Beta Lactam medicines**	**Beta Lactam medicines**	**Beta Lactam medicines**
amoxicillin	amoxicillin	amoxicillin	amoxicillin	amoxicillin	amoxicillin
amoxicillin + clavulanic acid	amoxicillin + clavulanic acid	amoxicillin + clavulanic acid	amoxicillin + clavulanic acid	amoxicillin + clavulanic acid	amoxicillin + clavulanic acid
ampicillin	ampicillin	ampicillin	ampicillin	ampicillin	ampicillin
benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin
benzylpenicillin	benzylpenicillin	benzylpenicillin	benzylpenicillin	cefalexin {c}	cefalexin {c}
dicloxacillin []	procaine benzylpenicillin	cefazolin	cefalexin {c}	cefazolin [] {a}	cefazolin [] {a}
phenoxymethylpenicillin	cefixime	cefixime	cefazolin [] {a}	cefixime	cefixime
procaine benzylpenicillin	cloxacillin []	cloxacillin []	cefixime	ceftriaxone {a}	ceftriaxone {a}
Complementary List	phenoxymethylpenicillin	phenoxymethylpenicillin	ceftriaxone {a}	cloxacillin []	cloxacillin []
ceftazidime	**Complementary List**	procaine benzylpenicillin	cloxacillin []	phenoxymethylpenicillin	phenoxymethylpenicillin
ceftriaxone []	ceftazidime	**Complementary List**	phenoxymethylpenicillin	procaine benzylpenicillin	procaine benzylpenicillin
imipenem [] + cilastatin []	ceftriaxone []	ceftazidime	procaine benzylpenicillin	**Complementary List**	**Complementary List**
Other Antibacterials	imipenem [] + cilastatin []	ceftriaxone []	**Complementary List**	cefotaxime {c}	cefotaxime {c}
azithromycin []	**Other Antibacterials**	imipenem [] + cilastatin []	cefotaxime {c}	ceftazidime	ceftazidime

chloramphenicol	azithromycin []	**Other Antibacterials**	ceftazidime	imipenem [] + cilastatin []	imipenem [] + cilastatin []
ciprofloxacin []	chloramphenicol	azithromycin []	imipenem [] + cilastatin []	**Other Antibacterials**	**Other Antibacterials**
doxycycline []	ciprofloxacin []	chloramphenicol	**Other Antibacterials**	azithromycin	azithromycin
erythromycin []	doxycycline []	ciprofloxacin []	azithromycin []	chloramphenicol	chloramphenicol
gentamicin []	erythromycin []	doxycycline []	chloramphenicol	ciprofloxacin []	ciprofloxacin []
metronidazole []	gentamicin []	erythromycin []	ciprofloxacin []	clarithromycin	clarithromycin
nalidixic acid []	metronidazole []	gentamicin []	doxycycline {a}	doxycycline {a}	doxycycline {a}
nitrofurantoin	nitrofurantoin	metronidazole []	erythromycin []	erythromycin []	erythromycin []
spectinomycin []	spectinomycin	nitrofurantoin	gentamicin []	gentamicin []	gentamicin []
sulfamethoxazole + trimethoprim	sulfamethoxazole + trimethoprim	spectinomycin	metronidazole []	metronidazole []	metronidazole []
trimethoprim	trimethoprim	sulfamethoxazole + trimethoprim	nitrofurantoin	nitrofurantoin	nitrofurantoin
Complementary List	**Complementary List**	trimethoprim	spectinomycin	spectinomycin	spectinomycin
clindamycin	clindamycin	**Complementary List**	sulfamethoxazole + trimethoprim	sulfamethoxazole + trimethoprim	sulfamethoxazole + trimethoprim
sulfadiazine	sulfadiazine	clindamycin	trimethoprim {a}	trimethoprim {a}	trimethoprim {a}
vancomycin	vancomycin	sulfadiazine	**Complementary List**	**Complementary List**	**Complementary List**
		vancomycin	clindamycin	clindamycin	clindamycin
			vancomycin	vancomycin	vancomycin

2015-2023

L.19 2015	L.20 2017	L.21 2019	L.22 2021	L.23 2023
Beta Lactam medicines	**Beta Lactam medicines**	**Access Group Antibiotics**	**Access Group Antibiotics**	**Access Group Antibiotics**
amoxicillin	amoxicillin	amikacin	amikacin	amikacin
amoxicillin + clavulanic acid	amoxicillin + clavulanic acid	amoxicillin	amoxicillin	amoxicillin
ampicillin	ampicillin	amoxicillin + clavulanic acid	amoxicillin + clavulanic acid	amoxicillin + clavulanic acid
benzathine benzylpenicillin	benzathine benzylpenicillin	ampicillin	ampicillin	ampicillin
benzylpenicillin	benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin	benzathine benzylpenicillin
cefalexin {c}	cefalexin	benzylpenicillin	benzylpenicillin	benzylpenicillin
cefazolin [] {a}	cefazolin [] {a}	cefalexin	cefalexin	cefalexin
cefixime	cefixime WATCH GROUP	cefazolin{a}	cefazolin{a}	cefazolin{a}
ceftriaxone {a}	cefotaxime WATCH GROUP	chloramphenicol	chloramphenicol	chloramphenicol
cloxacillin []	ceftriaxone {a} WATCH GROUP	clindamycin	clindamycin	clindamycin
phenoxymethylpenicillin	cloxacillin []	cloxacillin []	cloxacillin []	cloxacillin []
procaine benzylpenicillin	phenoxymethylpenicillin	doxycycline {a}	doxycycline {a}	doxycycline {a}
Complementary List	piperacillin + tazobactam WATCH GROUP	gentamicin	gentamicin	gentamicin
cefotaxime {c}	procaine benzylpenicillin	metronidazole	metronidazole	metronidazole
ceftazidime	**Complementary List**	nitrofurantoin	nitrofurantoin	nitrofurantoin

imipenem [] + cilastatin []	ceftazidime WATCH GROUP	phenomethylpenicillin	phenomethylpenicillin	phenomethylpenicillin
Other Antibacterials	meropenem {a} WATCH GROUP	procaine benzylpenicillin	procaine benzylpenicillin	procaine benzylpenicillin
azithromycin	**Complementary List - Reserve Group**	spectinomycin	spectinomycin	spectinomycin
chloramphenicol	aztreonam	sulfamethoxazole + trimethoprim	sulfamethoxazole + trimethoprim	sulfamethoxazole + trimethoprim
ciprofloxacin []	fifth generation cephalosporins (w/ or w/o beta-lactamase inhibitor) e.g., ceftaroline	**Watch Group Antibiotics**	trimethoprim	trimethoprim
clarithromycin	fourth generation cephalosporins (w/ or w/o beta-lactamase inhibitor) e.g., cefepime	azithromycin	**Watch Group Antibiotics**	
doxycycline {a}	**Other Antibacterials**	cefixime	azithromycin	azithromycin
erythromycin []	amikacin	cefotaxime	cefixime	cefixime
gentamicin []	azithromycin WATCH GROUP	ceftriaxone {a}	cefotaxime	cefotaxime
metronidazole []	chloramphenicol	cefuroxime	ceftriaxone {a}	ceftriaxone {a}
nitrofurantoin	ciprofloxacin [] WATCH GROUP	ciprofloxacin	cefuroxime	cefuroxime
spectinomycin	clarithromycin [+] WATCH GROUP	clarithromycin [+]	ciprofloxacin	ciprofloxacin
sulfamethoxazole + trimethoprim	Clindamycin	piperacillin + tazobactam	clarithromycin [+]	clarithromycin [+]

trimethoprim {a}	doxycycline {a}	vancomycin	piperacillin + tazobactam	piperacillin + tazobactam
Complementary List	gentamicin	**Complementary List**	vancomycin	vancomycin
clindamycin	metronidazole	ceftazidime	**Complementary List**	**Complementary List**
vancomycin	nitrofurantoin	meropenem {a}	ceftazidime	ceftazidime
	spectinomycin	vancomycin	meropenem {a} []	meropenem {a} []
	sulfamethoxazole + trimethoprim	**Reserve Group Antibiotics**	vancomycin	vancomycin
	vancomycin WATCH GROUP	**Complementary List**	**Reserve Group Antibiotics**	**Reserve Group Antibiotics**
	Complementary List	ceftazidime + avibactam	**Complementary List**	**Complementary List**
	vancomycin WATCH GROUP	colistin	cefiderocol	cefiderocol
	Complementary List - Reserve Group	fosfomycin	ceftazidime + avibactam	ceftazidime + avibactam
	daptomycin	linezolid	colistin	ceftolozane + tazobactam
	fosfomycin	meropenem + vaborbactam	fosfomycin	colistin
	oxazolidinones (e.g.: linezolid)	plazomicin	linezolid	fosfomycin
	polymyxins (e.g.: colistin)	polymyxin B	meropenem + vaborbactam	linezolid
	tigecycline		plazomicin	meropenem + vaborbactam
			polymyxin B	plazomicin
				polymyxin B

Appendix 2: Compilation of data from the United States Food and Drug Association database indicating which pharmaceutical companies received regulatory approval for antibiotics and which companies are no longer actively doing business at time of data collection.

Generic name	Class	First Year of FDA Approval	CURRENTLY Marketed in ANY form by	Discontinued Marketing of ANY Form of Product by	First Marketed by
Gentamicin	Aminoglycosides	1966	Akorn (1995), Sandoz (1980), Padagis US (1981), Fera Pharms (2004), Teligent (2018), Baxter Hlthcare (1982), Hospira (1983), Allergan (1988),	King Pharms, Bristol, Schering(>2001), Allergan (>2004), Novartis (>2001), Pharmafair, Intl Medication, Hikma (>1980), Wyeth Ayerst, Watson Labs(>1999) Pharm Spec (>1983), Kalapharm (1982), Fresenius Kabi (>2014) Abbot (1993), Hospira (>2004), Taro (>1996), Alpharma US Pharms, Solopak, Alcon Pharms (>1999), Pharmaderm, Fougera (>2004), Paco, Teva Parenteral (>1993), Bauch and Lomb (>2001), Cosette (>1994), B Braun (>2010), Pharmacia and UpJohn (>1980)	Schering

Amikacin	Aminoglycosides	1981	Sagent Pharmaceuticals (2016), Hikma (1994), Teva Pharmaceuticals (1993), Emcure (2013), Fresenius (2015), Insmed (2018)	Igi Labs, Hospira (>2004), Abbott (>1994), Apothecon (>2001),	Apothecon
Kanamycin	Aminoglycosides	1973	**DISCONTINUED BY ALL**	Hikma (>1981), Intl Medication, Abraxis Pharm, Watson Lab (>1985), Solopak, Quad Pharms, Pharmafair, Loch (>1992), Warner Chilcott, Fresenius Kabi (>2015), Apothecon (>2001), King Pharms	Apothecon
Neomycin	Aminoglycosides	1954	Padagis Us (1981), Endopharms (1962), Bausch and Lomb (1994) Casper Pharma (1971), Novartis (1963), Sandoz (1984), Watson Labs (1986), X Gen Pharms (2006), Akorn (2004), Amring (2005), Sandoz Inc (1983), Teva	Pharmafair, Naska, Pharmaderm, Altana, Parke Davis, Akorn (>1968), Lilly, Casper Farms (>2004), Comb, Pharmacia and UpJohn (>2009), Savage Labs, Bayer Labs (>1985), Merck (>1998), Dow Pharm (>1954), Medimetriks (>2015), Pfizer, Alcon Pharms (>1999), Ipharm, Bristol Myers Squibb, Lilly, Lannett (>2016),	Monarch Pharms

			(1964), Monarch Pharms (1966)	Roxane, Nostrum Labs (>2014), Fougera, GlaxoSmithKline, Schering, Actavis Labs, Allergan (>2003),	
Netilmicin	Aminoglycosides	1983	**DISCONTINUED BY ALL**	Schering (>1998)	Schering
Plazomicin	Aminoglycosides	2018	Cipla USA (2018)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Cipla USA
Tobramycin	Aminoglycosides	1975	Akron (1996), Chiesi (2012), Pulmoflow (2014), Mylan Speciality (1997), Novartis (1980), Eyevance (2009), Bauche and Lomb (1993), Fera Pharms (2001), Teva (1992), Amneal (2015), Dr Reddys Labs (2018), Sun Pharms (2019), Somerset (2017), Lupin (2017), Alembic (2019), Gland Pharms (2021), Alkem Labs (2021),	Lilly (>2007), Alcon Pharms (>1999), Apote< (>2002), Luoxin Aurovitas (>2021), Watson Labs (>2004), Igi Labs (>1994), Apothecon (2002), Eyevance (>2002),	Lilly

			Fresenius Kabi (2002), Hospira (1990), Hikma (1991), XGen Pharma (2001), Akorn (2014), Xelia (2014), Baxter Health Corp (2016), Gland Pharma (2021), Sandoz (1984),		
Paromomycin	Aminoglycosides	1969	Sun Pharm (1997), Heritage Pharms (2007)	Parkdale (>1969), Parke Davis, King Pfizer (>2002)	Parkdale
Streptomycin	Aminoglycosides	1946	Xgen Pharms (1998)	Pfizer (>1995), Lilly, Copanos,	Pfizer
Spectinomycin (Bs)	Aminoglycosides	1971	**DISCONTINUED BY ALL**	Pfizer (>2012)	Pfizer
Geldanamycin	Ansamycins	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NONE**
Herbimycin	Ansamycins	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NONE**
Rifaximin	Ansamycins	2004	Salix Pharms (2004)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Salix Pharms

Loracarbef	Carbacephem	1991	**DISCONTINUED BY ALL**	King Pharms (>2001),	King Pharms
Ertapenem	Carbapenems	2001	Savior Life Tech Corp (2019), ACS Dobfar SPA (2018), Eugia Pharma (2018), Gland Pharma (2021), Merck Sharp Dohme (2001)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Merck Sharp Dohme
Doripenem	Carbapenems	2007	**DISCONTINUED BY ALL**	Shionogi Inc (>2007)	Shionogi Inc
Imipenem/Cilastatin	Carbapenems	1985	ACS Dobfar (2011), HQ SPCLT Pharma (2019), Merck (1985)	Hospira (>2019)	Merck
Meropenem	Carbapenems	1996	Rempex (20017), Daewoong Pharm (2015), Eugia Pharma (2017), Amneal (2016), Savior Lifetech (2016), Gland (2016), HQ SPCLT Pharma (2019), B Braun Medical (2015), Pfizer (1996), ACS Dobfar (2011),	Hospira Inc (>2015), Sandoz (>2016),	Pfizer

Cefadroxil	Cephalosporins (First generation)	1978	Hikma (2006), Teva Pharms (>2006), Orchid Healthcare (2006), Aurobindo (2013), Aurobindo Pharma (2007), Lupin (2007),	Sandoz (>2009), Apothecon, Teva (>2014), Ani Pharms (>2014), Ivax Sub Teva Pharms (>1999), Purepac Pharms (1992), Ranbaxy Labs (>2002), Ranbaxy (2000), Sun Pharms (>2003), CSPC OUYI (>2017), Warner Chilcott (>2007), Bristol	Warner Chilcott
Cefazolin	Cephalosporins (First generation)	1973	Baxter Healthcare (1991), B Braun (2000), Sandoz (1988), Hikma Farmaceutica (2001), Samson Medicl (2006), ACS Dobfar (2008), Sandoz (2007), Qilu (2015)	GlaxoSmithKline (>2005), Abraxis Pharm, Hikma (>1991), Bedford, Dr Reddys (>2000), Teva Pharms (>1994), Facta Farma (>2016), Steri Pharma (2012), Fresenius Kabi (2009), Hospira (>2016), Cepha<one Pharma (>2009), Aurobindo (>2008), Lilly (2002)	GlaxoSmithKline

Cephradine	Cephalosporins (First generation)	1974	**DISCONTINUED BY ALL**	GlaxoSmithKline (>1974), Teva (>2000), Ivax Sub Teva Pharms, Vitarine, Barr (1998), Birstol Myers Squibb, Apothecon (>1993), Ersana,	GlaxoSmithKline
Cephapirin	Cephalosporins (First generation)	1974	**DISCONTINUED BY ALL**	Apothecon (>1993), Hilma (>1987), Abraxis Pharms	Apothecon
Cephalothin	Cephalosporins (First generation)	1974	**DISCONTINUED BY ALL**	Intl Medication, Bristol, Abbott, Abraxis Pharm, Baxter Healthcare (>1992), Lilly (>1993), GlaxoSmithKline	Lilly
Cefalexin/Cephalexin	Cephalosporins (First generation)	1971	Teva (1987), Belcher Pharms (1988), Chartwell RX (2005), Hikma (2006), Lupin (2005), Orchid Healthcare (2005), Aurobindo (2005), Yung Shin Pharm (2007), Alkem Labs (2010),	Ivax Sub Teva Pharms (>2006), Facta Farma (>2002), Barr (>1999), Vitarine (>1989), Sub Pharms Inds (>2011), Purepac Pharm, Stephens J (>1989), Yoshitomi (>1992), Apothecon (>1998), Lilly (>1992), Pragma (>2018), Ranbaxy Labs (>2003)	Pragma

Cefaclor	Cephalosporins (Second generation)	1979	Teva (2002), Yung Shin Pharm (2004), Hikma (2007),	Lilly (>2004), Ceph Intl (>2000), Facta Farma (2000), Ivax Sub Teva Pharms (>1999), Dava Pharms (>1996), Heritage Pharma (>2021), Ranbaxy (>2003), Watson Labs (2000), World Gen (>2002),	Lilly
Cefoxitin	Cephalosporins (Second generation)	1978	Hikma (2000), Hikma Farmaceutica (2010), ACS Dobfar (2009), Samson Medical (2015),	Fresenius Kabi (>2007), Hospira (>2014), ACS Dobfar SPA (>2016), Mylan Institutional (>2017), Merck (>1997),	Mylan Institutional
Cefotetan	Cephalosporins (Second generation)	1985	Teligent (1985), Fresenius Kabi (2007), B Braun (2007)	West Ward Pharm Corp (>2011), Hikma (>2011),	Teligent
Cefamandole	Cephalosporins (Second generation)	1978	**DISCONTINUED BY ALL**	Lilly (>2009)	Lilly
Cefmetazole	Cephalosporins (Second generation)	1989	**DISCONTINUED BY ALL**	Pharmacia and UpJohn (>2001)	Pharmacia and UpJohn
Cefonicid	Cephalosporins (Second generation)	1993	**DISCONTINUED BY ALL**	GlaxoSmithKline (>1993)	GlaxoSmithKline

Loracarbef	Cephalosporins (Second generation)	1991	**DISCONTINUED BY ALL**	King Pharms (>2001)	King Pharms
Cefprozil	Cephalosporins (Second generation)	1991	Teva (2005), Chartwell RX (2005), Sandoz (2005), Lupin (2005), Orchid Healthcare (2005), Apotex (2008), Aurobindo Pharma (2007), Apotex (2012),	Ranbaxy Labs (>2006), Teva Pharms (2009), Wockhardt (>2017), Corden Pharma (>2016),	Corden Pharma
Cefuroxime	Cephalosporins (Second generation)	1983	Hikma Farmaceutica (2004), B Braun (2001), Apotex (2002), Lupin (2003), Wockhardt (2005), Aurobindo Pharma (2006), Orchid Healthcare (2008), Alkem Labs (2010), ACS Dobfar SPA (1997), Teligent (1983),	GlaxoSmithKline (>2021), Ranbaxy Labs (>2002), Sun Pharm (>2008), Fosun Pharma (>2017), Ani Pharms (>2020), Watson Labs (>2000), Teva Pharms (>2002), Fresenius Kabi (<2011), Hospira (>2016), Samson Medical (>2009), Lilly (>2002),	Teligent

Cefixime	Cephalosporins (Third generation)	1989	Aurobindo Pharma (2015), Belcher (2017), Alkem Labs (2018), Lupin Ltd (2010),	Sandoz (>2017), Lederle (>2009), Lupin Pharms (>2018),	Lederle
Cefdinir	Cephalosporins (Third generation)	1997	Lupin (2006), Sandoz (2007), Teva Pharms (2007), Teva Pharms (2007), Orchid Healthcare (2007), Aurobindo Pharma (2007), Alkem Labs (2021),	AbbVie (>2015),	AbbVie
Cefditoren	Cephalosporins (Third generation)	2001	**DISCONTINUED BY ALL**	Vansen Pharma (>2012)	Vansen Pharma
Cefoperazone	Cephalosporins (Third generation)	1982	**DISCONTINUED BY ALL**	Pfizer (>2020)	Pfizer

Cefotaxime	Cephalosporins (Third generation)	1981	Hikma (2002),	Fresenius Kabi (>2008), Wockhardt (>2020), B Braun (>2007), Lupin (>2013), Hospira (>2012), Cephazone Pharma (2010), Aurobindo Pharma (>2009), Hospira Inc (>2016), Vladus Pharms (>2015) Sanofi Aventis US (>2015),	Vladus Pharms
Cefpodoxime	Cephalosporins (Third generation)	1992	Aurobindo Pharma (2007), Orchid Healthcare (2007), Sandoz (2008),	Sankyo (>2000), Sun Pharm Inds (>2008), Pharmacia and Upjohn (>2013),	Pharmacia and UpJohn
Ceftazidime	Cephalosporins (Third generation)	1985	Allergan (2015), ACS Dobfar (1985), B Braun (2011), Teligent (1985), Hospira (1986),	Wockhardt (>2008), Aurobindo Pharma (>2010), Baxter Healthcare (>1995), GlaxoSmithKline (>2002), Lilly (>2007),	Teligent
Ceftazidime + Avibactam	Cephalosporins (Third generation)	2015	Allergan (2015)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Allergan

Ceftibuten	Cephalosporins (Third generation)	1995	**DISCONTINUED BY ALL**	Si Pharms (>2011)	Si Pharms
Ceftizoxime	Cephalosporins (Third generation)	1983	**DISCONTINUED BY ALL**	Astellas (>2009)	Astellas
Moxalactam	Cephalosporins (Third generation)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	Lilly
Ceftriaxone	Cephalosporins (Third generation)	1984	Lupin (2003), Sandoz (2005), Wockhardt (2006), Akorn (2008), ACS Dobfar (2008), Hikma Farmacuetica (2008), Wockhardt (2007), Samson Medical (2014), Astral (2018), Qilu (2016), B Braun (2005), Baxter Healthcare (2005), Hikma (2015), Astral (2017),	Teva Pharms USA (>2007), Hospira Inc (>2012), Fresenius Kabi USA (>2011), Teva (>2006), Facta Farma (>2011), Cephazone Pharma (>2012), Bedford (>2014), Aurobindo Pharma (>2008), Agila Specits (>2014), Hoffmann La Roche (>2018), Roche,	Hoffmann La Roche

Cefepime	Cephalosporins (Fourth generation)	1996	B Braun (2010), ACS Dobfar (2008), Sagent Pharms Inc. (2017), Qilu (2016), Astral (2020), Samson Medical (2018), Baxter Healthcare (2008), Hospira Inc (1996)	Fosun Pharma (>2017),	Hospira Inc
Ceftaroline fosamil	Cephalosporins (Fourth generation)	2010	Apotex (2021), Allergan (2010)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Allergan
Cefiderocol	Cephalosporins (Fourth generation)	2019	Shionogi Inc (2019	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Shionogi
Ceftobiprole	Cephalosporins (Fifth generation)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	Basilea Pharmaceutica
Teicoplanin	Glycopeptides	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	Sanofi-Aventis

Vancomycin	Glycopeptides	Unclear: Suggested Ani Pharms, but in the US it seems like it should have been Baxter in 1958. Need to confirm	Azurity (2018), Ani Pharms (1964), Baxter Healthcare (1993), Xellia Pharms APS (2015), Fresenius Kabi (1987), Hospira (1988), Mylan Labs Ltd (2008), Pharm Assoc (2008), Hospira Inc (2009), Akorn (2012), Strides Pharma (2012), Watson Labs (2012), Sandoz (2010), Lupin ltd (2015) Sagent Pharms (2012), Hikma (>2018), Gland Pharma (2016), Eugia Pharma (2016), Hikma Pharms (2018), Orient Pharma co ltd (2019), Hainan Poly Pharm (2019), Hainan Poly (2021),	Pharmacia and Upjohn, Lederele (>1999), Quad Pharms, Teva Pharms USA (>2015), Emcure Pharms (>2021)	Unclear: Suggested Ani Pharms, but in the US it seems like it should have been Baxter in 1958. Need to confirm

			Samson Medical (2016),		
Telavancin	Glycopeptides	2009	Cumberland Pharms (2009), Theravance (2013)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Cumberland Pharms
Dalbavancin	Glycopeptides	2014	Allergan (2014)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Allergan

Oritavancin	Glycopeptides	2014	Melinta Therap (2014)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Melinta Therap
Clindamycin	Lincosamides (Bs)	1970	Bausch (2000), Actavis Labs UT Inc (2021TA), Pfizer (1970), Padagis US (1992), Cosette (1989), Watson Labs (1991), Sun Pharms Inds Ltd (2005), Epic Pharma LLC (2004), Zydus Pharms USA (2005), Lannett (2005), Lannett Co Inc (2005), Aurobindo Pharma (2009), Micro Labs (2018), Lyne (2012), Amneal (2014), Alembic Labs (2017),Heritage Pharms (2018), Almaject (1987), Hikma (1988), Fougera Pharms (1997), Taro Pharms INDS	Pharmacia and Upjohn (>1995), Teva (>2001), Abraxis Pharm, Quad Pharms, G and W labs (>2016), Solopak, Loch (>1993), Bristol Myers Squibb, Marsam Pharms (>1994), Igi Labs, Vantage Pharms (>2020), Boco Pharma (>1999), Teva Parenteral (>2002), Bedford, Wockhardt Bio AG (>2001), Novast Labs (>1996), Rising (>2017), Tolmar (>2016), Anda Repository (>2019), Abbott Labs (2001),	Pfizer

			(2004) Fresenius Kabi USA (2007), Akorn (2010), Sagent Pharms (2011), Padagis Israel (2010), Teligent (2016), Cadila (2018), Glasshouse Pharms (2018), Encube Ethicals (2019), Glenmark Pharms (2019), Solaris Pharma Corp (2020), Encube (2017), Taro Pharms (>2017), Mylan Pharms (>2009), Actavis Labs UT (2015), Taro (2019), Zydus Pharms (2018), Actavis Mid Atlantic (2015), Baxter Healthcare Corp (2017), Sandoz (2012), Akorn (2013), Abraxis Pharm (1989), Stiefel (2002), Mylan (>2004),		

			Almirall (2010), DARE (2021),		
Lincomycin	Lincosamides (Bs)	1964	XGen Pharms (2015), Microlabs (2021),	Pharmacia and Upjohn (>2018), Quad Pharms, Watson Labs (>1999), Praxgen (>2021)	Pharmacia and UpJohn

Daptomycin	Lipopeptide	2003	Cubist Pharms (2003), Teva Pharms USA (2016), Hospira Inc (2013), Mylan Labs (2018), Xellia Pharms (2016), Fresenius Kabi USA (2018), Sagent Pharms (2017), Dr Reddys (2019), Accord Healthcare (2019), Jiangsu Pharms (2019), Hisun Pharm Hangzhou (2021), Be Pharms (2019), Eugia Pharms (2021), Meitheam (2021), Hangzhou Zhongmei (2021), Qilu Pharm Hainan (2021), Baxter Healthcare (2022)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Cubist Pharms

Azithromycin	Macrolides (Bs)	1991	Akorn (2007), Fresenius Kabi (2005), Sandoz (2005), Pliva (2005), Wockhardt (2008), Lupin Ltd (2015), Hospira (2009), Gland Pharma (2009), Sun Pharms Inds (2013), Novel Labs (2016TA), Eugia Pharma (2015), Hainan Poly Pharm (2018), Amneal (2018), Aurobindo Pharma (2018), Epic Pharma (2018), CSPC OUYI (2018), Sunshine (2018), Bionpharma Inc (2018), Yung Shin Pharm (2020), Zydus (2018), Taro (2019), Alembic Pharms (2020), Pfizer (1991)	Teva Parenteral (>2006), Teva (>2021), Hikma (>2016), Mylan (>2021), Mylan ASI (2020), Apotex Corp (2015), Rising (>2017), PF Prism CV (>2005),	Pfizer

Clarithromycin	Macrolides (Bs)	1991	AbbVie Inc (1993), Sandoz (2005), Actavis Labs (2004), Mayne Pharma (2005), Teva (2005), Chartwell (2007), Aurobindo (2012), Strides Pharma (2013), Hec Pharm (2015), Sunshine (2018), Rising (2016),	AbbVie (>2019), Ivaz Sub Teva Pharms (>2014), Sun Pharms Inds (>2013), Hikma (>2019), Mylan (>2015), Ranbaxy (>2005), Ani Pharms (>2015), Wockhardt (>2014), Lupin Ltd (>2015), Nostrum Labs (>2016), Ajanta Pharma (>2019), Cumberland Pharms (>2020), Takeda Pharms USA (>2018)	AbbVie
Erythromycin	Macrolides (Bs)	1953	Valeant Intl (1984), Arbor Pharms (1964), Mayne Pharma (1981), Mylan (>1987), Saptalis (1988), Hospira (1964), Padagis US (1983), Wockhardt Bio AG (1987), Akorn (1996), Bausch and Lomb (>1994), Fougera Pharls (1997), Teligent (2017),	Taro (>1999), Bausch (>2001), Biofontera (>2016), Bristol (>1974), Fougera Pharms (>2000), Ivax Sub Teva Pharms (>2001), Barr (>2015), , Pharmacia and UpJohn, Syoset (>1999), Altana (>1994), Warner Chilcott (>2000), Parke Davis (>1977), Hospira (>1985), Johnson and Johnson (>1998), Merz Pharms (>1998), Akorn (>1996), Abbott (1988),	Lilly

			Amneal (2018), Torrent (2020), Calida Pharms (2021), Teva Pharms USA (2021), Lyne (2015), Ani Pharms (1978), Excela Pharma (2020),	Lilly (>1990), Paddock LLC, Alpharma US Pharms (>2002), Pharmaderm, Pharmafair (>1985), Elkins Sinn (>1996), Renaissance Pharma (>1997), Tolmar (>2004), Watson Labs (1993), Cosette (>2000), Life Labs (>1982), Dista (>1993), Naska, Par Pharm (2019), Abraxis Pharm, Quad Pharms, Baxter Healthcare (>1996), Teva Parenteral (>1996), Purepac Pharm, Lederele, Alra (>1996), Bristol Myers Squibb, Lilly (>1998) Ross Labs (>2004), Pfizer, Solvay, Robins AH, Westwood Squibb (>2002), Dow Pharm (>1992), Wyeth Ayerst,	
Roxithromycin	Macrolides (Bs)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Telithromycin	Macrolides (Bs)	2004	Sanofi Aventis US (2004)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Sanofi Aventis US

Spiramycin	Macrolides (Bs)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Fidaxomicin	Macrolides (Bs)	2011	Cubist Pharms (2011)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Cubist Pharms
Aztreonam	Monobactams	1986	Bristol Myers Squibb (1986), Fresenius Kabi USA (2010), Hospira Inc (2021), Gilead (2010)	Hikma (>2011)	Bristol Myers Squibb
Furazolidone	Nitrofurans	1958	**DISCONTINUED BY ALL**	Shire (>1999)	Shire
Nitrofurantoin (Bs)	Nitrofurans	1953	Casper Pharma LLC (1953), Almatica (1970), Impax Labs Inc (1993), Actavis Labs FL (2015), Nostrum Labs (2013), Amneal Pharms (2011), Novel Labs (2014), Sun Pharms Industries (2016), Zydus Pharms (2017), Actavis Mid Atlantic (2016), Alembic	Proctor and Gamble (>1998), Lannett (>2014), Pharmgen (1995), Aurobindo Pharma (>2015), Mylan (>2015), Elkins Sinn, Sandoz (>1970), Ivax Sub Teva Pharms, Whiteworth Town Plsn, Aurobindo Pharma (>2016), Ranbaxy Labs,	Proctor and Gamble

			Pharms (2021), Sandoz (2005), Watson Labs (1978), Amneal Pharms (2017), Sunny (2018),		

Linezolid	Oxazolidinones (Bs)	2000	Glenmark Pharms (2015), Hikma (2015), Teva Pharms (2012), Sandoz Inc (2015), Hetero Labs Ltd (2015), Amneal Pharms (2015), Sagent Pharms (2017), Fresenius Kabi USA (2016), Mylan Labs Ltd (2017), Alembic Pharms ltd (2015) Hospira (2015), Alkem Labs Ltd (2015), Zydus Pharms (2017), Eugia Pharma (2016), HQ SPCLT Pharma (2017), Nang Kuang Pharm Co (2016), Novel Labs Inc (2016), Celltrion (2019), Hospira Inc (2015), Pfizer (2000)	Teva Pharms USA (>2015), Rising (>2019), Gate Pharms (>2016),	Pfizer
Posizolid	Oxazolidinones (Bs)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	

Radezolid	Oxazolidinones (Bs)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Torezolid	Oxazolidinones (Bs)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Amoxicillin	Penicillins	1974	Teva (1976), Chartwell (1978), Dava Pharms (1988), Sandoz (1994), Hikma (2006), Aurobindo Pharma (2005), Hikma Pharms (2007), Wockhardt Bio Ag (2007), Aurobindo (2006), US Antibiotics (1979), Rising (2016), Red Hill (2019),	Belcher Pharms (>2016), Mylan, Labs Astral (1985), Strides Pharma (>2009), Apothecon, Sun Pharms Inds Ltd (>2008), GlaxoSmithKline (>1974), Ranbaxy Labs (>2003), Pragma (>2019), Apothecon (>2002), Parke Davis, Wyeth Ayerst, Cumberland Pharms (>2020), Takeda Pharms (>2018), Ani Pharms (>2015),	GlaxoSmithKline

Ampicillin	Penicillins	1965	Sandoz (1971), Istituto Bio Ita Spa (1987), HQ SPECLT Pharma (1993), Aurobindo Pharma (2010), Antibiotice (2009), Sagent Pharms (2015), ACS Dobfar (>2013), Mylan Labs (2014), Mylan Labs (2014),	Parke Davis, Consolidated Pharm, Lilly, Intl Medication, Hikma (>2019), Watson Labs (>2000), Apothecon (>1998), Hanford GC (>2013), Hospira Inc (>2018), Ivax Sub Teva Pharms, Teva (>1997), Vitarine, Heritage Pharma (>2000), Belcher Pharms (>1997), Mylan, Purepac Pharm (>1976), Lederele, Strides Pharma (>2019), Dava Pharms Inc (>2015), Wyeth Ayerst (>1996), Pfizer (>1977), Bristol, Bristol Myers Squibb (>2002), GlaxoSmithKline (>2000),	Wyeth Ayerst
Azlocillin	Penicillins	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	Bayer Pharms
Cloxacillin	Penicillins	1971	**DISCONTINUED BY ALL**	Apothecon (>1971), Teva (>2000), Glaxo Smith Kline (>1974)	Apothecon

Dicloxacillin	Penicillins	1968	Teva (1982)	Sandoz (>2016) Apothecon (>1998), GlaxoSmithKline (>1998), Wyeth Ayerst (>1991)	Wyeth Ayerst
Flucloxacillin	Penicillins	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Mezlocillin	Penicillins	1981	**DISCONTINUED BY ALL**	Bayer Pharms (>1998)	Bayer Pharms
Methicillin	Penicillins	1971	**DISCONTINUED BY ALL**	Apothecon (>1991)	Apothecon
Nafcillin	Penicillins	1965	Sandoz (1984), Istituto Bio Ita Spa (2011), Antibiotice (2011) Sagent Pharms (2012), Aurobindo Pharma (2012), Aurobindo Pharma ltd (2012), Fresenius (>2019), Baxter Healthcare (1989),	Apothecon, Watson Labs (2000), Mylan Labs (>2014), GlaxoSmithKline (>1993), Wyeth AyersT (1996)	Wyeth Ayerst

Oxacillin	Penicillins	1971	Sagent Pharms (2012), Aurobindo Pharma ltd (2013), Fresenius Kabi USA (2020), Piramal Critical (2017), Wockhardt Bio AG (2017), Baxter Healthcare (1989)	Apothecon, Sandoz (2016), Ani Pharms (2000), Teva (2000), Eklins Sinn, Istituto Bio Ita Spa (2020), Watson Labs Inc (2016), Mylan Labs ltd (2020), Hospira Inc (>2015), GlaxoSmithKline (>1994)	Sandoz
Penicillin G	Penicillins	1947	King Pharms LLC (1948), Sandoz (2001), HQ SPECLT Pharma (2009), Istituto Bio Ita Pharma (2009), ACS Dobfar Spa (2018), Baxter Healthcare (1990),	Lilly, Pfizer (>2018), Consolidated Pharm, Parke Davis, Pharmacia and Upjohn, Copanos, Bristol Myers Squibb, Watson Labs (>2000), Casper Pharma (>2000), Pfizer (>1989), Teva (>1964), Ivax Sub Teva Pharms, Teva (>1979), Apothecon, Wyeth Ayerst (>1951), Mylan (>1980), Purepac Pharm, Casper Pharma LLC (>2000)	Pfizer

Penicillin V	Penicillins	1958	Strides Pharma (1988), Sandoz (1995), Aurobindo Pharma (2008), Hikma Pharms (2013), Teva (1968),	GlaxoSmithKline (>1998), Apothecon (1998), Bristol, Lederele, Wyeth Ayerst (>1996), Parke Davis, Ivax Sub Teva Pharms, Belcher Pharms (>1997), Mylan (>1972), Purepac Pharm (>1976), Pfizer (>1974), Pharmacia and Upjohn, Lilly (1994),	Wyeth Ayerst
Piperacillin	Penicillins	1981	Istituto Bio Ita Spa (2003)	Wyeth Pharms Inc (>2008)	Wyeth Pharms Inc
Temocillin	Penicillins	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Ticarcillin	Penicillins	1976	**DISCONTINUED BY ALL**	GlaxoSmithKline (>2014), Wyeth Pharms Inc (>1981)	GlaxoSmithKline
Amoxicillin/clavulanate	Penicillin combinations	1984	Sandoz (2002), Teva (2002), Sandoz Inc (2002), Teva Pharms USA (2002), Sandoz Inc (2002), Hikma Pharms (2005), Wockhardt Bio	Sun Pharms Inds Ltd (>2008), Apotex Inc (>2014)	US Antibiotics

			AG (2008), Aurobindo Pharma Ltd (2011), Micro Labs Ltd India (2016), US Antibiotics (1984),		
Ampicillin/sulbactam	Penicillin combinations	1986	Hikma (2002), HQ SPECLT Pharma (2005), Istituto Bio Ita Spa (2005), Sandoz (2006), ACS Dobfar (2009), Aurobindo Pharma (2010), Astral (2016), Mylan Labs Ltd (2014), Antibiotice (2015), Pfizer (1986	Pharm Assoc (>2016), Hospira Inc (2015),	Pfizer

Piperacillin/tazobactam	Penicillin combinations	1993	Istituto Bio Ita Spa (2011), Sandoz (2010), Aurobindo Pharma Ltd (2011), Sandoz Inc (2014), Fresenius Kabi (2018), Qilu (2018), Fresenius Kabi USA (2018), Wockhardt Bio AG (2017), Provepharm SAS (2017), Sagent Pharms inc (2021), Astral (2019), Wyeth Pharms Inc (1993)	Hospira Inc (>2017), Mylan Labs ltd (>2021),	Wyeth Pharms Inc
Ticarcillin/clavulanate	Penicillin combinations	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Bacitracin	Polypeptides	1948	Padagis US (1971), Akorn (>1995), Bausch and Lomb (1995), Casper Pharma (1971),	X Gen Pharms (>2002), Pharmacia and Upjohn (>2004), Pfizer (>1950), Lilly, Apothekernes (>1972), Pharmaderm, Pharmafair, Paddock LLC, Quad Pharms, Combe, Naska, Fresenius Kabi USA	Pharmacia and UpJohn

				(>2002), Mylan ASI (2010), Xellia Pharms APS (>2014), Altana, Monarch Pharms (>2021), Dow Pharm (>1954),	
Colistin	Polypeptides	1962	Endo Pharms (1962)	Parke Davis	Endo Pharms
Polymyxin B	Polypeptides	1954	Akorn (1995), Bausch and Lomb (1994), Padagis US (1981), Casper Pharma (1971), Novartis (1963), Sandoz inc (1983), Watson Labs (1986), X Gen Pharms (1994), Amring Pharms (2005), Fresenius Kabi USA (2008), Xelia Pharms APS (2014), Eugia Pharma (2016), Allergan (1988),	GlaxoSmithKline (>1998), Pharmafair, Naska, Pharmaderm, Altana, Parke Davis, Monarch Pharms (>2021), Combe, Pharmacia and Upjohn, Dow Pharm (>1954), Alcon Pharms (1999), iPharm, Parkedale (>1996) Schering (>2000), Actavis Labs Fl Inc, Hikma (>2019), Paddock Inc, Rising (>2012), Gland (>2016), Forest Labs (>1972), Alcon (>1999), Pfizer,	Dow Pharm

Ciprofloxacin	Quinolones/Fluoroquinolones	1987	Wraser Pharms (2009), Novartis (1990), Bayer Healthcare (1987), Bayer Pharms (1990), Ivax Sub Teva Pharms (1990), Carlsbad (2004), Hikma (2004), Aiping Pharm Inc (2004TA), Hikma Farmaceutica (2008), Baxter Healthcare (2008), Dr Reddys Labs ltd (2004), Anchen Pharms (2007), Rising (2004), Ivax Sub Teva Pharma (2004), Carlsbad (2004), Akorn (2008), Hikma (2004), Unique Pharm labs (2004), Watson Labs (2004), Teligent (2004), Chartwell (2004), Taro (2004), FDC LTD (2008), Aurobindo	Fresenius Kabi USA (>2006), Bedford Labs (>2005), Dr Reddys (>2019),, Ani Pharms (>2010), Mylan Pharms (>2019), Fousun Pharma (>2019), Barr (>2004), Sun Pharms ltd (>2013), Rubicon (>2011), Amneal (>2005), Teva (>2001), Nostrum Labs (>2006), Pilva (>2006), Amrings Pharms (>2008), Teva Pharms (>2005), Bedford (>2008), Depomed Inc (>2011)	Bayer Healthcare

			Pharma (2007), Altair Pharms (2018), Yiling (2018), Hospira (2008), INFORLIFE (2008), Alk Abelo (2015), Laboratorios Salvat (2016),		
Enoxacin	Quinolones/Fluoroquinolones	1991	**DISCONTINUED BY ALL**	Sanofi Aventis US (>2002)	Sanofi Aventis US
Gatifloxacin	Quinolones/Fluoroquinolones	2003	Lupin Ltd (2013), Akorn (2014), Hi-Tech Pharmaceutical (2014TA), Sandoz Inc (2016), Torrent (2021), Allergan (2003)	Apotex Inc (>2015), Mylan (>2018),	Allergan
Gemifloxacin	Quinolones/Fluoroquinolones	2003	Lg Chem ltd (2003), Orbion Pharms (2015)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	LG Chem Ltd
Levofloxacin	Quinolones/Fluoroquinolones	1996	Hospira (2015), Infolife (2011), Hikma Farmaceutica (2011), Baxter Healthcare Corp (2013), Fresenius Kabi USA (2013),	Santen (>2014), Janssen Pharms (>2017), Mylan (>2019), Watson Labs Teva (>2017), Rubicon (>2016), Torrent Pharms (>2019), Mylan ASI (>2019), Watson	Janssen (Johnson and Johnson)

			Gland Pharma (2020), Eugia Pharma (2013), Bedford Labs (2010TA), Sicor Pharms (2005TA), Teva (2011), Dr Reddys Lab Inc (2011), Cipa Ltd (2012), Sandoz (2011), Cadilla (2012), Rising (2010), Lupin (2011), Hikma Pharms (2011TA), Mylan Pharma (2009TA), Akorn (2010), Celltrion (2011), Apotex (2011), Glenmark Generics (2011), Macleod Pharms (2012), Audobindo Pharma (2011), Obrion Pharms (2012), Hetero Labs Ltd (2015), Hec Pharm (2019), Lannett Co (2018), Micro Labs Lts India (2019),	Labs Inc (>2013), Emcure Pharms (>2019), Jubilant Generics (>2019), Mylan Labs (>2017), Zydus Phamrs (>2019)	

Lomefloxacin	Quinolones/Fluoroquinolones	1992	**DISCONTINUED BY ALL**	Pharmacia (>2005)	Pharmacia
Moxifloxacin	Quinolones/Fluoroquinolones	1999	Bayer Pharms (2001), Novartis (2003), Dr Reddys Labs Ltd (2014), Teva (2014), Teva Pharms (2009TA), Apotex (2017), Torrent (2014), Watson Labs (2015), Aurobindo Pharma (2014), Lupin Ltd (2014), Akorn (2017), Crossmedica Ska (2016), Fresenius Kabi USA (2015), Eugia Pharma (2017), Mylan (2015), Novel Labs Inc (2017), MSN (2017), Gland Pharma (2020), Alembic Pharms (2019), Upsher Smith Labs (2021), Mylan Labs (2017),	Bayer Healthcare (>2020), Sunshine (>2018),	Bayer Healthcare

Nadifloxacin	Quinolones/Fluoroquinolones	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Nalidixic acid	Quinolones/Fluoroquinolones	1964	**DISCONTINUED BY ALL**	Sun Pharms Industries (>1998), Watson Labs (>1996), Sanofi Aventis US (>2012),	Sanofi Aventis US
Norfloxacin	Quinolones/Fluoroquinolones	1986	**DISCONTINUED BY ALL**	Merck (>2016)	Merck
Ofloxacin	Quinolones/Fluoroquinolones	1990	Allergan (1993), Larken Labs (2003), Bausch and Lomb (2004), Teva (2003), Akorn (2004), Apotex (2004), Dr Reddys Labs Ltd (2006), FDC Inc (2009), Cadila Pharms (2014), Altaire Pharms (2013), Amneal (2019),	Janssen (>2011), Ortho McNeil Pharm (>1999), Daiichi (>2005), Bedford (>2002), Ranbaxy Labs (>2003), Sandoz inc (>2004), Alvogen (>2020), Sandoz (>2008), Alvogen >2009),	Janssen (Johnson and Johnson)
Trovafloxacin	Quinolones/Fluoroquinolones	1997	**DISCONTINUED BY ALL**	Pfizer (>2000)	Pfizer

Grepafloxacin	Quinolones/Fluoroquinolones	1997	**DISCONTINUED BY ALL**	Otsuka (>1999)	Otsuka (Rights acquired by Glaxo Wellcome)
Sparfloxacin	Quinolones/Fluoroquinolones	1996	**DISCONTINUED BY ALL**	Mylan (>2003)	Mylan
Temafloxacin	Quinolones/Fluoroquinolones	1992	**DISCONTINUED BY ALL**	Abbot Labs (1992)	Abbot Labs
Mafenide	Sulfonamides (Bs)	1969	Rising (1969), Mylan Institutional (1998), Novast Labs (2017), Par Form (2013),	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Rising acquired it as an orphan drug in 1969, no prior data on FDA available

Sulfacetamide	Sulfonamides (Bs)	1946	Allergan (1961), Bausch (1996), Bausch and Lomb (1982), Akorn (1983), Fougera Pharms (2006), Padagis US (1971), Taro (2009), Sandoz Inc (1993),	Alcon (>2002), Cosette (>2001), Schering (>2001), Miza Pharms (>1996), Pharmafair (>1988), Sola Barnes Hind (>1974), Novartis (>2000), Optopics (>1984), Alcon Pharms (1999), Ortho McNeil Pharm (>2000), Purepac Pharm, Alpharma US (>1976), Fougera, Pharmaderm, Savage Labs (>1996),	Schering
Sulfadiazine	Sulfonamides (Bs)	1941	Sandoz (1994)	Lannett (>2000), Lilly (>1986), Impax Labs (>1989), Lederele (>1985), AbbVie, Everylife, Forets Pharms, Wyeth Ayrest, Bristol Myers Squibb, Purepac Pharm, Alpharma US (>1976), Fougera, Padagis US (>1997), Pharmaderm, Pal Pak (>1975),	Lederele or Lily
Silver sulfadiazine	Sulfonamides (Bs)	1973	King Pharms (1973), Dr Reddys LA (1982), The	Franklin Pharms (>2000)	King Pharms

			Pharma Network LLC (1985)		
Sulfadimethoxine	Sulfonamides (Bs)	**Not Approved For Human Use**	**Veterinary Med Only**	**Veterinary Med Only**	Anada
Sulfamethizole	Sulfonamides (Bs)	1953	**DISCONTINUED BY ALL**	Forest Pharms, Wyeth Ayerst (>1988),	Wyeth Ayerst
Sulfamethoxazole	Sulfonamides (Bs)	1965	**DISCONTINUED BY ALL**	Roche (>2001), Watson Labs, Rising (1984), Heather, Barr (>1983), Ascot, Rising (>1984), Shionogi,	Roche
Sulfasalazine	Sulfonamides (Bs)	1950	Pfizer (1950), Pharmacia and Upjohn (1980), Nuvo Pharms Inc (2002), Chartwell (1973), Watson Labs (1976),	Solvay (>1974), Sandoz (>1994), Superpharm, Sun Pharm Industries (>2002),	Pfizer

Sulfisoxazole	Sulfonamides (Bs)	1948	**DISCONTINUED BY ALL**	Roche (>1997), Barr (>2015), Alra (>1996), Lilly, Roche Labs (>2004), MK Labs (>1973), Parke Davis (>1977), Roxane, Lannett (>1978), Purepac Pharm, Impx Labs, Ani Pharms (>2002), Heather, Valeant Pharm Intl, West Ward (>1991), Barr (1995), Pharmeral (>1989), Watson Labs, Rising (>2001), Vitarine (>1983), Lederele, Sola Barnes Hind (>1975), Solvay (>1975),	Roche

Trimethoprim-Sulfamethoxazole (Co-trimoxazole) (TMP-SMX)	Sulfonamides (Bs)	1973	Sun Pharm Industries (1973), Monarch Pharms (1973), Teva Pharls (1991), Akorn (1997), Vista Pharms (2005), Amneal Pharms NY (2005), Prasco (2006), Lannett Co Inc (2007), Chartwell Molecules (2007), Aurobindo Pharma (2010), Glenmark Generics (2010), Mylan Labs (2017), Somerset (2019), Lupin Ltd (2021), Pharm Assoc (1983),	Teva (>2014), Novel Labs (>1995), Quad Pharms, Fosun Pharma (>2021), Watson Labs (>2001), Heather, Mutual labs (>1998), Ani Pharms (>2002), USL Pharma, Pliva (>2001), Abraxis Pharm, Hikma (>1998), Interpharm, Bedford, Martec USA LLC, Roxane (>1994), Hospira (>1995), Able (>2001), Fosun Pharma (>2021) Mutual Pharm (>1998), Heritage Pharma Avet (>2015), Martec USA llc, Roxane, Superpharm (>1989), Alpharma US Pharms Naska (>1988), Shionogi,	Monarch Pharms
Sulfonamidochrysoidine (archaic)	Sulfonamides (Bs)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	Bayer

Demeclocycline	Tetracyclines (Bs)	1960	Akorn (2008), Amneal (2008), Epic Pharma LLC (2015),	Lederele (>1991), Corepharma (>2012), Impax Labs (>2004), Barr (>2013),	Lederele

Doxycycline	Tetracyclines (Bs)	1967	Amirall (2014), Mayne Pharma (2005), Fresenius Kabi USA (1983), Hikma (>1983), Sun Pharm Inds Ltd (2000), Strides Pharma (1993), Lannett Co (2005), Chartwell (1984), Mylan (1982), Lupin Ltd (2013), Mylan Labs Ltd (2012), Heritage Pharms Ltd (2011), Impax (2011), Amneal Pharms (2016), Cossette (2015), Zydus Pharms (2016), Alembic Pharms (2017), Mayne Pharma Inc (2017), Activis Labs (1982), Carbie Holdings (1982), Hikma Intl Pharms (1984), Sun Pharms Industries Ltd (1986), West Ward Pharms Ltd	Den-Mat (>2015), Mayne Pharma Intl (>2020), Warner Chilcott (>2004), Teva (>2014), Rachelle (>1980), Sandoz (>2002), Watson Labs (>2003), Sandoz Inc (2014), Mylan Pharms Inc (>2016), Rising (>2021), Halsey, Mutual Pharm (>1998), Par Pharm, Heather, Superpharm (>1985), Ranbaxy (>1993), PVT Form (>1986), Quad Pharms, Interpharm, Pliva (>1994), Heritage Pharma (>2005), Bausch (>2015), Rising (>2016), Impax Labs (>2011), Nostrum Labs Inc (2020), Zhejiyang Yongtai (>2020), Amici (>2021), Collagenex (>1998),	Pfizer

			(1989), Hikma Intl Pharms (2003), Eric Pharma llc (2005), Larken Labs (>2006), Actavis Elizabeth (2011), Heritage Pharms inc (2013), Prinston Inc (2016), Novel Pharms (2017), Cadila (2017), Nesher Pharms (2021), Apotex (2019), Changzhou Pharm (2019), Emcure Pharms ltd (2018), Acella (2020), Ajanta (2018), Alembic Pharms Ltd (2020), Galderma Labs LP (2001), Pfizer (1967),		

Metacycline	Tetracyclines (Bs)	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Minocycline	Tetracyclines (Bs)	1971	Vyne (2019), Orapharma (2001), Alvogen (1990), Rempex (1972), Bausch (1972), Zydus (1992), Watson Labs (1991), Watson Labs Teva (1991), Impax Labs (1999), Torrent (2000), Strides Pharma (2003), Dr Reddys Labs ltd (2007), Aurobindo Pharma (2008), Sun Pharm Industries (2016), Sandoz (2009), Sun Pharms Inds Inc (2013), Lupin Ltd (2011), Zydus Pharms (2017), Sidmak Labs India (2015), Alkem Labs Ltd (2019),	Triax Pharms (>1995), Lederele, Barr Labs (>2019), Impax Labs Inc (>2013), Mylan Pharms Inc (>2016), Rising (>2019),	Triax Pharms

			Epi Health (2017), Journey (2012),		
Oxytetracycline	Tetracyclines (Bs)	1964	**DISCONTINUED BY ALL**	Ferrante (>1967), Purepac Pharm, Impax Labs (>1967), Hikma (>1991), Proter (>1964), Pfizer (>2004), Casper Pharma LLC (>2004),	Pfizer

Tetracycline	Tetracyclines (Bs)	1950	Avet (>1957), Ailex Pharms LLC (2018), Allergan (2006), Watson Labs (1974), Chartwell Tetra (1988), Breckenridge (2018), Amneal Pharms NY (2018), Strides Pharma (1971)	Storz (>1993), Lederele (>1991), Schiff and Co (>1995) , Bristol (>1974), Warner Chilcott (>1978), Casper Pharma LLC (>2021), Ferrante (>1967), Purepac Pharm, Impax Labs (>2001), Hikma (>1991), Proter (>1964), Pharmacia and Upjohn (>1993), Solvay, Wyeth Ayerst, Par Pharm (>2004), Apothecon (>1997), Strides Pharma (>2017), Pfizer (>2004), Angus, Eklins Sinn, Valeant, Alpharma US Pharms, Ivax Sub Teva Pharms (>2014), Sun Pharm Industries (>2002), Hikma (>1977), Mylan >2014), Heather, Roxane (>1972), Ani Pharms (>1995), Abbott, Mast MM (>1977), Superpharm (>1985), PVT Form, PFIPharmecs (1955),	Lederele

				Bristol (>1974), Shire (1997)	

Clofazimine	Drugs against mycobacteria (Tuberculosis)	1986	**DISCONTINUED BY ALL**	Novartis (>2019)	Novartis
Dapsone	Drugs against mycobacteria (Tuberculosis)	2005	Allergan (2005), Almirall (2016), Jacobus (1979), Nostrum Labs Inc (2016), Virtus Pharms (2016), Actavis LLC (2017), Alvogen (2016), Novitum Pharma (2016), Rising (2019), Taro (2017), Taro Pharms (2019), Torrent Pharms Ltd (2021TA)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Allergan
Capreomycin	Drugs against mycobacteria (Tuberculosis)	1971	**DISCONTINUED BY ALL**	Akorn (>2019), Mylan Labs Ltd (>2017), Hisun Pharm Hangzhou (>2018)	Akorn
Cycloserine	Drugs against mycobacteria (Tuberculosis)	1964	Purdue (1964)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Purdue
Ethambutol (Bs)	Drugs against mycobacteria (Tuberculosis)	1967	STI Pharla Inc (1967), Akorn (1999), Barr (2001), Lupin Ltd (2009),	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	STI Pharma Inc

Ethionamide	Drugs against mycobacteria (Tuberculosis)	1965	Wyeth Pharms (1965)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Wyeth Pharms

Isoniazid	Drugs against mycobacteria (Tuberculosis)	1952	Anda Repository (1997), Sandoz inc (2005), Barr (1972), CMP Pharma Ltd (1983), Thepharmanetwork LLC (2014),	Dow Pharm (>1970), Medpointe Pharm LLC, Novartis, Panray (>1980), Lilly, Sandoz (>2016), Whiteworth Town PLSN (>1985), Purepac Pharm (>1985), Sun Pharm Industries (2002), Impax Labs (>1992), Hikma Intl Pharms (>2008), Ivax Sub Teva Pharms (>1974), Phoenix Labs NY (>1975), Watson Labs (>1998), MK Labs (>1972), Perrigo, Halsey, Nexgen Pharms (>1974), Pharmavite, Duramed Pharms Barr (>1997), Quad Pharms, Lannett (>2001), Bristol Myers Squibb, Sanofi Aventis US (>2021), Roche, Everylife (>1972)	Sandoz

Pyrazinamide	Drugs against mycobacteria (Tuberculosis)	1971	Novitum Pharma (1971), Akorn (1992), Macleods Pharms Ltd (2020),	Sanofi Aventis US (>2021)	Novitum Pharma
Rifampicin (Rifampin in US)	Drugs against mycobacteria (Tuberculosis)	1971	Sanofi Aventus US (1971), Sandoz (1997), Hikma (1999), Akorn (2001), Lannett Co Inc (2008), Mylan Labs Ltd (2008), Lupin Pharms ltd (2013), Fresenius Kabi US (2014), Hikma Pharms (2016), Oxford Pharms (1971)	Emcure Pharms Ltd (>2021), Watson Pharms Ltd (>2020), Hikma Intl Pharms (> 2005),	Sanofi Aventis US
Rifabutin	Drugs against mycobacteria (Tuberculosis)	1992	Pfizer (1992), Lupin Ltd (2014), Novitum Pharma (2021), Redhill (2019)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Pfizer
Rifapentine	Drugs against mycobacteria (Tuberculosis)	1998	Sanofi Aventus US (1998)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Sanofi Aventis US
Streptomycin	Drugs against mycobacteria (Tuberculosis)	1946	Xgen Pharms (1998)	Pfizer (>1995), Lilly, Copanos,	Pfizer

Arsphenamine	Others	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Chloramphenicol (Bs)	Others	1951	Fresenius Kabi USA (1982),	Optopics (>1982), Altana (>1968), Akorn (>1992), Ivax Sub Teva Pharms (>1997), Elkins Sinn, Alcon (>1999), Gruppo Lepetit, Pharmafair, Parke Davis (>1998), Parkedale (>2009), Allergan (>2002), Alcon (>2000), Armenpharm (>1967), Angus,	Parke Davis
Fosfomycin	Others	1996	Cipla (2022), Xiromed (2020), Alkem Labs Ltd (2021), Zambon Spa (1996)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Zambon Spa
Fusidic acid	Others	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	

Metronidazole	Others	1963	Ailex Pharms LLC (2018), Pfizer (1963), Baxter Healthcare (1981), B Braun (1982), Galderma Labs LP (1988), Bausch (1992), Watson Labs (1984), Strides Pharma (1985), Watson Labs Inc (1985), Amici (1986), Fougera Pharms (2004), Tolmar (2006), Cosette (2007), Taro (2006), Alembic Pharms (2009), Alembic Pharms Ltd (2009), Unichem (2014), Aurobindo Pharma Ltd (2015), Heritage Pharms Inc (2015), Cadila (2016), Flamingo Pharms (2016), Alembic Labs (2017), Lupin Ltd (2017), Cadila	Casper Pharma LLC (>2021), Labs AF (>1996), Ivax Sub Teva Pharms (>2004), Watson Labs (2021), Fosun Pharma (>2021), Multual Pharm (>1998), Chartwell Molecules (>2021), Abbott (>1996), West Ward Pharms Int (>2021), LNK (>1984), Intl Medication, Superpharm (>1991), Halsey, Teva Pharms USA (>2019), Pliva (>2019), Abraxis Pharm, Halsey, Able (>2005), Abraxis Pharm, Mylan Labs ltd (>2019), Ortho McNeil Pharm (>1992), Savage Labs,	Pfizer

			Pharms Ltd (2017), Padagis Israel (2019), Aleor Dermaceuticals (2021), Solaris Pharma Corp (2021), Glenmark Pharms Ltd (2022), Hospira (1983), Inforlife (2019), Gland Pharma ltd (2020), Valeant Pharms North (1997), Chemo Research SL (2014), Allergan (2006) Teva Pharms (2005), Zambon Spa (1996)		

Mupirocin	Others	1987	Padagis US (2002), Anda (2003), Taro (2005), Fougera Pharms (2005), Glenmark Pharms (2011), Glenmark Pharms Inc (2013), Aleor Dermaceuticals (2021), Encube (2021)	GlaxoSmithKline (>2020),	GlaxoSmithKline
Platensimycin	Others	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Quinupristin/Dalfopristin	Others	1999	King Pharms (1999)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	King Pharms
Thiamphenicol	Others	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	**NEVER RECEIVED APPROVAL**	
Tigecycline (Bs)	Others	2005	Sandoz Inc (2015), Apotex (2018), Fresenius Kabi USA (2016), Xellia Pharms APS (2019), Eugia Pharma (2019), Accord Healthcare Inc (2018), Amneal	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	PF Prism CV

			(2018), Meitheal (2021), PF Prism CV (2005)		
Tinidazole	Others	2004	Mission Pharma (2004), Hikma (2012), Novel Labs Inc (2012), Unique Pharms Lab (2013), Edenbridge Pharms (2015),	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	Mission Pharma
Trimethoprim (Bs)	Others	1980	Allergan (1988), Mayne Pharma (1982), Watson Labs (1985), Novel Labs (2011), Bausch and Lomb (1997), Sandoz inc (1998), Akorn (1998),	Allegis (>2016), Monarch Pharms (>2009), Sun Pharm Industries (>2015), Teva (2012), Roche (>1997),	Roche or Monarch Pharms

Appendix 3: Analysis of Web of Science Data

On 6 July 2023, I began an exhaustive search of any academic, government, NGO, or industry related references that discussed antibiotic shortages on a global scale. I determined the need for a collective corpus that would ideally cross multiple disciplines and lack overt bias. To ensure I had a broad sampling of works, I chose the Web of Science database as the starting point for my corpus. As one of the oldest research database systems in use, and with a core functionality that enables ease of citation connection, references, and keyword search functionality, I felt this corpus could provide a reasonable representative sample. However, one known limitation to this search is that due to Web of Science's high cost, its focus on scientific research rather than social science research, and implicit language bias for sources using English keywords does mean that there are printed articles that are missing from Web of Science's collection. Many countries experiencing shortages do not write or publish in English. However, by presenting statistics and analysis of what has been written in English, trends reflecting an increase in concern regarding shortages can be tracked. This corpus, therefore, is not intended to be a fully comprehensive look at all potential mentions of historical shortages since the 1980s, but rather a survey that represents examples of triggering events that could identify shortage presences at these times. As limited as this study is, its results call for a far more expansive study to be undertaken in the future to truly understand the broad reaching complexities surrounding this issue.

I began my work on the Web of Science database using the keywords "antibiotic shortage." This preliminary inquiry led to exactly 500 results. I then individually screened these results to exclude any articles that discussed the shortage of existing remedies to treat bacterial infections or a shortage on trial data – a total of 291 exclusions. *Innovation* pipeline shortages of antibiotics were also screened, to avoid discussions of a need for new drugs that

does not yet exist. This amounted to a total of 102 additional articles removed from my base results.

I kept any results which included discussions on a current (or past) antibiotic shortage, fears related to future antibiotic shortages, experiences regarding antibiotic shortages, or concerns over the state of antibiotic shortages in general. All of these shortage concerns needed to be in relation to antibiotics that were already on the market and not hypothetical new drugs not yet released. The final tally of applicable articles was 107. I then organized these articles based on the main areas of interest to the article itself:

Location	Total Number of Articles
United States	44
World Wide	17
Europe	17
Asia	15
Africa	11
Australia	2
Brazil	1

Additional searches using "stockout" or "short supply" rather than "shortage" yielded no relevant results. The dates in which the articles were published were also tracked.

This method provides a corpus of data indicating the varying trends of shortage identification and perception since the earliest starting point of published material utilizing this keyword on Web of Science: 1997. The graph below indicates the dates when these articles were written, with Covid-19 clearly serving as an outlier, but simultaneously as a continuation of steadily increasing attention to antibiotic shortages worldwide. Despite the natural drop in reporting following the "end" of the Covid-19 pandemic, instances of journal articles written about antibiotic shortages still remain high.[1044]

[1044] This chart only tracks data from 2023 up to the beginning of July 2023. At this point, only six articles hard been published and saved on Web of Science's database, which is on par with the 2017 figure. 2022, which saw eight articles published, is the second highest amount per year in all the years prior to the Covid-19 pandemic.

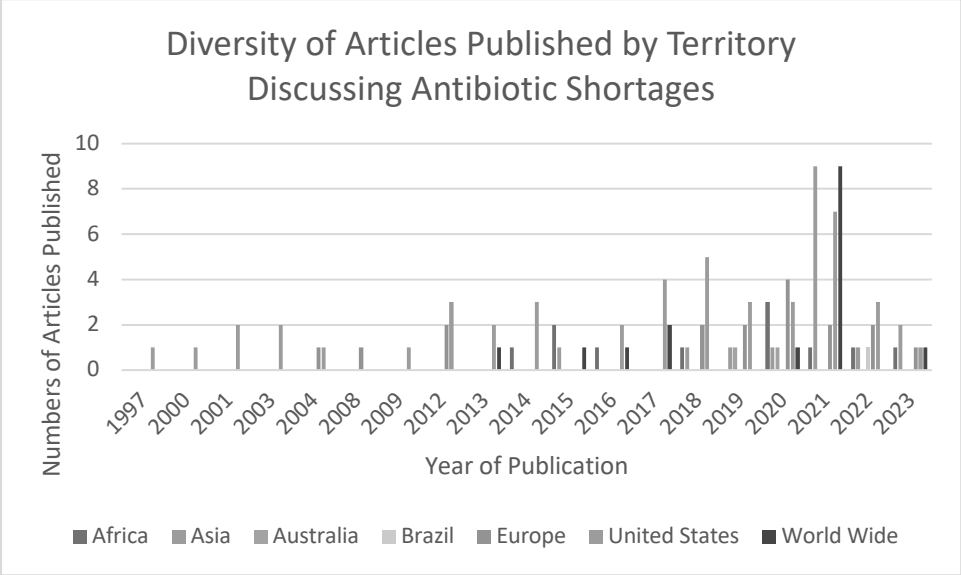

Figure 8 Web of Science Articles Discussing Antibiotic Shortages

Similarly, where before 2012 it was rare for any territory outside of the United States to actively write and report findings regarding antibiotic shortages, from 2015 onwards the diversity of territories involved in reporting on shortages began to increase, as did the number of articles per territory that were being written. While this peaked in 2021 with more world-wide and Asia based articles discussing antibiotic shortages in some capacity, the continued trend of three or more territories reporting on shortages indicates that territories outside of the United States were seeing continued importance in writing and publishing articles related to concern over *current* antibiotic accessibility.

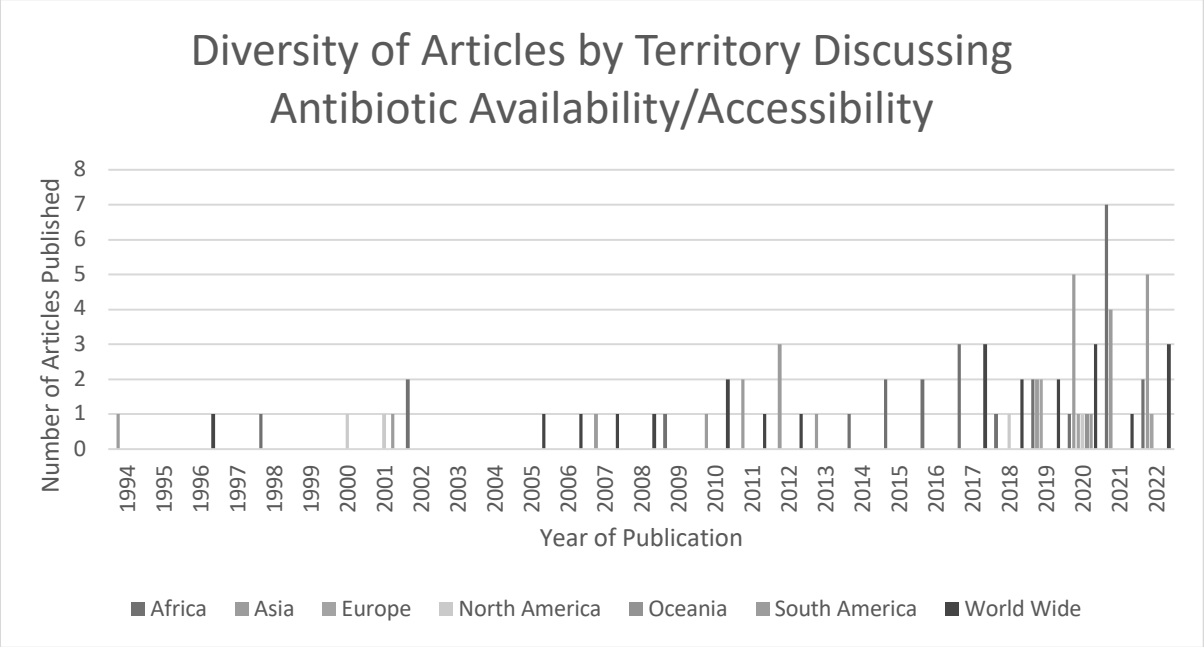

Figure 9 Diversity of Articles Published by Territory Discussing AB Shortages

The category "worldwide" was used when one or more continental area was being discussed in relation to the shortages, or if no specific territory was mentioned. The United States, Australia, and Brazil were used as independent countries, rather than North America, Oceania, or South America as they were the only countries within those continental borders to be assessed within an article found in this corpus.

Following the generation of this highly specific search, I expanded search terms to target concerns regarding antibiotic *availability* and *accessibility*. While drug 'shortages' have varying definitions and distinctions that make it difficult to track comparable figures between nation states, the primary intention behind investigating antibiotic shortages is to understand if a patient is able to adequately access appropriate medication for bacterial infections. By expanding the search queries to include discussions relating to availability, a broader picture is provided.

As with my initial search queries on shortages, I limited the scope of my initial results to only include discussions of on antibiotic that have already received regulatory approval and are legally available for purchase/sale. My initial search query of "antibiotic availability"

resulted in 4,246 results on 21 July 2023.[1045] "Antibiotic accessibility" yielded 545 results on 31 January 2023.[1046] I excluded the search term "shortage" pre-emptively to avoid duplicate results, however there was no change in the number of applicable results despite this exclusion. The articles I kept for the purposes of this study were any articles that were specifically expressing concern over a *lack* of antibiotics, problems acquiring antibiotics, difficulties in access, confirmation of availability/accessibility, and barriers relating to successful patient receipt of antibiotic treatment, calculations on exact measures of availability (including measures where access was generally good but were less than 100% available).[1047] I excluded any results that discussed theory or policy relating to antibiotic availability, potential availability of new antibiotics, discussions of innovation, non-antibiotic related availability concerns, tracking of prescription or non-prescription availability/consumption rates, appropriate use, non-human use, perceptions of if availability affected doctor prescription choices, brief mentions of a "lack of antibiotics" that contained no follow up or additional information, or discussions of over-use of antibiotics.[1048] Articles that discussed a need to reduce antibiotic availability were excluded from the total tally, but saved separately for additional evaluation and consideration.

[1045] This amount grew to 4,255 by 31 July 2023 when analysis officially ended on this query. At end of study, to ensure these items were not missed, I adjusted the search results to reveal recently added and re-read through the first fifty results to ensure there were no extant items.
[1046] For this search, to ensure no duplications with pervious inquiry, I also implemented a pre-emptive screen of any article that contained "availability" in any field.
[1047] Additional articles were screened for repeats, reprints, or withdrawals. If a paper was marked as withdrawn and a reprint was issued at a later time, only the most recent paper was included in calculations to avoid repeating documentation.
[1048] Of note, excluded where articles that mentioned the "limited availability of effective antibiotics" which proceeded to discuss matters unrelated to the availability of antibiotics. While the assumption and reference to a lack of antibiotics existed, these articles took the premise of this lack as granted without providing evidence to justify its existence. The same circumstance is seen in articles that discussed the "widespread availability of antibiotics" without specifying geographic range, specific antibiotic, or citing sources to confirm this widespread availability was accurate. Therefore, any articles that only discussed an assumption of availability rather than providing evidentiary data proving availability (or its lack) were excluded from this analysis. Exceptions to this rule were made only in the cases where quotes from medical practitioners or providers were collected and examined qualitatively regarding perceptions of antibiotic availability. While not the main point of the published article, these quotes indicate perception of use and were therefore included.

Finally, excluded from this study were any articles that mentioned the "rapidly decreasing availability of useful antibiotics" or a need to monitor local availability without details on which antibiotics, what kind of usefulness, or additional information.[1049] Of note, however is that many articles calling for the innovation of new antibiotics included verbiage of this kind. The implicatory nature of there being a shortage of useful/quality antibiotics was of interest, particularly in concern to the Dry AP phenomenon that I was studying, but without specifics or designations – ultimately these references were considered to be too vague to be included in this particular work.

Some concerns with this search include what is considered "available." While some articles detail the specific antibiotics included in the study, it is not clear at which point "antibiotics can be considered available" in all articles. Comparisons of available antibiotics to the Essential Medicines List (see Chapter Two) would help provide more clarity on whether a patient can reasonably expect their ailment to be appropriately treated with an available antibiotic.

Ease of antibiotic access and use is a common refrain regarding antibiotic use. Over-use, over consumption, and irresponsible or irrational use are all terms used identify practitioner/patient relationships with antibiotics. The natural presumption is that should a product be *over* used, then it cannot, by default, be short in the first place. It is here that I believe distinctions need to be made regarding which antibiotics are over used, the quality of these antibiotics, and the access to alternative antibiotics. Which antibiotics are overused? Are those antibiotics the appropriate antibiotic for the identified ailment? If not, is that

[1049] Examples include: Daniel G. Meeker, Samir V. Jenkins, Emily K. Miller, Karen E. Beenken, Allister J. Loughran, Amy Powless, Timothy J. Muldoon, et al., "Synergistic Photothermal and Antibiotic Killing of Biofilm-Associated Staphylococcus Aureus Using Targeted Antibiotic-Loaded Gold Nanoconstructs," *ACS Infectious Diseases* 2, no. 4 (April 8, 2016): 241–50. https://doi.org/10.1021/acsinfecdis.5b00117
and: Peng F Wong, Andrew D Gilliam, Senthil Kumar, Jonathan Shenfine, Graham N O'Dair, and David J Leaper, "Antibiotic Regimens for Secondary Peritonitis of Gastrointestinal Origin in Adults," Edited by Cochrane Colorectal Cancer Group, *Cochrane Database of Systematic Reviews*, April 20, 2005. https://doi.org/10.1002/14651858.CD004539.pub2.
However, similar language was noted during the selection process of this research.

antibiotic considered “overused” because rates of consumption are marked as high? Are those consumption rates high when alternative antibiotic rates are low?

Of the 4,791 combined total articles reviewed for this study, only 84 yielded relevant search results in the following geographic areas.

Africa	25
Asia	25
Europe	4
North America	4
Oceania	1
South America	2
World Wide	23
Total:	**84**

Unlike the previous chart, the United States, Australia, and Brazil were not the only countries to be represented within continental borders and as such continents were used as territorial ranges within this chart to more clearly depict the geographic areas. The one article that conducted a study in Oceania did so across multiple-pacific island nations included in the continental borders of Oceania and therefore was not restricted to one country despite only one article having been published.

By year, these articles can be best viewed in the following chart:

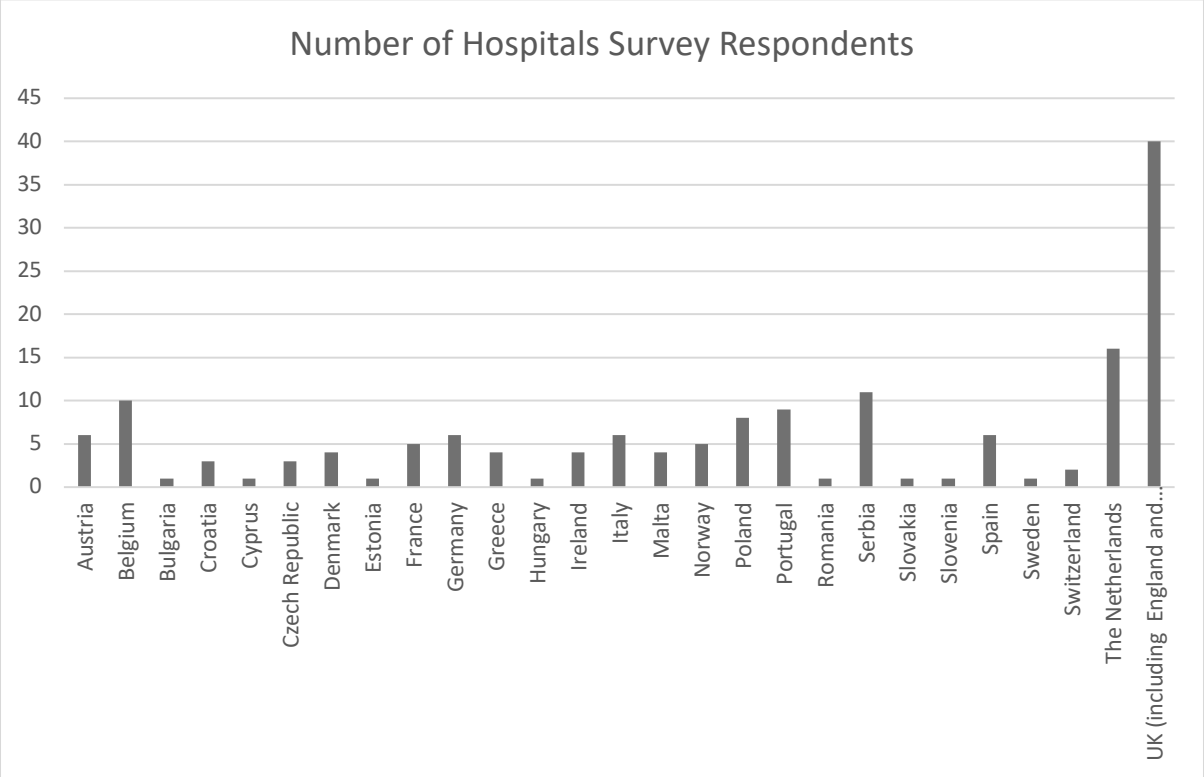

Figure 10 Diversity of Articles by Territory Discussing AB Availability/Accessibility

While it is unsurprising that there were more articles published in the later 2020s as a result of Covid-19, the lack of articles from North America and Europe compared to the "shortage" search immediately highlighted a difference linguistically to the reporting of lack of medications and perceptions there-in.

Appendix 4: Dr. Fox's modified dataset, showing only the antibiotics that I have reviewed and including the additional categories of identification I have added for additional clarity.

Drug Name	# Of shortages	Date summary of shortages	Total days short:	Notes, suppositions
Amikacin	1	January 2009-April 2017	3010	Reason given: Manufacturing Delays
Amoxicillin	7	January 2011-June 2011, November 2014-August 2015, November 2015-March 2016, August 2015-August 2018, February 2016-December 2016, November 2022-April 2023, October 2022-April 2023	2277	Category includes both Amoxicillin and Amoxicillin/Clavulanate. Most shortages are relatively short comparatively, one extended shortage on Amoxicillin/Clavulanate XR Tablets lasted 1079 days from August 2015-August 2018 for unknown reasons. After shortage was resolved, there were no additional Amoxicillin shortages until the 2022 shortages following survey of RSV.
Ampicillin	9	October 2002-June 2004, November 2005-January 2007, October 2007-January 2008, September 2009-February 2010, June 2011-April 2023, June 2014-April 2015, December 2015-March 2017, October 2017-February 2018, February 2017-October 2017	6702	Some indications are still in shortage and shortage data is approximated for purposes of study. Supply and demand started shortages, transitioning to "Unknown" and "Raw material" in specific for the longest delay
Azithromycin	10	January 2004-April 2004, October 2009-August 2010, March 2010-March 2010, February 2011-June 2012, December 2012-August 2015, January 2018-June 2021, April 2018- June 2018, November 2022-	3669	Comes in many different formulations including injections, suspension, and oral formations.

		April 2023, January 2022-July 2022, December 2022-April 2023		
Aztreonam	6	January 2005-March 2005, August 2005-February 2007, August 2008-September 2010, January 2012-October 2013, September 2014-January 2015, January 2016-April 2016	2192	Longest shortage marked for manufacturing delays, others mostly marked with unknown reasons.
Bacitracin	15	Fifteen Shortages from 2001-2020. February 2001-September 2002, January 2003-September 2003, December 2003-March 2005, August 2007-August 2007, April 2009 - April 2009, October 2009 - January 2010, August 2010 - March 2011, May 2014-March 2015, September 2016-March 2017, June 2019-October 2019, July 2019-June 2020, July 2019-June 2020, January 2010-March 2020	3286	There were two extended shortages from July 2019 to June 2020, one for Bacitracin Ophthalmic and one for Bacitracin Zinc: they were reported on similar days and resolved at similar days. Implies the same API had been affected in both instances
Cefazolin injection	2	April 2012-April 2016, April 2018-April 2023,	3290	Both multi-year shortages were due to reported manufacturing delays.
Cefepime injection	4	March 2005-June 2006, October 2006-February 2007, January 2012-August 2012, May 2014-September 2022	3839	"Unknown" reasons occurred during shorter shortages, but supply and demand was the stated reason for the longer shortage from May to September 2022

Cefotaxime injection	2	May 2001-June 2001, January 2008-March 2012, September 2012-April 2023	5420	Ongoing shortage from September 2012, supply and demand given as reason for shortage.
Cefotetan	7	November 2002-July 2006, August 207-November 2007, February 2008-March 2009, February 2011-September 2011, October 2012-March 2013, April 2014-May 2017, July 2020-November 2021	3755	Shortages began due to manufacturing problems/delays followed by Unknown Reasons - potentially excess demand as continued manufacturing problems strained alternative formulations. Continued manufacturing delays were repeatedly reported in the most recent shortage years.
Cefoxitin	2	December 2002-November 2007, October 2016-May 2021	3427	Includes sodium injection version of compound. Unknown reason for first shortage, but second was due to manufacturing delays.
Cefpodoxime	5	April 2009-March 2010, May 2011-September 2016, March 2018-November 2018, June 2017-October 2017, July 2017-October 2017	2746	Shortage includes oral solutions, suspensions, and tablets. Concurrent shortages crossed different formulations. Though most reasons for these shortages were listed as "unknown," regulatory delays and "Short dated product" were offered as two explanations. It is possible that once shortages were marked in one formulation, the reasons others experienced a shortage was due to increased and unexpected demand, or due to the same API manufacturer being unable to supply alternate formulations as the same plant was implicated.
Ceftazidime	2	August 2003-October 2003, November 2011-April 2023	4221	Business decision was marked as reason for first brief delay, the extended delay was reported as a manufacturing delay.
Ceftriaxone injection	3	July 2007-October 2007, February 2014-November 2019, July 2007-October 2007	2606	Manufacturing Delays the primary cause of shortages

Cefuroxime	7	July 2005-January 2006, May 2009-October 2009, November 2012-September 2015, January 2014-September 2014, February 2016-May 2016, October 2016-June 2020, April 2022-April 2023	3400	Material shortage from 2012-2015 was the longest stretch until the increased demand from 2016-2020 leaving large shortages for these formulations (both injectable). One indication is still in shortage as of April 2023.
Ciprofloxacin	9	October 2001-November 2001, February 2003-March 2004, October 2009-August 2015, May 2010-August 2015, July 2011-August 2011, October 2015-November 2019, March 0218-April 2023, February 2018-August 2019, December 2021-April 2023	8874	A treatment for Anthrax, there was a shortage not long after 9/11 that was quickly resolved. In the years that followed multiple formulations, from tablets to suspensions, to injections were all short for "unknown" or "raw materials" issues. Most shortages were between 1-6 years in length.
Clarithromycin	6	April 2009-January 2010, April 2010-April 2014, February 2010-March 2010, June 2014-October 2014, June 2014-October 2014, February 2018-October 2020	2965	An extended shortage from 2010-2014 was caused due to "manufacturing" problems. After this shortage was resolved, between June and October 2014, two indications of this formulation were discontinued and marked as business decision to cease development. Extended shortage began in 2018 through October 2020.
Clindamycin Injection	2	June 2010-July 2011, August 2012-April 2023,	4275	This shortage is for the injection version of Clindamycin only, there are other versions (creams etc.) that did have shortages for small spans of times however the extreme length of this formulation due to "manufacturing delays" highlights this shortage's unique concerns

Doxycycline	9	June 2008-December 2008, June 2009-August 2012, November 2012-May 2015, July 2013-January 2014, August 2014-January 2015, March 2016-July 2016, July 2017-May 2018, March 2019-December 2020, October 2019-April 2023	4880	Some indications are still in shortage and shortage data is approximated for purposes of study. Manufacturing delays and raw material shortages appear to have compounded to create a chain of delays.
Erythromycin	15	Fourteen shortages from 2003-2022. March 2003-May 2005, August 2008-December 2008, March 2009-June 2011, August 2009-May 2010, March 2011-April 2011, May 2012-January 2013, March 2013-November 2014, June 2014-June 2014 July 2016-September 2019, March 2017-January 2018, December 2019-Mrach 2020, February 2019-August 2020, April 2020-April 2021, August 2020-August 2021, July 2022-April 2023	5274	Comes in many different formulations, these shortages indicate the gel, suspension, oral, tablets, ointment, or injectable forms of Erythromycin, indicating a variety of API manufacturers with different preparations/methodologies necessary
Gentamicin	10	March 2001-2003, November 2001-June 2003, September 2010-April 2015, September 2010-September 2011, April 2016-November 2017, April 2018-June 2020, January 2020-December 2020, February 2021-April 2023, September 2021-July 2022, April 2022-May 2023	6557	Some indications are still in shortage and shortage data is approximated for purposes of study
Isoniazid	7	May 2001-June 2001, January 2009-August 2010, December 2012-January 2015, June 2013-August 2013, November 2013-	1739	Lengthiest shortages last between 2009-2015 with other shortages relatively short by comparison. One indication is still short as of

		December 2013, October 2014-December 2014, September 2022-May 2023		April 2023 with expected resolution in May 2023.
Meropenem	10	March 2002-March 2002, September 2002-September 2003, September 2004-August 2005, December 2005-April 2006, October 2012-June 2013, March 2012-June 2012, July 2013-August 2014, December 2014-February 2015, August 2015-April 2016, September 2018-September 2020	2551	Supply and demand problems seemed to preface manufacturer delays and "unknown" reasons for delay.
Nitrofurantoin oral suspension	1	June 2018-April 2023	1771	Shortage is ongoing and length of time is an estimate. Cause for shortage listed as "business decisions"
Penicillin G benzathine	9	November 2002-April 2005, January 2007-November 2007, November 2013-June 2014, March 2016-December 2017, September 2016-May 2018, April 2016-January 2019, January 2020-June 2020, April 2022-April 2023, July 2022-December 2022	4326	Some indications are still in shortage and shortage data is approximated for purposes of study. Three shortages marked during Covid years, likely as increased demand called for treatment of secondary infections. However, the lengthiest shortages occurred prior to 2020.

Piperacillin or Piperacillin/Tazobactam	7	May 2001-December 2003, August 2001-March 2004, October 2005-Novmber 2006, January 2005-August 2005, July 2010-May 2011, March 2011-March 2011, May 2013-September 2020	5494	Piperacillin/tazobactam went short initially May 2001, three months later the Piperacillin formulation on its own went short in August 2001. Both remained in shortage for about 2.5 years each. Piperacillin remained stable in future Piperacillin/tazobactam shortages in the years that followed indicating potential support/separate API manufacturers for Piperacillin compared to the combination drug. (Tazobactam on its own did not experience a shortage on its own, or in other combination therapies that it was a part of during these shortages).
Rifampin	8	December 2007-May 2008, December 2009-January 2010, December 2010-July 2012, March 2013-August 2014, September 2015-November 2015, December 2021-April 2023, February 2021-May 2021, March 2022-October 2022	2189	Delays range from a few months to 1-2 years, there are relatively consistent yearly shortages through 2007-2015 with no shortages from 2016-2020. Afterwards, lengthy delays were reported and are still occurring as of April 2023.
Sulfacetamide ophthalmic ointment	6	December 2006, August 2012, June 2013-August 2014, August 2016-January 2017, November 2019-April 2023, December 2022-April 2023	1989	In December 2006 and August 2012 two indications of this formulation discontinued their lines creating shortages in the market that were not intended to be immediately resolved. By 2013, extended shortages began to affect the market of more than one year. At time of data collection, two indications were still short.
Tobramycin	6	March 2002-November 2003, January 2003-March 2004, August 2009-May 2010, May 2010-June	5215	Various indications of Tobramycin were in shortage for increasingly long durations. This calculation includes oral suspension, injection, powders, and ophthalmic solutions to highlight

		2019, August 2018-April 2019; March 2020-April 2021		how the longevity and broad span of this drug's shortage crossed multiple fields and time frames. Reason given for almost all indications was "manufacturing problems" with only the ophthalmic indication stating "unknown" reason for shortage
Vancomycin	4	February 2002-March 2002, August 2002-September 2003, August 2005-August 2006, February 2009-April 2023	5936	The longest shortage has reported an "unknown" reason for its delay, where others site business decisions and manufacturing delays. The longest shortage is still short at time of reporting in April 2023. These dates include both injectable and oral capsule formulations

Appendix 5: Additional clarity and clarification of Dr. Fox's shortage data indicating the presence of generic drugs and the status of their shortage lifespan.

Generic name	Brand names	Method/Quantity	CURRENTLY Marketed EML Appropriate Form/Dosage	Discontinued Marketing of EML Appropriate Form/Dosage	Known Shortages	Dates of Shortage
amikacin	Amikin	Injection: 250 mg/mL (as sulfate) in 2 mL vial.	Emcure Pharmaceuticals (2013), Fresenius Kabi LLC (2015), Hikma Pharmaceuticals USA Inc (1992), Sagent Pharmaceuticals (2016) Teva Pharmaceuticals (1993)	Abbott Laboratories (1994-?), Abbot Laboratories Hosp Products Div (1994-?) Hospira Inc (1993-?), Igi Laboratories Inc (1995-?)	1	January 2009-April 2017
amoxicillin	Larotid, Polymox, Trimox, Dispermox, Moxatag, Amoxil	Powder for injection: 250 mg; 500 mg; 1 g (as sodium) in vial. Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (as trihydrate) [c]. Solid oral dosage form: 250 mg; 500 mg; 1g (as trihydrate).	Aurobindo (2005), Chartwell Life Molecules LLC (1982), Dava Pharmaceuticals Inc (1988), Hikma Pharmaceuticals (2006), Micro Labs LTD (June 2022), Sandoz (1994), Teva Pharmaceuticals USA Inc (1982), US Antibiotics LLC (1982), Wockhardt Bio AG (2007),	Apothecon Inc Div Bristol Myers Squibb (1982-?), Chartwell RX Sciences LLC (1982-?), GlaxoSmithKline (1982-?), Laboratorios Atral Sarl (1985-?), Mylan Pharmaceuticals (1982-?), Parke Davis Div Warner Lambert Co (1982-?), Strides Pharma Global PTE Ltd (1988-?), Sun Pharmaceutical industries ltd (1999-?), US Antibiotics LLC (1985-?), Wyeth Ayerst Laboratories (1982-?)	2	January 2011-June 2011, November 2014-August 2015,

amoxicillin + clavulanic acid	Amoxicillin and Clavulanate Potassium, Augmentin	Powder for injection: 500 mg (as sodium) + 100 mg (as potassium salt); 1000 mg (as sodium) + 200 mg (as potassium salt) in vial. Powder for oral liquid: 125 mg (as trihydrate) + 31.25 mg (as potassium salt)/5 mL; 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c]. Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt); 875 mg (as trihydrate) + 125 mg (as potassium salt).	Aurobindo Pharma Ltd (2011), Hikma Pharmaceuticals (2005), Micro Labs Ltd India (2016), Sandoz Inc (2002), Teva Pharmaceuticals USA Inc (2002),	Apotex Inc (2008-?), Sun Pharmaceutical (2002-?), US Antibiotics LLC (1984-?)	5	November 2015-March 2016, August 2015-August 2018, February 2016-December 2016, November 2022-April 2023, October 2022-April 2023

ampicillin	Omnipen-N, Penbritin-S, Polycillin-N, Totacillin-N,	Powder for injection: 500 mg; 1 g (as sodium) in vial.	Antibiotice SA (2009), Eugia Pharma Specialities Ltd (2010), HQ Speciality Pharma Corp (1993), Istituto Biochimico Italiano Spa (1987), Mylan Laboratories Ltd (2014), Sagent Pharmaceuticals Inc (2015), Sandoz Inc (1982),	ACS Dobfar SPA (2013-?), Apothecon Inc Div Bristol Myers Squibb (1988-?), Bristol Laboratories Inc Div Bristol Myers Co (1982-?), Consolidated Pharmaceutical Group Inc (1982-?), Eli Lilly and co (1985-?), GlaxoSmithKline (1982-?), Hikma Pharmaceuticals Usa Inc (1986-?), Hospira Inc (2015-?), Watson Laboratories Inc (1988-?), Wyeth Ayerst Laboratories (1982-?)	9	October 2002-June 2004, November 2005-January 2007, October 2007-January 2008, September 2009-February 2010, June 2011-April 2023, June 2014-April 2015, December 2015-March 2017, October 2017-February 2018, February 2017-October 2017

benzathine benzylpenicillin (Penicillin G Benzathine)	Bicillin-C-R, Bicillin L-A,	Powder for injection: 1.2 million IU (≈ 900 mg) in vial [c]; 2.4 million IU (≈ 1.8 g) in vial.	**No Manufacturers Of Requisite Strength/Form**	**No Manufacturers Of Requisite Strength/Form**	4	April 2005-July 2007, April 2005-October 2007, March 2016-December 2017, September 2016-2018,
benzylpenicillin (Penicillin G)	Pfizerpen, Pentids	Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial.	ACS Dobfar Spa (2018), HQ Specialty Pharma Corp (2009), Istituto Biochimico Italiano Spa (2009), Pfizer Laboratories Div Pfizer Inc (1982), Sandoz inc (2001),	Apothecon Sub Bristol Myers Squibb Co (1982-?), Bristol Myers Squibb Spa (1982-?), Consolidated Pharmaceutical Group Inc (1982-?), Eli Lilly and Co (1982-?), John D Copanos and co Inc (1982-?), Parke Davis Div Warner Lambert Co (1982-?), Pharmacia and Upjohn Co (1982-?), Purepac Pharmaceutical CO (1982-?), Watson Laboratories Inc (1988-?)	5	November 2013-June 2014, November 2002-April 2005, January 2020-June 2020, January 2007-November 2007, April 2016-January 2019,
cefalexin (Cephalexin)	Keflex	Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL (anhydrous). Solid oral dosage form:	Alkem Laboratories Ltd (2010), Aurobindo Pharma Ltd (2005), Belcher Pharmaceuticals LLC (1988), Chartwell Rx	Apothecon Inc Div Bristol Myers Squibb (1988-?), Barr Laboratories Inc (1987-?), Eli Lilly and co (1987-?), Facta Farmacuetica Spa (1982-?),		

		250 mg; 500 mg (as monohydrate).	Sciences LLC (2005), Hikma Pharmaceuticals (2006), Lupin Ltd (2005), Orchid Healthcare (2005), Teva Pharmaceuticals USA Inc (1987), Yung Shin Pharmaceutical Industrial Co Ltd (2007),	Hikma Pharmaceuticals (2009-?), Ivax Pharmaceuticals Inc Sub Teva Pharmaceuticals USA (1982-?), Jerome Stevens Pharmaceuticals Inc (1988-?), Pragma Pharmaceuticals LLC (1982-?), Purepac Pharmaceutical Co (1987-?), Ranbaxy Laboratories Ltd (2003-?), Sun Pharmaceutical Industries Ltd (1987-?), Vitarine Pharmaceuticals Inc (1987-?), Yoshitomi Pharmaceutical Industries Ltd (1988-?)		
cefazolin{a}	Ancef, Kefzol	Powder for injection: 1 g (as sodium salt) in vial. a > 1 month.	ACS Dobfar Spa (1982), B Bruan Medical inc (2000), Hikma Farmaceutica Portugal Lda (1988), Qilu Pharmaceutical Co ltd (2015), Sandoz Inc (1988),	Abraxis Pharmaceutical Products (1986-?), Aurobindo Pharma Ltd (2008-?), Bedford Laboratories Div Ben Venue Laboratories Inc (1988-?), Cephazone Pharma LLC (2009-?), Dr Reddys Laboratories ltd (1989-?), Eli Lilly and Co (1985-?), Facta Farmaceutici Spa (1991-?), Fresenius Kabi USA LLC (1998-?), GlaxoSmithKline (1982-?), Hospira Inc (2005-?), Steri Pharma LLC (1991-?), Teva Pharmaceuticals USA (1989-?)	2	April 2012-April 2016, April 2018-April 2023,

chloramphenicol	Chloromycetin	Capsule: 250 mg. Oily suspension for injection*: 0.5 g/mL (as sodium succinate) in 2 mL ampoule. *Only for the presumptive treatment of epidemic meningitis in children older than 2 years and in adults. Oral liquid: 150 mg/5 mL (as palmitate). Powder for injection: 1 g (sodium succinate) in vial.	Fresenius Kabi (1982)	Angus Chemical Co (1982-?), Gruppo Lepetit SPA SUB Merrell DOW Pharmaceuticals Inc (1982-?), Parkedale Pharmaceuticals Inc (1982-?)	1	December 2013-June 2016
clindamycin	Cleocin Phosphate	Capsule: 150 mg (as hydrochloride). Injection: 150 mg/mL (as phosphate); 600 mg/4 mL (as phosphate); 900 mg/6 mL (as phosphate). Oral liquid: 75 mg/5 mL (as palmitate) [c].	Abraxis Pharmaceutical Products (1988), Almaject Inc (1987), Baxter Healthcare Corp (1989), Fresenius Kabi USA LLC (2007), Hikma Pharmaceuticals USA Inc (1987), Micro Labs Ltd (2018), Pfizer Inc (1982), Sagent Pharmaceuticals Inc (2011)	Bedford Laboratories Div Ben Venue Laboratories Inc (1994-?), Bristol Myers Squibb Pharma Co (1989-?), IGI Laboratories Inc (1989-?), Loch Pharmaceuticals Inc (1988-?), Marsam Pharmaceuticals LLC (1988-?), Pharmacia and Upjohn Co (1982-?), Rising Pharma Holding Inc (2017-?), Solopak Laboratories Inc (1988-?), Teva Parental	2	June 2010-July 2011, August 2012-April 2023,

				Medicines Inc (1989-?), Watson Laboratories Inc (1988-?)		
cloxacillin []	Cloxapen	Capsule: 500 mg; 1 g (as sodium). Powder for injection: 500 mg (as sodium) in vial. Powder for oral liquid: 125 mg/5 mL (as sodium) *cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration due to better bioavailability.	**DISCONTINUED BY ALL**	Apothecon Inc Div Bristol Myers Squibb (1982-?), GlaxoSmithKline (1982-?), Teva Pharmaceuticals USA Inc (1982)	1	July 2003: Discontinued

doxycycline {a}	Oracea, Vibramycin	Oral liquid: 25 mg/5 mL [c]; 50 mg/5 mL (anhydrous) [c]. Powder for injection: 100 mg in vial. Solid oral dosage form: 50 mg [c]; 100 mg (as hyclate). a Use in children <8 years only for life-threatening infections when no alternative exists.	Acella Pharmaceuticals LLC (2020), Actavis Elizabeth LLC (2011), Actavis Laboratories FL Inc (1982), Alembic Pharmaceuticals Ltd (2017), Amneal Pharmaceutical Holdings GMBH (2016), Cadila Healthcare ltd (2017), Carbie Holdings Cayman Co LTD DBA Puracap Caribe (1982), Changzhou Pharmaceutical Factory (2019), Chartwell RX Sciences LLC (1989), Chartwell Scheduled LLC (1984), Cosette Pharmaceuticals Inc (2015), Fresenius Kabi USA LLC (1983), Heritage Pharmaceuticals Inc DBA Avet Pharmaceuticals Inc (2011), Hikma International Pharmaceuticals LLC (1984), Lannet Co Inc (2005), Lupin Ltd (2013), Mayne Pharma International PTY LTD (1985), Mayne Pharma Inc (2017), Mylan Laboratories LTD (2012), Novel Laboratories Inc (2017), Par Sterile Products LLC (Dec 2022), Pfizer	Ajanta Pharma LTD (2018-?) Amici Pharmaceuticals LLC (2021), Amneal EU Ltd (Oct 2022-?), Appco Pharma LLC (2006-?), Bausch Health US LLC (2005-?), Chartwell Pharma NDA B2 Holdings (2018-?), Emcure Pharmaceuticals LTD (2018), Galderma Laboratories LP (2001-?), Halsey Drug Co Inc (1985-?), Heather Drug Co Inc (1983-?), Heritage Pharma Labs Inc (2005-?), Hikma Pharmaceuticals USA Inc (1983-?), IMPAX Laboratories inc (2010-?), Interpharm Inc (1988-?), Mutual Pharmaceutical Co Inc (1982-?), Mylan Pharmaceuticals Inc (1983-?), Nesher Pharmaceuticals USA LLC (2021-?), Nosrum Laboratories Inc (2020-?), Praxgen Pharmaceuticals LLC (March 2022-?), Par Pharmaceutical inc (1983-?), Pliva Inc (1992-?), Private Formulations Inc (1986-?), Rachelle Laboratories Inc (1982-?), Ranbaxy Pharmaceuticals Inc (1983-?),	9	June 2008-December 2008, June 2009-August 2012, November 2012-May 2015, July 2013-January 2014, August 2014-January 2015, March 2016-July 2016, July 2017-May 2018, March 2019-December 2020, October 2019-April 2023

			Laboratories Div Pfizer Inc (1982), Prinston Pharmaceutical Inc (2016), Strides Pharma Global Pte Ltd (1982), Sun Pharmaceutical Industries Ltd (1986), West-Ward Pharmaceuticals International LTD (1989), Zydus Pharmaceuticals USA Inc (2016)	Rising Pharma Holding Inc (2010-?) Sandoz Inc (2000), Superpharm Corp (1984-?), Teva Pharmaceuticals USA Inc (1984-?), Warner Chilcott bermuda LTD (1985-?), Warner Chilcott Div Warner Lambert Co (1985-?), Watson Laboratories Inc (1982-?), Zhejiang Yongtai Pharmaceutical CO Ltd (2020-?),		

gentamicin	Apogen	Injection: 10 mg/mL (as sulfate); 40 mg/mL (as sulfate) in 2 mL vial.	Baxter Healthcare Corp (1982), Hospira Inc (1983), Fresenius Kabi USA LLC (1982),	B Braun medical Inc (1987-?),Bristol Laboratories inc Div Bristol Myers Co (1982-?), Hikma Pharmaceuticals USA Inc (1982-?), Hospira Inc (1986-?), International Medication Systems Ltd (1982-?), Kalapharm Inc (1982-?), King Pharmaceuticals Inc (1982-?), Pharmaceutical Specialist Assoc (1983-?), Pharmacia and Upjohn Co (1982-?), Pharmafair Inc (1985-?), Shering Corp Sub Schering Plough Corp (1982-?), Solopak Laboratories Inc (1985-?), Teva Parenteral Medicines inc (1991-?), Watson Laboratories Inc (1982-?), Wyeth Ayerst Laboratories (1982-?),	10	March 2001-2003, November 2001-June 2003, September 2010-April 2015, September 2010-September 2011, April 2016-November 2017, April 2018-June 2020, January 2020-December 2020, February 2021-April 2023, September 2021-July 2022, April 2022-May 2023

metronidazole	Flagyl, Metromidol, Protostat, Satric, Metro I.V.	Injection: 500 mg in 100 mL vial. Oral liquid: 200 mg/5 mL (as benzoate). Suppository: 500 mg; 1 g. Tablet: 200 mg to 500 mg.	Alembic Labs LLC (2017), Alembic Pharmaceuticals LTD (2009) , Amici Pharmaceuticals LLC (1986), Aurobindo Pharma LTD (2015), B Braun Medical Inc (1983), Baxter healthcare Corp (1982), Cadila Healthcare LTD (2016), Flamingo Pharmaceuticals LTD (2016), Gland Pharma Ltd (2020), Heritage Pharmaceuticals Inc (2015), Hospira (1983), Inforlife SA (2019), Lupin LTD (2017), Pfizer Inc (1982), Pliva Inc (1984), Strides Pharma Global PTE Ltd (1985), Teva Pharmaceuticals USA Inc (1984), Unichem Laboratories LTD (2014), Watson Laboratories Inc (1984),	Abbot Laboratories Pharmaceutical Products Division (1983-?), Abraxis Pharmaceutical Products (1984-?), Able Laboratories Inc (2003-?), Chartwell Molecules LLC (1983-?), Fosun Pharma USA Inc (1982-?), Halsey Drug Co Inc (1985-?), Hikma Pharmacueticals USA Inc (1984-?), International Medication Systems Ltd (1985-?), Ivax Pharmaceuticals Inc Sub Teva Pharmaceuticals USA (1982-?), Laboratorios Aplicaciones Farmaceuticas SA DE CV (1996-?), LNK International Inc (1984-?), Mutual Pharmaceutical Co Inc (1983-?), Ortho McNeil Pharmaceutical Inc (1983-?), Rising Pharma Holding Inc (2017), Savage Laboratories Inc Div Altana Inc (1985-?), Superpharm Corp (1984-?),		

nitrofurantoin	Furadantin, Furalan,	Oral liquid: 25 mg/5 mL [c]. Tablet: 100 mg.	Actavis Mid Atlantic LLC (2016), Casper Pharma LLC (1982), Nostrum Laboratories Inc (2013), Novel Laboratories Inc (2014),	Amneal Pharmaceuticals (2011-?), Elkins Sinn Div Ah Robins Co Inc (1982-?), Ivax Pharmaceuticals Inc Sub Teva Pharmaceuticals USA (1982-?), Lannett Co, Inc (1982-?), Proctor and Gamble Pharmaceuticals Inc, Sub Procter and Gamble Co (1982-?), Sandoz (1982-), Watson Laboratories Inc (1982-?), Whiteworth Towne Paulsen Inc (1982-?),	3	March 2006-November 2006, March 2019-December 2019, June 2018-April 2023
phenomethylpenicillin	Penicillin V, Beepen-VK, Pen-VEE K, Penapar-VK	Powder for oral liquid: 250 mg/5 mL (as potassium). Tablet: 250 mg; 500 mg (as potassium).	Aurobindo Pharma Ltd (2008), Hikma Pharmaceuticals (2013), Sandoz Inc (1995), Strides Pharma Global PTE LTD (1988), Teva Pharmaceuticals USA Inc (1982),	Apothecon Inc Div Bristol Myers Squibb (1982-?), Apothecon Sub Bristol Myers Squibb Co (1982-?), Belcher Pharmaceuticals Inc (1982-?), Bristol Laboratories Inc Div Bristol Myers Co (1982-?), Eli Lilly and Co (1982-?), GlaxoSmithKline (1982-?), Ivax Pharmaceuticals Inc Sub Teva Pharmaceuticals USA (1982-?), Lederle Laboratories Div American Cynamid Co (1982-?), Mylan Pharmacueticals Inc (1982-?), Parke Davis Div Warner Lambert Co (1982-?), Pfizer Laboratories Div Pfizer Inc (1982-?), Pharmacia and		

				Upjohn Co (1982-?), Pureac Pharmaceutical Co (1982-?), Wyeth Ayerst Laboratories (1982-?),		
procaine benzylpenicillin	Penicillin G Procaine	Powder for injection: 1 g (=1 million IU); 3 g (=3 million IU) in vial. *Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.	**No Manufacturers Of Requisite Strength/Form**	**No Manufacturers Of Requisite Strength/Form**		

spectinomycin	Trobicin	Powder for injection: 2 g (as hydrochloride) in vial.	**No Manufacturers Of Requisite Strength/Form**	Pfizer Inc (1982-?)	2	June 2001/July 2005: Discontinued
sulfamethoxazole + trimethoprim	Bactrim, Septra, Cotrim	Injection: 80 mg + 16 mg/mL in 5 mL ampoule; 80 mg + 16 mg/mL in 10 mL ampoule. Oral liquid: 200 mg + 40 mg/5 mL. Tablet: 100 mg + 20 mg; 400 mg + 80 mg; 800 mg + 160 mg.	Akorn Operating Co LLC (1997), Amneal Pharmaceuticals NY LLC (2005), Aurobindo Pharma LTD (2010), Chartwell Molecules LLC (2007), Glenmark Generics Ltd (2010), Lannett Co Inc (2007), Monarch Pharmaceuticals LLC (1982), Mylan Laboratories Ltd (2017), Novitium Pharma LLC (Feb 2022), Pharmaceutical Associates Inc (1983), Prasco LLC DBA Prasco Laboratories (2006), Somerset Therapeutics LLC (2019), Sun Pharmaceutical Industries Inc (1982), Teva Pharmaceuticals USA (1991), Vista Pharmaceuticals Inc (2005),	Abraxis Pharmaceutical Products (1987-?), Alpharma US Pharmaceuticals Division (1988-?) Ani Pharmaceuticals Inc (1987-?), Bedford Laboratories div Ben Venue Laboratories Inc (1992-?), Fosun Pharma USA Inc (1982-?), Heather Drug Co Inc (1984-?), Heritage Pharma Labs Inc DBA Aveet Pharmaceuticals Lab Inc (1987-?), Hikma Pharmaceuticals USA Inc (1987-?), Hospira Inc (1992-?), Interpharm inc (1987-?), Lupin Ltd (2021-?), Martec USA LLC (1988-?), Mutual Pharmaceutical Co Inc (1984-?), Naska Pharmacal Co Inc Div Rugby Darby Group Cosmetics (1988-?), Novel Laboratories Inc (1985-?), Pliva Inc (1985-?), Roxane Laboratories Inc (1991-?), Shionogi USA Inc (1987-?), Superpharm Corp (1985-?),	6	September 2003-January 2004, April 2009-January 2010, February 2010-March 2010, April 2010-April 2014, June 2014-October 2014, June 2014-October 2014, February 2018-October 2020

				Teva Pharmaceuticals USA Inc (1983-?), USL Pharma Inc (1985-?), Watson Laboratories Inc (1983-?),		
trimethoprim	Proloprim, Trimpex	Tablet: 100 mg; 200 mg. Oral liquid: 50 mg/5 mL [c].	Mayne Pharma LLC (1982), Novel Laboratories Inc (2011), Novitium Pharma LLC (Oct 2022), Watson Laboratories Inc (1985),	Hoffman La Roche Inc (1982-?) Monarch Pharmaceuticals Inc (1982- ?), Sun Pharmaceuticals Industries Inc (1986- ?), TVA Pharmaceuticals USA Inc (1987- ?)	1	January-April 2007 (discontinued)
Watch Group Antibiotics						

azithromycin	Azithromycin	Capsule: 250 mg; 500 mg (anhydrous). Oral liquid: 200 mg/5 mL.	ACI Healthcare Ltd (2022), Alembic Pharmaceuticals Ltd (2020), Amneal Pharmaceuticals LLC (2018), Aurobindo Pharma Ltd (2018), Bionpharma Inc (2018), Chartwell RX Sciences LLC (2008), CSPC OUYI Pharmaceutical Co Ltd (2019), Epic Pharma LLC (2018), Pfizer Chemicals div Pfizer Inc (1995), Pfizer Inc (1996), Pliva Inc (2005), Sun Pharmaceutical Industries Ltd (2013), Thea Pharma Inc (2007), Lupin Ltd (2015), Sandoz (2005), Sunshine Lake Pharma CO Ltd (2018), Yung Shin Pharmaceutical Industrial Co Ltd (2020), Teva Pharmaceuticals USA Inc (2005), Zydus Worldwide DMCC (2018),	Apotex Corp (2011-?), Mylan ASI LLC (2007-?), Pfizer Pharmaceuticals Inc (1998-?) Rising Pharma Holding Inc (2017-?), Taro Pharmaceutical Industries Ltd (2019-?), Teva Parenteral Medicines Inc (2006-?),	10	January 2004-April 2004, October 2009-August 2010, March 2010-March 2010, February 2011-June 2012, December 2012-August 2015, January 2018-June 2021, April 2018- June 2018, November 2022-April 2023, January 2022-July 2022, December 2022-April 2023

cefixime	Suprax	Powder for oral liquid: 100 mg/5 mL [c]. Solid oral dosage form: 200 mg; 400 mg (as trihydrate).	Alkem Laboratories Ltd (2018), Aurobindo Pharma Ltd (2015), Belcher Pharmacueticals LLC (2017), Lupin Ltd (2012),	Lederle Laboratories Div American Cyanamid Co (1989), Lupin Pharmaceuticals Inc, Sandoz Inc (2017),	(shortages in 2022)	
cefotaxime		Powder for injection: 250 mg (as sodium) in vial. *3rd generation cephalosporin of choice for use in hospitalized neonates.	**No Manufacturers Of Requisite Strength/Form**	**No Manufacturers Of Requisite Strength/Form**	3	May 2005-June 2001, January 2008-March 2012, September 2012-April 2023
ceftriaxone {a}	Rocephin	Powder for injection: 250 mg; 1 g; 2 g (as sodium) in vial. *Do not administer with calcium and avoid in infants with hyperbilirubinaemia. a > 41 weeks corrected gestational age.	ACS Dobfar Spa (2008), Akorn Operating Co LLC (2008), Astral Steritech PVT LTD (2018), B Braun Medical Inc (2005), Hikma Farmaceutica (Portugal) SA (2008), Qilu Pharmaceutical CO LTD (2016), Sandoz Inc (2005), Wockhardt Ltd (2006),	Aurobindo Pharma Ltd (2008-?), Bedford Laboratories Div Ben Venue Laboratories Inc (2008-?), Cephazone Pharma LLC (2007-?), Facta Farmaceutici Spa (2007), Fresenius Kabi USA LLC (2006-?), Hoffmann La Roche Inc (1984-?), Hospira Inc (2005-?), Lupin Ltd (2003-?), Teva Pharmaceuticals USA Inc (2006-?),	1	February 2014-November 2019
cefuroxime		Powder for injection: 250 mg; 750 mg; 1.5 g (as sodium) in vial.	ACS Dobfar Spa (1997-?), B Braun Medical Inc (2001), Hikma Farmaceutica Portugal LDA (2004), PAI Holdings LLC DBA	Fresenius Kabi USA LLC (2001-?), Hospira Inc (2008-?), Watson Laboratories Inc (1993-?),	3	November 2012-September 2015, February

			Pharmaceutical Associates Inc (1983),			2016-May 2016, October 2016-June 2020
ciprofloxacin	Cipro, Proquin XR	Oral liquid: 250 mg/5 mL (anhydrous) [c]. Solution for IV infusion: 2 mg/mL (as hyclate) [c]. Solid oral dosage form: 250 mg; 500 mg (as hydrochloride).	Aurobindo Pharma Ltd (2007-), Bayer (1987-), Carlsbad Technology Inc (2004-), Chatrwell Life Molecules LLC (2004-), Dr Reddys Laboraotires Ltd (2004-), Hikma Pharmaceuticals (2004-), Ivax Phamaceuticals Inc Sub Teva Pharmaceuticals USA (2004-), Laboratoriees A Div of 500 JB Chemicals andPharmaceuticals Ltd Unique Pharmaceutical (2004-), Rising Pharma Holding Inc (2004-), Taro Pharmaceutical Industries Ltd (2004-), Watson Laboratories (2004-), Yiling Pharmaceuticals Inc (2018-),	Aiping Pharmaceutical Inc (2004-), Amneal Pharmaceuticals LLC (2005-), Barr Laboratories (2004-), Depomed Inc (2005-), Hikma Farmaceutica (Portugal) SA (2008-), Mylan Pharmacueticals Inc (2004-), Nostrum Laboratories Inc (2004-), Pliva Inc (2005-), Sun Pharmaceutical Industries Ltd (2004-), Teva Pharmaceuticals (2004-),	9	October 2001-November 2001, February 2003-March 2004, October 2009-August 2015, May 2010-August 2015, July 2011-August 2011, October 2015-November 2019, March 0218-April 2023, February 2018-

						August 2019, December 2021-April 2023
clarithromycin [+] Therapeutic alternatives: - erythromycin* *as second choice treatment for pharyngitis in children (EMLc only)		Powder for oral liquid: 125 mg/5 mL; 250 mg/5 mL. Powder for injection: 500 mg in vial. Solid oral dosage form: 500 mg. †clarithromycin is also listed for use in combination regimens for eradication of H. pylori in adults.	Actavis Laboratories FL Inc (2004-), Alembic Pharmaceuticals LTD (2022-) Aurobindo Pharma LTD (2012-), Chartwelle life Molecules LLC (2007-), Hec Pharm USA INC (2015-), Mayne Pharma LLC (2005-), Sandoz Inc (2005-), Sunshine Lake Pharma Co Ltd (2018), Strides Pharma Global PTE LTD (2013-), Teva Pharmaceuticals USA Inc (2005-),	AbbVie Inc (1991-), Ajanta Pharma Ltd (2019-), Hikma Pharmaceuticals USA Inc (2004-), Ivax Pharmaceuticals Inc Sub Teva Pharmaceuticals USA (2005-), Lupin Ltd (2015-), Mylan Pharmaceuticals Inc (2005-), Nostrum Laboratories Inc (2016-), Ranbaxy Laboratories Ltd (2005-), Sun Pharmaceutical Industries Ltd (2007), Wockhardt Ltd (2006-),	6	April 2009-January 2010, April 2010-April 2014, February 2010-March 2010, June 2014-October 2014, June 2014-October 2014, February 2018-October 2020

piperacillin + tazobactam		Powder for injection: 2 g (as sodium) + 250 mg (as sodium); 4 g (as sodium) + 500 mg (as sodium) in vial.	Astral Steritech PVT Ltd (2019-), Eugia Pharma Specialities LTD (2011-), Fresenius Kabi USA LLC (2018-), Instituto Biochimico Italiano SPA (2011-), Proverpharm SAS (2017-), Qilu Pharmaceutical Co LTD (2018-), Sagent Pharmaceuticals Inc (2021-), Steriscience PTE LTD (2014-), Sandoz Inc (2010-), Wockhardt Bio AG (2017-),	Hospira Inc (2009-), Wyeth Pharmaceuticals Inc (1985-)	7	May 2001-December 2003, August 2001-March 2004, October 2005-Novmber 2006, January 2005-August 2005, July 2010-May 2011, March 2011-March 2011, May 2013-September 2020
vancomycin		Capsule: 125 mg; 250 mg (as hydrochloride).	Akorn Operating Co LLC (2012), Ani Pharmaceuticals Inc (1986-), Lupin LTD (2015-), Orient Pharma co LTD (2019-), Strides Pharma Global PTE LTD (2012-), Watson Laboratories Inc (2012-),	Fresenius Kabi USA LLC (2012-)	4	February 2002-March 2002, August 2002-September 2003,

						August 2005-August 2006, February 2009-April 2023
Complementary List						
ceftazidime		Powder for injection: 250 mg; 1 g (as pentahydrate) in vial.	ACS Dobfar SPA (1985-), Hospira Inc (1986-), Pai Holdings LLC DBA Pharmaceutical Associates Inc (1985-),	B Braun Medical Inc (2011-), Eli Lilly and Co (1985-), GlaxoSmithKline (1990-), Wockhardt Ltd (2008-),	2	August 2003-October 2003, November 2011-April 2023
meropenem {a} [] Therapeutic alternatives *: - imipenem + cilastatin *complicated intraabdominal infections and high-risk febrile neutropenia only. Meropenem		Powder for injection: 500 mg (as trihydrate); 1 g (as trihydrate) in vial. a > 3 months.	ACS Dobfar Spa (2011-), Amneal Pharmacueticals (2016-), Brooks Steriscience Ltd (2022-), Daewoong Pharmaceutical Co Ltd (2015-), Eugia Pharma Specialities Litd (2017-), Gland Pharma Ltd (2016), HQ Specialty Pharma Corp (2019-), Pfizer Inc (1996-), Savior Lifetec Corp (2016),	Hospira Inc (2010-), Sandoz (2011-),	10	March 2002-March 2002, September 2002-September 2003, September 2004-August 2005, December 2005-April 2006, October 2012-June

is the preferred choice for acute bacterial meningitis in neonates.						2013, March 2012-June 2012, July 2013-August 2014, December 2014-February 2015, August 2015-April 2016, September 2018-September 2020
vancomycin		Powder for injection: 250 mg; 500 mg; 1 g (as hydrochloride) in vial.	Aspiro Pharma LTD (2022-), Baxter Healthcare Corp (1999-), Eugia Pharma Specialities LTD (2016-), Fresenius Kabi USA LLC (1987-), Gland Pharma LTD (2016-), Hainan Poly Pharmaceutical Co LTD (2019-), Hikma Farmaceutica Portugal SA (2020-), Hospira Inc (1988-), Meitheal Pharmaceuticals LLC (2022-), Mylan Laboratories Ltd (2018-),	Ani Pharmaceuticals Inc (1982-), Avet Lifesciences Ltd (2013-), Hikma Pharmaceuticals USA LTC (1986-), Knack Pharmaceuticals Inc (2022-), Pharmacia and Upjohn CO (1988-), Sandoz Inc (2010-), Steriscience Pte LTD (1982-), Teva Pharmaceuticals USA (2015-) Wellia Pharmaceuticals APS (2015-),	4	February 2002-March 2002, August 2002-September 2003, August 2005-August 2006, February

			Pharmaceutical Associates Inc (2008-), Xellia Pharmaceuticals APS (2015-),			2009-April 2023
Reserve Group Antibiotics						
Complementary List						
cefiderocol		Powder for injection: 1 g (as sulfate toxylate) in vial.	Shionogi Inc (2019-)			
ceftazidime + avibactam		Powder for injection: 2 g + 0.5 g in vial.	Allergan Sales LLC (2015-)		2	July 2016-January 2017, February 2020-July 2021
colistin		Powder for injection: 1 million IU (as colistemethate sodium) in vial.				

fosfomycin		Powder for injection: 2 g; 4 g (as sodium) in vial.				
linezolid		Injection for intravenous administration: 2 mg/mL in 300 mL bag. Powder for oral liquid: 100 mg/5 mL. Tablet: 400 mg; 600 mg.	Alkem Laboratories Ltd (2015-), Celltrion Inc (2019-), Eugia Pharma Specialities Ltd (2016-), Fresenius Kabi USA LLC (2016-), Glenmark Pharmacueitcals SA (2015-), Hetero Labs Ltd Unit V (2015-), Hikma Pharmaceuticals Internatoinal LTd (2022-), Hikma Pharmaceuticals USA Inc (2015), Hospira Inc (2015-), HQ Specialty Pharma Corp (2017-), Mylan Laboraotries Ltd (2017-), Nang Kuang Pharmaceutical Co LTD (2016-), Pfizer Inc (2000-), Sandoz Inc (2015-), Sagent Pharmaceuticals Inc (2017-), Zydus Pharmaceuticals USA Inc (2017-),	Amneal Pharmaceuticals (2015-), Gate Pharmaceuticals (2016-), Rising Pharma Holdings Inc (2015-), Teva Pharmaceuticals USA (2012-),	2	November 2005-January 2006, April 2014-May 2014
meropenem + vaborbactam	Vabomere	Powder for injection: 1 g (as trihydrate) + 1 g in vial.	Rempex Pharmacueticals Inc A Wholly Owned Sub of Melinta Therapeutics LLC (2017-),			
plazomicin	Zemdri	Injection: 500 mg/10 mL.	Cipla USA Inc (2018-),			

polymyxin B	Aerosporin	Powder for injection: 500,000 IU in vial.	Eugia Pharma Specialities LTD (2016-), Fresenius Kabi USA LLC (2008-), Gland Pharma LTD (2016-), Xellia Pharmacueticals APS (2014-), Xgen Pharmacueticals DJB Inc (1994-),	GlaxoSmithKline (1982-), Hikma Pharmaceuticals USA Inc (1982-), Rising Pharma Holding Inc (2011-),		
Anti-Tuberculosis Medications						
ethambutol		Oral liquid: 25 mg/mL [c]. Tablet: 100 mg; 400 mg (hydrochloride). Tablet (dispersible): 100 mg [c]	Sti Pharma LLC (1982-), Akorn Operating Co LLC (1999-), Lupin Ltd (2009-),	Barr Laboratories Inc (2001-)	2	December 2012-January 2016, May 2020-May 2022
ethambutol + isoniazid + pyrazinamide + rifampicin		Tablet: 275 mg + 75 mg + 400 mg + 150 mg.	**NO COMBINATION CURRENTLY IN CIRCULATOIN**			
ethambutol + isoniazid + rifampicin		Tablet: 275 mg + 75 mg + 150 mg.	**NO COMBINATION CURRENTLY IN CIRCULATOIN**			

Isoniazid	I.N.H.	Oral liquid: 50 mg/5 mL [c]. Tablet: 100 mg; 300 mg. Tablet (dispersible): 100 mg [c].	Barr Laboratories Inc (1982-), CMP Pharma Inc (1983-), Mikart LLC (1997-), Sandoz Inc (2005-), Thepharmanetwork LLC (2014-),	Bristol Myers Squibb Co (1982-), Chartwell Molecular Holdings LLC (1982-), Chatwell RX Sciences LLC (1997-), Dow Pharmaceutical corp Sub Dow chemical co (1982-), Duramed Pharmaceuticals Inc Sub Barr Laboratories Inc (1983-), Eli Lilly and co (1982-), Epic Pharma LLC (1982-), Everylife (1982-), Halsey Drug Co Inc (1982-), Hikma International Pharmaceuticals LLC (2005-) Hoffman La Roche Inc (1982-), Impax Laboratories Inc (1982-), Ivax Pharmaceuticals Inc Sub Teva Pharmacueticals USA (1982-), L Perrigo Co (1982-), Lannett Co Inc (1986-), Medpointe Pharmacueticals Medpointe Healthcare Inc (1982-), MK Laboratories Inc (1982-), Nexgen Pharma Inc (1982-), Novartis Pharmacueticals Corp (1982-), Panray Cor Sub Ormont Drug and Chemical Co Inc (1982-), Pharmavite Pharmaceuticals (1982-), Phoenix Laboratories Inc	7	May 2001-June 2001, January 2009-August 2010, December 2012-January 2015, June 2013-August 2013, November 2013-December 2013, October 2014-December 2014, September 2022-May 2023

				(1982-), Purepac Pharmaceutical Co (1982-), Sun Pharmaceutical industries Inc (1982-), Watson Laboratories Inc (1982-), Whiteworth Towne Paulsen Inc (1982-),		
isoniazid + pyrazinamide + rifampicin	Rifater	Tablet (dispersible) : 50 mg + 150 mg + 75 mg [c].	**NO COMBINATION CURRENTLY IN CIRCULATOIN**	Sanofi Aventis US LLC (1994-),		
isoniazid + rifampicin	Rifampin and Isoniazid	Tablet: 75 mg + 150 mg; 150 mg + 300 mg. Tablet (dispersible): 50 mg + 75 mg [c].	**NO COMBINATION CURRENTLY IN CIRCULATOIN**	Sanofi Aventis US LLC (1994-), Hikma International Pharmaceuticals LLC (2005-),		
isoniazid + rifapentine		Tablet (scored): 300 mg + 300 mg.	**NO COMBINATION CURRENTLY IN CIRCULATOIN**	**NO COMBINATION EVER SOLD**		
moxifloxacin	Avelox, Vigamox	Tablet: 400 mg.	Aurobindo Pharma LTD (2014-), Crossmedika SA (2016-), Dr Reddys Laboratories Ltd (2014-), MSN Laboratories Private LTD (2017-), Novel Laboratories Inc (2017-),	Bayer Healthcare Pharmaceuticals Inc (1999-), Mylan Pharmaceuticals Inc (2015), Torrent Pharmaceuticals LTD (2014-), Sunshine Lake Pharma Co Ltd (2018-)	5	January 2012-February 2012, January 2015-May 2015,

			Teva Pharmaceuticals USA (2014-),			October 2017-September 2018, June 2019-December 2020
Pyrazinamide	Aldinamide	Oral liquid: 30 mg/mL [c]. Tablet: 400 mg; 500 mg Tablet (dispersible): 150 mg.	Novitum Pharma (1971), Akorn Operating Co LLC (1992), Macleods Pharms Ltd (2020),	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**		
Rifabutin	Mycobutin	Solid oral dosage form: 150 mg.* *For use only in patients with HIV receiving protease inhibitors.	Pfizer (1992), Lupin Ltd (2014), Novitum Pharma (2021),	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	1	March 2005-June 2005
Rifampicin (Rifampin in US)	Rifadin, Rimactane	Oral liquid: 20 mg/mL [c]. Solid oral dosage form: 150 mg; 300 mg.	Chartwell Molecular Holdings LLC (2008-), Epic Pharma Inc (1997-), Lupin Pharms ltd (2013), Oxford Pharms (1971), Sandoz (1997),	Watson Pharmaceuticals Inc an Indirect Wholly owned sub of Teva Pharmaceuticals USA Inc (2016-)	8	December 2007-May 2008, December 2009-January 2010, December 2010-July 2012, March 2013-August 2014,

						September 2015-November 2015, December 2021-April 2023, February 2021-May 2021, March 2022-October 2022
Rifapentine	Priftin	Tablet: 150 mg; 300 mg.	Sanofi Aventus US (1998)	**NOT CURRENTLY DISCONTINUED BY ANY COMPANY**	3	August 2011-August 2011, February 2020-September 2020, November 2021-April 2023
Anti-Tuberculosis Medications: Complementary List						
amikacin		Injection: 100 mg/2 mL (as sulfate) in 2 mL vial; 250 mg/mL (as sulfate) in 2 mL vial.	Avet Lifesciences LTD (2013-), Fresenius Kabi USA LLC (2015-), Hikma Pharmacueticals USA Inc (1992-), Sagent	Abbot Laboratories (1994-), Abbot Laboratories Hosp Products Div (1994-), Apothecon Inc Div Bristol Myers Squibb (1982-),	1	January 2009-April 2017

			Pharmacueticals INC (2016-), Teva Pharmaceuticals USA (1993-),	Hospira Inc (1994-), Igi Laboratories Inc (1995-),		
amoxicillin + clavulanic acid*	Augmentin	Powder for oral liquid: 250 mg (as trihydrate) + 62.5 mg (as potassium salt)/5mL [c]. Tablet: 500 mg (as trihydrate) + 125 mg (as potassium salt). *For use only in combination with meropenem or imipenem+cilastatin.	Aurobindo Pharma LTD (2012-), Micro Labs Ltd India (2016-), US Antibiotics LLC (1984-), Sandoz Inc (2002-), Wockhardt Bio Ag (2008-),	Apotex Inc (2009-), Sun Pharmaceutical Industries Ltd (2002-),	5	November 2015-March 2016, August 2015-August 2018, February 2016-December 2016, November 2022-April 2023, October 2022-April 2023
bedaquiline {a}		Tablet: 20 mg [c]; 100 mg. {A} ≥ 5 years	Janssen Therapeutics div Janssen Products LP (2012-),	**Not currently discontinued by any manufacturer**		
clofazimine		Solid oral dosage form: 50 mg; 100 mg.	**Not currently produced by any manufacturer**	Novartis Pharmaceutical Corp (1986-2005)	1	April 2005 (Discontinued)

o cycloserine Therapeutic alternatives: - terizidone		Solid oral dosage form: 125 mg [c]; 250 mg.	Cerovene Inc (1982-),	**Not currently discontinued by any manufacturer**		
delamanid {a}		Tablet (dispersible): 25 mg [c]. {A} ≥ 3 years Tablet: 50 mg. {a} ≥ 6 years	**Not yet approved by FDA**	**Not yet approved by FDA**		
o ethionamide Therapeutic alternatives: - protionamide		Tablet : 125 mg ; 250 mg. Tablet (dispersible) : 125 mg [c].	Wyeth Pharmaceuticals LLC (1982-),	**Not currently discontinued by any manufacturer**	1	January 2005-March 2005
levofloxacin	Levaqiun	Tablet: 250mg; 500 mg; 750 mg. Tablet (dispersible): 100 mg [c].	Apotex Inc (2011), Aurobindo Pharma Limited (2012-), Cadila Health care Ltd (2012-), Celltrion Inc (2011), Chartwell Molecular Holdings LLC (2012-), Dr Reddys Laboratories Inc (2011-), Glenmark Generics Ltd (2011), Hec Pharm USA (2019-), Inc Hetero Labs Ltd unit V (2015), Lupin Ltd (2011-), Macleods Pharmaceuticals Ltd (2012-), Orbion Pharmaceuticals Private Ltd (2012-), Sandoz Inc (2011-), Teva	Janssen Pharmaceuticals Inc (1996-), Jubilant Generics Ltd (2015-), Mylan Pharmaceuticals Inc (2011-), Torrent pharmaceuticals Limited (2011-), Watson Laboratories (2013-),	4	February 2008-April 2008, July 2011-October 2012, July 2014-September 2015, March 2018-March 2018

			Pharmaceuticals USA Inc (2011-),			
linezolid		Powder for oral liquid: 100 mg/5 mL. Tablet : 600 mg. Tablet (dispersible) : 150 mg [c].	Alkem Laboratories Ltd (2015-), Celltrion Inc (2019), Glenmark Phamaceuticals SA (2015), Hetero Labs Ltd Unit V (2015-), Hikma Pharmaceuticals USA Inc (2015-), Novel Laboratories Inc (2016-), Pfizer Inc (2000-), Zydus Pharmaceuticals USA Inc (2017-),	Amneal Pharmaceuticals (2015-), Gate Pharmaceuticals (2016-), Rising Pharma Holdings Inc (2015), Teva Pharmaceuticals USA (2012-),	2	November 2005-January 2006, April 2014-May 2014
o meropenem Therapeutic alternatives: - imipenem + cilastatin		Powder for injection: 500 mg (as trihydrate); 1 g (as trihydrate) in vial.	ACS Dobfar Spa (2011-), Amneal Pharmaceuticals (2016-), Brooks Steriscience Ltd (2022), Daewoong Pharmaceutical Co Ltd (2015-), Eugia Pharma Specialities Ltd (2017-), Gland Pharma Ltd (2016-), Pfizer (1996-), HQ Specialty Pharma Corp (2019-), Savior Lifetec Corp (2016-),	Hospira Inc (2010-), Sandoz Inc (2011-),	10	March 2002-March 2002, September 2002-September 2003, September 2004-August 2005, December 2005-April

						2006, October 2012-June 2013, March 2012-June 2012, July 2013-August 2014, December 2014-February 2015, August 2015-April 2016, September 2018-September 2020
moxifloxacin		Tablet : 400 mg. Tablet (dispersible) : 100 mg [c].	Aurobindo Pharma Ltd (2014-), Crossmedika SA (2016-), Dr Reddys Laboratories Ltd (2014-), MSN Laboratories Private LTD (2017-), Novel Laboratories Inc (2017-), Teva Pharmaceuticals USA (2014-),	Bayer Healthcare Pharmaceuticals Inc (1999-), Mylan Pharmaceuticals Inc (2015-), Sunshine Lake Pharma Co Ltd (2018-), Torrent Pharmaceuticals Ltd (2014-),	5	January 2012-February 2012, January 2015-May 2015, October 2017-September 2018, June

						2019-December 2020
p-aminosalicylic acid		Granules: 4 g in sachet.	Eurocept Pharmaceuticals (1994)	**Not currently discontinued by any manufacturer**		
streptomycin [c]		Powder for injection: 1 g (as sulfate) in vial.	Pharmacueticals DJB Inc (1998-)	Pfizer Laboratories Div Pfizer Inc (1982-), Eli Lilly and Co (1982-),	1	September 2011-November 2011

Appendix 6: Preliminary Analysis of New Zealand Supply Chain Frailty

Name of Manufacturer	Number of Sponsors Utilizing Manufacturer	# of Unique Forms. Produced	Number of Ingre.	Specific Ingredients	Specific Ingre.	Specific Ingre.	Specific Ingre.	Specific Ingre.
Sandoz GmbH (Austria)	6	18	5	Amoxicillin	Amoxicillin/ Clavulanic Acid	Phenoxy-methyl-penicillin	Benzathine benzylpenicillin	Benzylpenicillin
Qilu Antibiotics Pharmaceutical Co Ltd No. 849 (China)	1	11	4	Cefazolin	Ceftazidime	Cefuroxime	Ceftriaxone	
Quimica Sintetica SA (Spain)	5	13	3	Ciprofloxacin	Fosfomycin	Chloramphenicol		
Sandoz Industrial Products SA (Spain)	4	12	3	Amoxicillin	Amoxicillin/Clavulanic Acid	Piperacillin + Tazobactam		
Shandong Anxin Pharmaceutical Co Ltd No 849 (China)	4	3	3	Piperacillin + Tazobactam	Ceftolozane + Tazobactam	Amikacin		
ACS Dobfar SpA Viale (Italy)	2	6	2	Cefotaxime	Avibactam + Ceftazidime			
Bayer AG (Germany)	2	3	2	Ciprofloxacin	Moxifloxacin			
Centrient Pharmaceuticals India Private Limited (India)	3	10	2	Amoxicillin	Amoxicillin/Clavulanic Acid			
Deretil SA (Spain)	2	5	2	Amoxicillin	Amoxicillin/Clavulanic Acid			
DSM Anti-Infectives AB (Sweden)	2	5	2	Amoxicillin/Clavulanic Acid	Phenoxymethylpenicillin			

Appendix 7: List of Interviews

Richard Laing: 11 November 2022

Jonathan Quick: 11 November 2022

Hans Hogerzeil: 2 February 2023

Erin Fox: 31 March 2023

Anil Koul: 13 April 2023

Kathleen Holloway: 20 April 2023

Martijn Van Gerven: 23 August 2023

Mel Spigelman: 21 December 2023

Anonymous Expert: 2 February 2024

Mike Dunne: 2 February 2024

John Rex: 1 March 2024

Ruxandra Draghia-Akli: 11 March 2024

Kevin Outterson: 12 April 2024

Expert Witness: 17 April 2024

James Love: 23 April 2024

James Love: 24 April 2024

James Love: 30 April 2024

James Anderson: 9 May 2024

- Résumé en Français-

Une infrastructure en plein effritement :

La problématique de la stabilité de l'accès aux anciens et aux nouveaux antibiotiques

En 2019, l'anthropologue médicale Clare Chandler publie un article dans *Palgrave Communications* dans lequel elle décrit les antibiotiques comme une forme d'infrastructure systémique qui soutient la société[1050]. Grâce aux antibiotiques, tout, de l'intoxication alimentaire aux cancers en passant par les amputations, peut être traité de façon optimale. Ils soutiennent, sous de multiples formes, l'ossature de l'ordre mondial actuel et constituent une composante nécessaire de notre société. Comme l'écrit Chandler, « tout en conservant l'aura mystique et le caractère désirable que leur confère leur puissance… les antimicrobiens [sont] considérés [comme] essentiels à la vie humaine, l'accès à ces médicaments étant d'ailleurs enchâssé dans les soins de santé primaires dans la déclaration d'Alma-Ata signée par 134 pays en 1978.[1051] » Sans ces médicaments, l'ensemble des soins de santé primaires est menacé. Certaines personnes vivent déjà cette réalité aujourd'hui. Pour d'autres, il s'agit d'un avenir qui se rapproche à grande vitesse.

Cependant, on ne peut considérer comme une infrastructure quelque chose qui fonctionne de façon isolée. Dans ses travaux, la sociologue américaine Susan Leigh Star distingue neuf composantes clés constitutives d'une infrastructure : l'intégration, la transparence, la portée, l'apprentissage à travers l'appartenance, les liens avec les conventions de pratique, l'intégration de normes, la construction sur une base préexistante, le fait qu'elles deviennent visibles lorsqu'elles connaissent une défaillance, et qu'elles ne puissent être remises en état que par de petites actions graduelles (pas d'un seul coup ou de

[1050] Clare I. R. Chandler, « Current Accounts of Antimicrobial Resistance: Stabilisation, Individualisation and Antibiotics as Infrastructure », *Palgrave Communications* 5, n°1 (May 21, 2019) : 1-13. https://doi.org/10.1057/s41599-019-0263-4.

[1051] Chandler, « Current Accounts of Antimicrobial Resistance », 9.

façon globale)[1052]. Pour que les antibiotiques jouent le rôle d'infrastructure sanitaire, ils doivent être eux-mêmes soutenus *par* une infrastructure. On retrouve ici à la fois la notion d'intégration et le fait d'être construit sur une base préexistante. Notre thèse soutient que pour que les antibiotiques remplissent cette fonction, ils doivent reposer sur une infrastructure conçue pour favoriser l'accès aux antibiotiques. Si l'antibiotique est inaccessible (en raison de son coût ou parce qu'il n'est pas disponible), il ne peut pas remplir, dans les faits, sa fonction de pilier des soins de santé dans le monde.

Bien qu'il existe incontestablement de nombreuses structures de soutien facilitant l'accès aux antibiotiques, cette thèse n'en analyse en détail que trois : la section Antibactériens de la liste modèle OMS des médicaments dits essentiels, le « pipeline » de développement des antibiotiques et la chaîne d'approvisionnement des antibiotiques. Chacune de ces structures soutient l'accessibilité aux antibiotiques d'une façon différente et chacune a connu des changements importants entre les années 1970 et 2023. Pour les analyser, cette thèse s'inscrit dans le cadre des travaux en philosophie et sociologie des sciences et technologie (*Science and Technology Studies*, STS) tels ceux de Bruno Latour, Mark Thomas Young, Susan Leigh Star, Jérôme Denis et David Pontille. Elle détaille la façon dont l'histoire de la liste modèle OMS, du pipeline et de la chaîne d'approvisionnement révèle un besoin profond de maintenance prolongée et continue de l'infrastructure. Un défaut de maintenance pourrait entraîner la faillite de l'infrastructure antibiotique décrite par Chandler et avoir des effets sanitaires néfastes, la non-accessibilité des médicaments mettant à mal la fiabilité des soins de santé mondiaux.

Il est rarement question de maintenance dans la littérature des STS et la philosophie des sciences. Avec des précurseurs dans les années 1970, ce champ a pris de l'essor à partir des années 2000. Néanmoins, personne n'a encore étudié de façon approfondie la

[1052] Susan Leigh Star, « The Ethnography of Infrastructure », *American Behavioral Scientist* 43, n°3 (1999) : 381-82, https://doi.org/10.1177/00027649921955326.

maintenance des médicaments ni celle de leur développement et de leur accessibilité. En revanche, ce sujet semble être largement abordé dans le secteur de l'ingénierie, des constructions technologiques (comme les motos ou les ordinateurs) et d'autres aspects pratiques de ce type[1053]. Les pipelines, en l'occurrence les oléoducs ou les gazoducs, bénéficient d'une attention similaire, particulièrement sur le moment et la manière d'entreprendre les réparations et sur la meilleure façon d'optimiser les ventes lorsque les opérations de maintenance retardent le service[1054]. Par ailleurs, les sociologues français Jérôme Denis et David Pontille ont récemment souligné le caractère indispensable des infrastructures[1055] et le fait que quand on étudie leur construction, il est indispensable d'envisager les modalités de leur maintenance en continu.

Bruno Latour, philosophe, anthropologue et sociologue français, attire l'attention sur ce qui est indispensable à la société dans *Pandora's Hope,* le livre qu'il a publié en 1999. Dans cet ouvrage*,* il emploie le terme *blackboxing* pour identifier une sorte de cécité spatiale qui règne lorsque la technologie fonctionne efficacement. Il prend comme exemple la situation d'un conférencier en train de se servir d'un projecteur. Tant que le projecteur fonctionne, personne ne le remarque vraiment et personne ne s'interroge sur sa finalité parce qu'il fait ce pour quoi il a été conçu. En revanche, si ce projecteur cesse de fonctionner en plein milieu de la conférence, soudain, son existence même attire l'attention[1056]. De la même

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[1053] Parmi les travaux qui traitent spécifiquement de la philosophie de la maintenance, citons :
Stephen Graham et Nigel Thrift, « Out of Order: Understanding Repair and Maintenance », *Theory, Culture & Society* 24, n° 3 (2007) : 1-25, https://doi.org/10.1177/0263276407075954.
Mark Thomas Young et Mark Coecklebergh, dir., *Maintenance and Philosophy of Technology: Keeping Things Going,* Routledge Studies in Contemporary Philosophy, (New York, United States: Taylor & Francis Group, 2024).
Mark Thomas Young, « Maintenance », *in The Routledge Handbook of the Philosophy of Engineering*, Diane P. Michelfelder et Neelke Doorn, dir., 356–68, Routledge Handbooks in Philosophy (New York, United States *: Taylor & Francis, 2021).
[1054] P.K. Dey, « Decision Support System for Inspection and Maintenance: A Case Study of Oil Pipelines », *IEEE Transactions on Engineering Management* 51, n° 1 (2004) : 47-56, https://doi.org/10.1109/TEM.2003.822464.
[1055] Jérôme Denis et David Pontille, *Le Soin des Choses : Politiques de la Maintenance* (Paris : La Découverte, 2022) 54.
[1056] Bruno Latour, *Pandora's Hope: Essays on the Reality of Science Studies* (Cambridge, Massachusetts: Harvard University Press, 1999) : 183.

façon, l'infrastructure antibiotique est souvent enfermée dans une boîte noire. Tant que l'accès aux antibiotiques est efficace, ils sont capables de répondre aux besoins sanitaires mondiaux sans susciter la moindre question ni le moindre commentaire. Mais une fois que des parties de cette infrastructure commencent à se fragmenter ou à connaître des défaillances (par exemple, quand la résistance aux antimicrobiens augmente plus vite que la production de nouveaux antibiotiques, quand des initiatives de financement tournent court ou que la chaîne d'approvisionnement est perturbée), l'infrastructure elle-même devient plus apparente que jamais. La panique et l'inquiétude suscitées par la possibilité d'une ère post-antibiotique soulignent à quel point cette boîte noire était indispensable au départ[1057].

Dans son ouvrage de 2020, Mark Thomas Young, philosophe des techniques à l'université de Vienne, attire l'attention sur ce point dans un chapitre consacré à ce qui fait de la maintenance une composante d'une infrastructure invisible[1058]. Young utilise le concept de la boîte noire de Latour pour montrer combien « les aspects importants des processus scientifiques et technologiques sont opaques et doivent donc être rendus visibles avant de pouvoir être soumis à une analyse critique ». Il développe également la réflexion de Star sur la transparence en soulignant que pour qu'une chose soit une infrastructure, elle *doit* se soustraire à notre attention[1059]. Elle est nécessaire et indispensable, mais invisible. De ce fait, sa maintenance est souvent plus difficile à mettre en œuvre. Néanmoins, toute infrastructure doit obéir à ce principe étant donné que ce qu'elle *produit* (en l'occurrence, l'accès à des

[1057] Pour de plus amples informations sur l'éventualité d'une ère post-antibiotique, veuillez consulter :
Kristofer Hansson et Adam Brenthel, « Imagining a Post-Antibiotic Era: A Cultural Analysis of Crisis and Antibiotic Resistance », *Medical Humanities* 48, n°3 (2022) : 381– 88. https://doi.org/10.1136/medhum-2022-012409.
Dominik Koesling et Claudia Bozzaro, « The Post-antibiotic Era: An Existentiel Threat for Humanity », *Intergenerational Justice Review*, August 31, 2023, Vol. 8 n° 2 (2022): Existential and unknown risks for future generations (II), https://doi.org/10.24357/IGJR.8.2.1230.
Sara Reardon. « WHO Warns against 'Post-Antibiotic' Era », *Nature*, April 30, 2014, https://doi.org/10.1038/nature.2014.15135.
[1058] Mark Thomas Young, « Now You See It (Now You Don't): Users, Maintainers and the Invisibility of Infrastructure », in *Technology and the City. Philosophy of Engineering and Technology*, M. Nagenborg, T. Stone, M. González Woge et P.E. Vermaas (dir.), 36: 101–19, Religion and Philosophy, (Springer, Cham, 2021), https://doi.org/10.1007/978-3-030-52313-8_6.
[1059] Young, « Now You See It (Now You Don't) », 102- 3.

antibiotiques efficaces) occupe nettement plus de place dans l'esprit humain que l'infrastructure qui permet cette production[1060]. Or, *il arrive* que les infrastructures tombent en panne. Ce ne sont pas des entités éternelles, il faut s'en occuper quand elles connaissent des défaillances.

Pour suivre ces défaillances de l'infrastructure ou les zones nécessitant une maintenance ciblée, notre thèse se concentre principalement sur la période 1977-2023. Cette tranche contemporaine de l'histoire des antibiotiques marque une période de changement et de transition unique au sein de l'industrie pharmaceutique, en particulier parce qu'elle met en évidence un fossé de plus en plus profond entre les pratiques de soins de santé dans les pays à revenu élevé et dans ceux dont le revenu est faible à intermédiaire. On a beaucoup écrit sur la pratique pharmaceutique, l'histoire des antibiotiques et les grands scientifiques impliqués dans la création de cette histoire avant 1980. Cette thèse se réfère notamment aux travaux de Scott Podolsky[1061], Robert Bud[1062], Vivian Quirke[1063] et Claas Kirchhelle[1064]. Même s'ils ne sont pas axés sur la notion d'infrastructure antibiotique, qui d'ailleurs n'existe pas encore pour les travaux relatifs à la période antérieure aux années 1970, les exemples et mécanismes qu'ils retracent nous permettent à notre tour de décrire comment es antibiotiques sont devenus une infrastructure. Bien que ce ne soit pas l'objet de cette thèse, le travail de Kirchhelle en particulier dépasse le domaine de la santé humaine. Il s'intéresse à l'utilisation des antibiotiques en santé animale et au fait qu'il s'agisse également d'une branche de l'infrastructure favorisant la santé et le bien-être au niveau global. Ainsi, le but des chapitres

[1060] Young, « Now You See It (Now You Don't) », 103- 4.
[1061] Scott Podolsky*, The Antibiotic Era: Reform, Resistance, and the Pursuit of Rational Therapeutics, (*Baltimore: John Hopkins University, 2015).
[1062] Robert Bud, *Penicillin: Triumph and Tragedy*. (Oxford, United Kingdom: Oxford University Press, 2007).
[1063] Viviane M. Quirke, « Penicillin (The History) », in *Van Nostrand's Scientific Encyclopedia*, Glenn D. Considine (dir.), 1re éd. (Hoboken, United States: Wiley, 2007), https ://doi.org/10.1002/9780471743989.vse10080.
[1064] Claas Kirchhelle, *Pyrrhic Progress: The History of Antibiotics in Anglo-American Food Production*, New Jersey: Rutgers University Press, 2020.

analytiques de cette thèse est de comprendre comment ces éléments se recoupent, de se fonder sur eux puis de mettre en évidence la façon dont cette infrastructure est actuellement en place.

Le chapitre 1 de notre thèse s'intitule *Historiographie des antibiotiques, le pipeline, aspects financiers et accès.* Il s'intéresse à l'état du développement et de la production des antibiotiques depuis 1980. À cette époque, l'industrie pharmaceutique avait commencé à évoluer vers un modèle économique caractérisé par une financiarisation accrue dans l'intention de générer des profits, tout en détournant progressivement l'attention générale d'un produit qui, à un moment donné, avait changé la donne et fait figure de miracle. Après l'âge d'or du développement des antibiotiques dans les années 1950 et 1960, on a observé un déclin progressif de leur innovation tout au long des années 1970, ce qui a finalement conduit à une pénurie à partir des années 1980[1065] [1066]. D'un point de vue purement pratique, ce déclin est tout à fait compréhensible. Les antibiotiques sont des médicaments très efficaces, et après l'expiration du monopole des brevets sur les nouveaux antibiotiques, il est devenu plus difficile et plus aléatoire pour les entreprises de fabriquer des produits supérieurs à des médicaments génériques toujours très performants[1067].

En même temps que cet âge d'or s'achevait, les années 1960 et 1970 ont favorisé la montée du capitalisme néolibéral et de la suprématie des actionnaires[1068]. La priorité n'était pas de créer quelque chose simplement pour le bien de la société mais plutôt de veiller à ce

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[1065] Søren Brøgger Christensen, « Drugs That Changed Society: History and Current Status of the Early Antibiotics: Salvarsan, Sulfonamides, and β-Lactams », *Molecules* 26, n°19 (October 7, 2021): 3. https://doi.org/10.3390/molecules26196057.
[1066] Julian Davies, « Where Have All the Antibiotics Gone? » *The Canadian Journal of Infectious Diseases & Medical Microbiology* 17, n°5 (2006): 287. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2095086/.
[1067] Jeremy A. Greene, *Prescribing by Numbers: Drugs and the Definition of Disease* (Baltimore, United States: The Johns Hopkins University Press, 2007), 1-2.
[1068] Mariana Mazzucato, *The Value of Everything: Making and Taking in the Global Economy* (Northwood, United Kingdom: Penguin Allen Lane, 2018).
Edward Nik-Khah, « Neoliberal Pharmaceutical Science and the Chicago School of Economics », *Sage Publications, Ltd.* 44, n°4 (August 2014): 489– 517. https://www.jstor.oerg/stable/43284157.
Lynn A. Stout, « The Toxic Side Effects of Shareholder Primacy », *The University of Pennsylvania Law Review* 161, n°7 (June 2013) : 2006.

que les investisseurs obtiennent un retour sur investissement satisfaisant. Les structures du marché pharmaceutique étaient en train de changer pour s'adapter à ces théories néolibérales qui devenaient dominantes à un moment où les économies mondiales connaissaient les premières crises. Pour les laboratoires pharmaceutiques, le profit devenait aussi important que la recherche et le développement de médicaments. Jean-Paul Gaudillière et Kaushik Sunder Rajan ont affirmé dans un article récent que *la santé* était en fait devenue un concept abstrait à partir duquel on pouvait potentiellement « cultiver » de la valeur [1069]. En substance, les situations de mauvaise santé sont si étroitement liées aux notions d'« accès aux médicaments » et de « consommation » de ces derniers qu'en l'absence de médicaments, le concept de soins de santé n'a plus de sens[1070].

En raison de l'émergence dans les années 1980 de l'environnement économique instable qui a vu certains pays faire faillite et a conduit à l'intervention de la Banque mondiale dans la gestion de leur dette, de son allégement et des pratiques de prêt, d'énormes disparités dans les infrastructures de soins de santé et l'accessibilité aux médicaments sont apparues entre les pays à revenu élevé et ceux qui ont un revenu faible à intermédiaire[1071]. De ce fait, les années 1980 ont marqué le début d'un clivage important entre la croissance des entreprises d'une part, et une baisse tangible de l'intérêt pour les antibiotiques au sein de ces entreprises d'autre part. C'est le début de l'effritement de l'infrastructure dans le sens où les médicaments et leurs effets toujours nécessaires ont commencé à devenir moins accessibles, moins disponibles, et par suite, moins utiles pour les patients. En conséquence, c'était un point de départ idéal pour nos recherches à venir.

[1069] Jean-Paul Gaudillière et Kaushik Sunder Rajan, « Making Valuable Health: Pharmaceuticals, Global Capital and Alternative Political Economies », *BioSocieties* 16, n°3 (September 2021): 313. https://doi.org/10.1057/s41292-021-00247-3.
[1070] Gaudillière et Sunder Rajan, « Making Valuable Health: Pharmaceuticals, Global Capital and Alternative Political Economies », 313.
[1071] Packard, *A History of Global Health*, 254-259.

Pour analyser et évaluer l'histoire de cette infrastructure antibiotique et les trois piliers que nous avons identifiés comme ses composantes, cette thèse est constituée d'un chapitre historiographique et de quatre chapitres analytiques, chaque chapitre s'appuyant sur le point de vue et l'orientation du précédent. Les chapitres ne sont pas organisés chronologiquement mais de manière thématique. Cependant, ils s'imbriquent les uns dans les autres pour venir à l'appui, à la fois de notre concept analytique principal d'infrastructure antibiotique et de l'explication globale de la manière dont elle a été créée et maintenue d'une part, et de la façon dont elle a commencé à se détériorer au cours des dernières décennies, d'autre part.

La Liste des médicaments essentiels de l'OMS, un moyen de faciliter l'accès aux médicaments

Le chapitre 2, premier chapitre analytique de cette thèse, traite de l'OMS et de sa liste des médicaments essentiels. L'OMS étant l'un des principaux producteurs de données et de rapports sur la résistance aux antimicrobiens, elle était particulièrement bien placée pour présenter des recommandations pratiques sur la gestion de ces préoccupations sanitaires croissantes[1072]. Sa liste des médicaments essentiels illustre l'évolution de la réponse de l'OMS à la résistance aux antimicrobiens, ainsi que son inquiétude grandissante concernant l'accès à des médicaments efficaces. Publiée pour la première fois en 1977, elle sert d'indicateur quant aux tendances mondiales dans la lutte contre la résistance aux antimicrobiens, à l'engagement de l'OMS en faveur de l'accès aux médicaments et aux tensions croissantes auxquelles sont soumises les initiatives qui travaillent dans ce sens. Les révisions de la liste au fil du temps reflètent les défis culturels, sociopolitiques et financiers

[1072] K. Overton, N. Fortané, A. Broom, S. Raymond, C. Gradmann, E. S. F. Orubu, Scott H. Podolsky, S. R. Van Katwyk, Muhammad H. Zaman et Claas Kirchhelle. « Waves of Attention: Patterns and Themes of International Antimicrobial Resistance Reports, 1945– 2020. » BMJ Global Health 6 (2021): 4. https://doi.org/doi:10.1136/bmjgh-2021-006909.

mondiaux[1073] qui ont eu un impact sur la capacité de l'OMS à atténuer et à gérer le problème de la résistance aux antimicrobiens par l'intermédiaire d'un accès efficace aux médicaments.

Rebaptisée « liste modèle de l'OMS des médicaments essentiels » et désignée par l'acronyme LME tout au long de cette thèse, elle a été mise à jour tous les deux ans pour tenir compte des changements advenus entre chaque version. Dès le départ, l'objectif de ses concepteurs était de réagir au fait qu'on mettait au point trop de médicaments dans le monde. Pour les pays à revenus limités, une liste recensant les médicaments les plus importants devait contribuer à réduire une partie de la confusion engendrée par les pratiques de marketing des laboratoires pharmaceutiques.

La mise en place de la LME étant elle-même une innovation, elle révèle également la façon dont la santé publique – et la santé mondiale – étaient en train d'évoluer vers un processus de pharmaceuticalisation. Randal Packard remarque que cette tendance se retrouve dans plusieurs mesures de santé publique depuis les années 1970[1074]. Même si cette liste n'est pas censée être la seule intervention en matière de gestion des maladies, son existence même témoigne de la dépendance accrue de la société mondiale à des médicaments de plus en plus nombreux pour répondre à des problématiques sanitaires. Certains de ces médicaments contenaient les mêmes composés mais les conventions de dénomination compliquaient encore davantage le fait de déterminer si un médicament était bio-équivalent, bio-similaire ou entièrement distinct. En 1983, le *Pan American Sanitary Bureau* a constaté que « pour les 700 ingrédients actifs disponibles aux États-Unis, il existe environ 20 000 dénominations, soit une moyenne de 30 dénominations par produit pharmaceutique » [1075]. Ces médicaments

[1073] Comme l'Accord de l'OMC sur les aspects des droits de propriété intellectuelle qui touchent au commerce (ADPIC)
[1074] Randall M. Packard, *A History of Global Health* (Baltimore, United States: John Hopkins University Press, 2016), 207-254.
[1075] « Policies for the Production and Marketing of Essential Drugs. » Washington DC, United States: Pan American Sanitary Bureau, April 18, 1983, 14-15.
https://iris.paho.org/bitstream/handle/10665.2/6594/25835.pdf?sequence=1&isAllowed=y

faisaient l'objet d'un marketing intensif dont les messages sous-entendaient en substance que le fait de ne pas acheter le médicament le plus récent et le plus performant aurait des conséquences négatives sur la santé.

L'objet initial de la LME était donc de mettre à disposition de tous les pays une liste de médicaments à se procurer en priorité pour répondre aux besoins sanitaires de base des populations. Elle n'était pas axée sur les antibiotiques ; ces derniers ne représentaient qu'un faible pourcentage des médicaments recommandés. Cependant, en étudiant la façon dont cette liste intègre le sujet des antibiotiques, cette thèse soutient que la LME elle-même est un moyen d'assurer l'accessibilité aux antibiotiques. À ce titre, elle contribue à une infrastructure antibiotique performante. Le 2 février 2023, l'ancien directeur du Département des médicaments essentiels de l'OMS, Hans Hogerzeil, a déclaré dans un entretien que le simple fait d'ajouter un médicament à la LME contribuait à faire « baisser le prix de ce médicament », ce qui assurait un meilleur accès global à ce produit[1076]. De ce fait, il est important de suivre les effets de la liste dans ce domaine, malgré l'importance qu'y revêtent d'autres familles de médicaments.

Toutefois, nous observons ici une dichotomie unique : comme nous l'avons indiqué précédemment, la LME visait à limiter l'achat excessif de médicaments non essentiels mais elle avait aussi comme raison d'être l'amélioration de l'accès adéquat aux médicaments nécessaires et efficaces. Avec l'augmentation de la résistance aux antimicrobiens, ce besoin est devenu de plus en plus saillant. Au fil du temps, la section antibiotiques de la LME a commencé à montrer que, malgré son intention initiale de limiter les médicaments, elle avait désespérément besoin d'inclure des médicaments plus efficaces qui n'existaient pas encore. De toute évidence, l'infrastructure était menacée.

[1076] Hans Hogerzeil, entretien mené par Erin L. Paterson, 2 février 2023.

Les premiers avertissements concernant la résistance aux antimicrobiens sont apparus sur la LME en 1990 [1077]. À l'époque, il n'y avait pas de recommandations sur la façon de traiter les souches de bactéries résistantes mais un avertissement indiquait que « la prévalence croissante des souches de bactéries pathogènes courantes résistantes à des antimicrobiens largement disponibles et relativement bon marché inclus dans la liste modèle érode dangereusement leur efficacité. Il est important et urgent d'aborder en laboratoire la surveillance de la sensibilité aux antimicrobiens de façon plus systématique et coordonnée au niveau international.[1078]» Cette recommandation ne demandait pas la mise au point de nouveaux antibiotiques mais plutôt la surveillance d'une menace telle qu'elle était perçue à ce moment-là.

Les professionnels de la santé estimaient essentiellement que, malgré l'existence de la résistance, il suffirait de surveiller et promouvoir une utilisation prudente des antibiotiques pour faire face aux crises liées à la résistance aux antimicrobiens[1079]. Plus de dix ans plus tard, les modifications apportées à la LME n'ont pourtant pas résulté de l'accroissement de la résistance aux antimicrobiens mais de l'impulsion des militants de la lutte contre le VIH/SIDA. À mesure que de nouveaux médicaments contre le VIH/SIDA étaient développés, leur inclusion dans la LME a été repoussée en raison de leur prix d'achat élevé et du fait qu'ils étaient tous protégés par des brevets. L'OMS craignait qu'ils ne soient trop chers pour les pays à revenu faible et intermédiaire. Toutefois, leur exclusion de la liste a rendu l'accès à des médicaments nécessaires de plus en plus difficile pour les patients. *AIDS Coalition to*

[1077] Overton, *et al.*, « Waves of Attention », 4.
[1078] Rapport du Comité d'experts de l'OMS, « L'utilisation des médicaments essentiels », Série de rapports techniques 796, quatrième rapport du Comité d'experts de l'OMS (Genève, Suisse : Organisation mondiale de la santé, 1990), 13.
[1079] Mirza Alas Portillo, Erin L. Paterson, Nadya Wells, Frédéric Vagneron et Claas Kirchhelle, « Emerging Financial Models for Antibiotic Development (2000-2016). Witness Seminar conducted by the DryAP project and in collaboration with the Global Health Centre, Geneva Graduate Institute », Université de Strasbourg, 2024, 54, https://doi.org/10.34931/N7PK-3N88.

Unleash Power (ACT-UP), Médecins Sans Frontières (MSF) et *Health Action International* (HAI) ont fustigé cette décision et en ont réclamé une nouvelle[1080].

En 2001, l'OMS a demandé à tous ses états membres de donner leur point de vue sur la LME alors en vigueur, ainsi que sur le plan que l'organisation envisageait pour ce programme. Alors que la plupart des réponses initiales semblaient favorables à ce plan, les États-Unis ont répondu par un mémorandum de 35 pages dénonçant les suggestions de l'OMS à tous les niveaux[1081]. En 2002, l'OMS a été contrainte de modifier son plan initial en réponse à cette levée de boucliers. Parmi les deux « modifications » principales, celle qui a eu le plus d'impact a été l'obligation de fonder l'ajout ou la suppression d'un médicament de la liste non plus sur l'expérience mais sur des preuves scientifiques[1082].

Jusque-là, les comités d'experts de l'OMS sélectionnaient les médicaments en fonction des critères suivants : « efficacité, sécurité, qualité, stabilité, facilité de stockage, prix et disponibilité »[1083]. Ils étaient ensuite classés en fonction des informations à la disposition du comité d'experts, ce qui permettait de déterminer leur valeur sur la liste et leur utilité globale[1084]. Ces informations provenaient de données recueillies dans le cadre de l'utilisation du médicament et de son impact sur les communautés qui y avaient recours, mais une grande partie de ces données étaient issues du bouche-à-oreille ou simplement de l'expérience personnelle d'un membre du comité d'experts. En langage familier, on s'est mis à appeler le processus décisionnaire de la commission le GOBSAT, en anglais *Good Old Boys Sitting Around the Table*, c'est-à-dire une « bande de potes assis autour d'une table » dont l'expérience supplantait toutes les autres informations qui auraient dû être prises en

[1080] Jeremy A. Greene, « Making Medicines Essential: The Emergent Centrality of Pharmaceuticals in Global Health. » *BioSocieties* 6, n°1 (2011): 23.
[1081] Richard Liang, Brenda Waning, Andy Gray, Nathan Ford et Ellen 't Hoen, « 25 Years of the WHO Essential Medicines Lists: Progress and Challenges », *The Lancet* 361 (2003): 1724.
[1082] L'autre modification reprécisait la finalité de la section complémentaire de la LME et indiquait que les médicaments coûteux seraient ajoutés à la liste, mais qu'ils ne devraient être considérés que comme des suggestions générales dans le cas où leur prix serait prohibitif pour un pays.
[1083] « A Scoring System for Selection of Essential Drugs », *Essential Drugs Monitor*, 1990, 19.
[1084] Jonathan Quick, entretien mené par Erin L. Paterson, 11 novembre 2022.

compte et débattues[1085]. Le basculement vers la médecine fondée sur les preuves a permis de garantir que ce serait désormais des essais contrôlés randomisés et des données recueillies sur 10 000 à 20 000 cas (en tenant compte des variations d'âge et de sexe) qui fourniraient des arguments parfaitement documentés et défendables pour la LME, et non plus des observations individuelles[1086]. Désormais, l'OMS n'autoriserait plus les médicaments sur la base de l'expérience personnelle ; l'inclusion de chaque médicament sur la LME serait entièrement étayée et débattue publiquement.

Le premier antibiotique breveté à figurer sur la liste a été l'azithromycine en 2003. Initialement, son utilisation n'était suggérée que pour un traitement par dose unique dans les cas d'infection génitale à *Chlamydia trachomatis* et dans les cas de trachome[1087] mais en pratique, elle a été utilisée dans beaucoup d'autres situations. Le concept de traitement par dose unique a provoqué une augmentation des ventes et des usages dans un large éventail de cas hors indications si bien qu'en 2008, la Chine étudiait des cas de gonorrhée résistante à l'azithromycine[1088]. Dans les années qui ont suivi, d'autres antibiotiques ont été inscrits sur la LME mais cette inscription s'est accompagnée de plus de cas de résistance et de débats à ce sujet[1089] [1090].

Lors d'une dernière mise à jour de la liste en 2017, une nouvelle classification y a été ajoutée qui distingue plusieurs catégories d'antibiotiques : *Action, Watch* (surveillance) et

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[1085] Jonathan Quick, entretien mené par Erin L. Paterson, 11 novembre 2022.
Hans Hogerzeil, entretien mené par Erin L. Paterson, 2 février 2023.
[1086] Jonathan Quick, entretien mené par Erin L. Paterson, 11 novembre 2022.
[1087] Rapport du Comité d'experts de l'OMS, « La sélection et l'utilisation des médicaments essentiels », Série de rapports techniques 920, La Liste modèle des médicaments essentiels de l'OMS (Genève, Suisse : Organisation mondiale de la santé, 2003), 12.
[1088] Liu-Feng Yuan, Yue-Ping Yin, Xiu-Qin Dai, Rachel V Pearline, Magnus Unemo et Xiang-Sheng Chen, « Resistance to Azithromycin of Neisseria Gonorrhoeae From 2 Cities in China », *Sexually Transmitted Diseases* 38, n°8 (2011): 764.
[1089] Rapport du Comité d'experts de l'OMS, « La sélection et l'utilisation des médicaments essentiels », Série de rapports techniques 1035, La Liste modèle des médicaments essentiels de l'OMS (Genève, Suisse : Organisation mondiale de la santé, 2021), 684.
[1090] Rapport du Comité d'experts de l'OMS, « La sélection et l'utilisation des médicaments essentiels », Série de rapports techniques 1006, La Liste modèle des médicaments essentiels de l'OMS (Genève, Suisse : Organisation mondiale de la santé, 2017), 9.

Reserve, ce qui donne l'acronyme AWaRe (*averti* en anglais). Ce principe constituait une inversion brutale de la raison d'être initiale de la LME dans les années 1970. Au lieu de promouvoir une liste dans le but de constituer un ensemble des médicaments *les plus essentiels*, liste plus facile à appréhender qu'une série de milliers de noms, les catégories AWaRe ont redéfini le terme *essentiel* comme l'indicateur des catégories les plus nécessaires. Si les antibiotiques de la catégorie *Action* peuvent être utilisés à volonté pour traiter des infections, il ne faudrait avoir recours aux antibiotiques *Watch* que lorsqu'une résistance a été identifiée. Quant aux antibiotiques *Reserve*, il ne devraient pas être employés du tout, sauf s'il n'y a pas d'autre choix et qu'il n'y a pas d'alternative efficace.

Sur le plan de la politique et des enjeux, la LME de 2017 déclarait ouvertement que la résistance était rapidement en passe de devenir un problème, que certains médicaments – même ceux qui étaient très efficaces – ne devaient être utilisés que dans des circonstances extrêmes, et qu'il était nécessaire de disposer de *nouveaux* médicaments capables de gérer les résistances.

La LME est une composante de l'infrastructure des antibiotiques car c'est un moyen d'améliorer l'accès aux médicaments. Elle fournit aux pays et aux différents formulaires pharmaceutiques hospitaliers une liste concise des médicaments les plus importants à avoir à disposition et elle a évolué afin d'encourager l'approvisionnement en médicaments de ce type pour répondre aux besoins mondiaux. Quand un médicament entre dans la liste, il est entendu que son prix sera abaissé à un niveau abordable, en conséquence de quoi son accessibilité sera assurée. Le processus d'approbation du médicament en question dans les différents pays est également accéléré, ce qui augmente les chances qu'il devienne accessible. Considérée dans son ensemble, cette liste soutient l'infrastructure antibiotique globale en suscitant une voie d'acquisition. Cependant, en raison de la montée de la résistance aux antimicrobiens, de plus en plus de médicaments de la LME perdent leur efficacité contre les infections

bactériennes. De fait, cette composante de l'infrastructure antibiotique perd également de son efficacité parce qu'elle ne comporte pas les recommandations requises pour assurer l'accès aux médicaments nécessaires.

Le troisième chapitre de cette thèse examine comment l'appel à l'action, et plus particulièrement l'appel à la production de nouveaux médicaments, s'est construit autour d'une focalisation sur « l'assèchement du pipeline de développement des antibiotiques ». Il montre également que ce pipeline a beau être une autre composante de l'infrastructure antibiotique globale, il ne peut pas fonctionner de façon autonome.

Évaluation de l'accès aux nouveaux antibiotiques à travers la mise en œuvre de partenariats public-privé destinés à remédier à l'assèchement du pipeline de développement des antibiotiques

Entre 2000 et 2016, l'augmentation des taux de résistance aux antimicrobiens a entraîné une succession de « vagues d'attention » (selon les termes de Kristen Overton *et al.*) de la part des décideurs politiques, des développeurs et des activistes concernant les antibiotiques et leur développement[1091]. Ces vagues ont coïncidé avec plusieurs initiatives internationales visant à améliorer les performances pharmaceutiques de l'Europe face à la réussite financière du concurrent états-unien. En 2001, au moment où la LME subissait des changements structurels, les Pays-Bas ont demandé à l'OMS d'élaborer un document précisant quels médicaments – encore inexistants – devraient être mis au point[1092]. Ce rapport, publié en 2004 et intitulé *Priority Medicines for Europe and the World,* a été l'un des premiers documents majeurs de l'OMS à qualifier la résistance aux antimicrobiens de menace, mais aussi à souligner la nécessité urgente de créer de nouveaux antibiotiques et de

[1091] Overton, *et al.*, « Waves of Attention », 4.
[1092] Richard Laing, entretien mené par Erin L. Paterson, 11 novembre 2022.

réduire le niveau de résistance dans le monde entier[1093]. Rédigé par des membres du comité exécutif de la LME, il exposait pourquoi la résistance aux antimicrobiens devait être considérée comme un problème sanitaire mondial et suggérait le recours à des partenariats public-privé pour financer le développement de nouveaux antibiotiques.

Les partenariats public-privé (PPP) n'étaient plus vraiment une nouveauté alors. Plusieurs d'entre eux, cités dans le rapport, avaient été mis en place à la fin des années 1990 et au début des années 2000. Parmi les plus importants, citons *International AIDS Vaccine Initiative* (IAVI), *Medicines for Malaria Venture* (MMV) et *Malaria Vaccine Initiative*[1094]. *TB Alliance* n'a été fondée que deux ans avant la publication du rapport mais elle a également fourni un exemple fiable de partenariat public-privé. Notons cependant que *TB Alliance* se considère comme un partenariat de développement de produit (PDP), c'est-à-dire axé avant tout, comme son nom l'indique, sur le développement d'un produit au sein de son dispositif de partenariat. Les notions de PDP et PPP se recoupent, l'acronyme PPP étant souvent employé pour désigner les deux types de dispositifs, même si les PDP reposent sur une intention plus spécifique, celle de créer et de mettre sur le marché un produit concret. Quoi qu'il en soit, dans les deux cas, l'idée était que l'argent public pourrait soutenir les entreprises privées dans le développement d'un produit dont la valeur financière n'était pas forcément suffisamment élevée pour les motiver spontanément. À ce stade, tout reposait sur l'incitation financière. Les incitations de type *push and pull* sont devenues les méthodes prédominantes pour inciter les entreprises privées à travailler pour l'intérêt public.

Dans le même temps, l'Europe s'inquiétait de voir combien le marché pharmaceutique était devenu lucratif aux États-Unis par rapport aux marchés européens[1095]. L'*Innovative*

[1093] Warren Kaplan et Richard Laing, « Priority Medicines for Europe and the World », Proposal. Geneva: World Health Organization, 2004.
[1094] Kaplan et Laing, « Priority Medicines for Europe and the World », 100- 102.
[1095] EFPIA, « The Pharmaceutical in Figures » (Belgium: European Federation of Pharmaceutical Industries and Associates, 2006), 3.

Medicines Initiative (IMI) a été créée en 2008 sous l'égide de l'Union européenne pour encourager les scientifiques européens à travailler dans le secteur des produits pharmaceutiques européens et à en accroître la production[1096]. Comme la LME, l'IMI n'était pas entièrement dévolue aux antibiotiques mais sa vaste palette de projets et d'objectifs en comprenait plusieurs qui ciblaient les antibiotiques. La plupart d'entre eux n'étaient pas conçus pour développer ou finir par mettre un médicament sur le marché. Ils privilégiaient plutôt la recherche fondamentale en amont et le développement d'une bibliothèque moléculaire pour que les futurs scientifiques puissent collaborer plus efficacement.

En ce qui concerne les antibiotiques et la résistance aux antimicrobiens, neuf programmes ont été lancés. Le premier, *New Drugs for Bad Bugs* (ND4BB), a chapeauté sept de ces programmes : TRANSLOCATION, ENABLE, COMBACTE-CARE, COMBACTE-MAGNET, COMBACTE-NET, iABC et DRIVE-AB. PreDiCT-TB, la seule exception, était orienté spécifiquement vers la recherche sur la tuberculose et le développement d'**une « série d'outils que les concepteurs de médicaments [pourraient] utiliser pour augmenter leur probabilité de choisir les bons composés analogues à un médicament donné, et réussir les essais cliniques »**[1097].

Lorsque l'IMI a été renouvelée sous le nom d'IMI2 en 2014, elle s'est référée directement au *Priority Medicines Report* (dont une mise à jour avait été publiée en 2013) dans la façon dont elle structurait ses programmes visant au développement de nouveaux

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Ole J. Bjerrum, « New Safe Medicines Faster: A Proposal for a Key action into the European Union's 6th Framework Programme », *Pharmacology & Toxicology* 86, n° Supplément I (2000): 23.

[1096] Innovative Medicines Initiative, EFPIA, « The Innovative Medicines Initiative (IMI) Strategic Research Agenda: Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society », Strategic Research Agenda, Innovative Medicines Initiative, September 15, 2006.

[1097] IMI Innovative Medicines Initiative, « IMI Innovative Medicines Initiative | PreDiCT-TB | Model-Based Preclinical Development of Anti-Tuberculosis Drug Combinations », May 1, 2012, http://www.imi.europa.eu/projects-results/project-factsheets/predict-tb.

antibiotiques[1098]. L'IMI2 a hébergé le programme *AMR Accelerator* et ses neuf projets distincts consacrés à la recherche sur la résistance aux antimicrobiens[1099].

L'objectif et l'intention des deux itérations de l'IMI n'étaient pas forcément d'aboutir directement au développement d'un produit. Cependant, à partir de 2014, il est devenu de plus en plus difficile d'ignorer le fait que la résistance aux antimicrobiens nécessitait de nouveaux médicaments dans un délai proche. Les membres des départements de recherche sur les antibiotiques de l'IMI ont été chargés de conseiller et d'assister Jim O'Neill alors qu'il rassemblait ses propres données pour la publication en 2016 du rapport *Review on Antimicrobial Resistance*. Il y concluait que, cette année-là, 700 000 personnes mouraient d'infections résistantes chaque année et que ce nombre passerait probablement à 10 millions de morts par an d'ici 2050 avec, en parallèle, une perte financière potentielle estimée à 1 000 milliards de dollars américains[1100]. Pour O'Neill, il ne suffisait donc plus ni de surveiller les infections, ni d'espérer améliorer les mesures de contrôle, ni d'attirer toujours plus l'attention sur une utilisation prudente des antibiotiques.

L'année où le rapport O'Neill a été publié, deux nouveaux partenariats public-privé ont été lancés : GADRP, financé par l'OMS et MSF, et CARB-X qui bénéficie d'un financement international mais est largement soutenu par la *Biomedical Advanced Research and Development Authority* (BARDA) du gouvernement des États-Unis[1101].

Pour mieux comprendre comment ces différents groupes et organisations ont vu le jour, nous avons collaboré avec Mirza Alas Portillo, Claas Kirchhelle et Frédéric Vagernon du projet DryAP, et avec Nadya Wells du *Geneva Graduate Institute* pour animer un *witness*

[1098] Warren Kaplan, Veronika Wirtz, Aukel Mantel-Teeuwisse, Pieter Stolk et Richard Laing. « Priority Medicines for Europe and the World 2013 Update. » Geneva: World Health Organization, July 9, 2013.
[1099] Le site internet du projet propose des informations plus précises sur ces différents projets à l'adresse suivante : IMI AMR Accelerator, « AMR Accelerator Project Portfolio » (consulté le 5 avril 2024), https ://amr-accelerator.eu/amr-accelerator-project-portfolio/.
[1100] Jim O'Neill, « Tackling Drug-Resistant Infections Globally: Final Report and Recommandations », Review on Antimicrobial Resistance, Wellcome Trust and department of Health, 2016, 1.
[1101] Alas Portillo, *et al.*, « Emerging Financial Models for Antibiotic Development (2000-2016). », 56.

seminar avec des représentants de PDP/PPP, de l'OMS et de l'industrie pharmaceutique[1102]. Ce séminaire nous a permis d'analyser de façon approfondie les similitudes et les différences qui existent entre ces groupes et leurs résultats, ainsi que la façon dont ces entités ont été formées et les raisons de leur formation à un moment précis. Les discussions qui ont eu lieu entre les parties prenantes pendant ce séminaire ont révélé que la mise en place de partenariats public-privé (PPP) était un moyen de soutenir le développement des antibiotiques (et l'infrastructure dans son ensemble). La solution des PPP est à la fois un exemple de cette tentative de transformation visant à corriger et maintenir le pipeline des antibiotiques et de l'intégration possible de solutions créatives dans la maintenance de l'infrastructure elle-même. Elle s'inscrit dans la compréhension globale de la manière dont la maintenance peut être appliquée à une infrastructure qui s'effrite ou est en train de tomber en panne. Tout au long de ce séminaire de témoins, les discussions ont porté principalement sur le pipeline, sur ses liens avec les PPP et sur l'impact de ces derniers[1103]. Bien qu'il n'en ait pas été question directement, le séminaire a permis de mettre en lumière cet aspect de l'infrastructure antibiotique.

Ce que nous avons découvert et discuté au cours de ce séminaire, c'est que l'IMI, GARDP et CARB-X ont chacun des portefeuilles incroyablement différents. Le tableau ci-dessous indique leurs différences principales mais, pour résumer, l'IMI était un PPP de dimension européenne avec un large éventail de programmes individuels. Elle n'avait pas nécessairement pour objectif de mettre au point un produit mais plutôt de former un certain nombre de chercheurs afin qu'ils disposent d'une solide expérience dans le développement des antibiotiques et qu'ils soient rompus à la collaboration entre institutions et avec l'industrie pharmaceutique. Par contraste, GARDP est une organisation beaucoup plus petite

[1102] On trouvera la liste complète des différents témoins *in* Alas Portillo, *et al.*, « Emerging Financial Models for Antibiotic Development (2000-2016). », 7.
[1103] Alas Portillo, *et al.*, « Emerging Financial Models for Antibiotic Development (2000-2016). », 54, https://doi.org/10.34931/N7PK-3N88.

qui travaille activement au développement de produits. C'est le fruit d'une collaboration entre MSF et l'OMS, dans le prolongement de leur travail sur d'autres campagnes de lutte contre les maladies négligées. Comme il s'agit d'une organisation plus récente, il n'est pas surprenant qu'elle ne commercialise pas encore de médicament. Cependant, elle a commencé à soumettre ses produits pour approbation auprès des organismes réglementaires. Il est probable qu'il parvienne à commercialiser un médicament dans les années à venir.

Ainsi, GARDP a commencé à travailler à l'amélioration de l'accès aux antibiotiques à travers sa collaboration avec le laboratoire Shionogi. En effet, GARDP coopère avec Shionogi pour assurer l'accessibilité de l'un de ses médicaments, le céfidérocol. Leur engagement témoigne des intentions de l'entreprise de garantir l'accès à ses propres produits à l'avenir.

Quant à CARB-X, il n'a encore rien commercialisé, comme GARDP, mais il a servi de mécanisme de financement, ce qui a permis à plus d'une douzaine d'entreprises de passer le cap des essais cliniques de phase 1, les mettant ainsi sur la bonne voie pour réussir leurs recherches par la suite. Cette organisation aussi s'inquiète de l'accessibilité des futurs antibiotiques. L'un des financeurs et partenaires les plus importants de CARB-X est BARDA, une subdivision du *Department of Health and Human Services* américain fondée en 2006, à une époque où les États-Unis en particulier s'inquiétaient d'une potentielle menace bioterroriste et du fait que le pays ne disposerait peut-être pas de suffisamment d'antibiotiques en cas d'attaque. CARB-X a élargi sa réflexion sur la biosécurité et a demandé que tous ses accords de partenariat comprennent une clause d'accessibilité pour garantir l'accès des patients aux nouveaux antibiotiques qui seraient développés.

PPP/PDP	**Date de lancement**	**Objectifs déclarés**	**Financé par ?**	**Médicament commercialisé ?**	**Prise en compte de l'accessibilité ?**
Innovative Medicines	2008 (2013 – lancement de la	« Améliorer la santé en accélérant le	Financé conjointement par l'Union européenne (représentée par la	Non	Non

Initiative (IMI 1&2)	branche Développement, ENABLE)	développement et l'accès pour les patients à des médicaments innovants, en particulier dans les zones où les besoins médicaux ou sociaux ne sont pas satisfaits. »	Commission européenne) et l'industrie pharmaceutique européenne (représentée par l'EFPIA, la Fédération européenne des associations et industries pharmaceutiques).		
GARDP	2016	« Accélère le développement et l'accès aux traitements des infections bactériennes résistantes. »	Australie (DoH), *Bill & Melinda Gates Foundation*, Canton de Genève, EDCTP3, UE (HERA [via l'OMS]), Allemagne (BMBF et BMG), Jaman (MHLW), *Leo Model Foundation*, Luxembourg (ministère de la Santé), Médecins Sans Frontières, Pays-Bas (MOFA et VWS), Principauté de Monaco, Agence de la santé publique du Canada, *The RIGHT Foundation, South African Medical Research Council,* Suisse (SDC, SERI, FOPH), Royaume-Uni (DFID, DHSC – GAMRIF et NIHR), Wellcome.	En quelque sorte. Grâce à son partenariat avec Shionogi, le céfidérocol est maintenant disponible pour des pays qui n'auraient pas pu en disposer autrement	Oui – Partenariat avec Shionogi pour la distribution du céfidérocol
CARB-X.	2016	« Partenariat mondial à but non lucratif qui accélère la mise au point de produits antibactériens pour lutter contre les bactéries résistantes qui constituent une cause majeure de décès dans le monde. »	ASPR, BARDA, Wellcome, Allemagne (ministère fédéral de l'Éducation et de la Recherche), UK DHSC - GAMRIF, Canada, NIAD, Fondation Novo Nordisk.	Non	Oui

Tableau 1 Comparaison de trois PPP

Le mise en place de partenariats public-privé (ou de partenariats de développement de produits) pour créer les nouveaux antibiotiques nécessaires à la lutte contre la résistance aux antimicrobiens est un élément essentiel de l'infrastructure globale des antibiotiques. On doit pouvoir avoir recours à de nouveaux médicaments contre les nouveaux cas de résistance lorsque les anciens produits ont perdu leur efficacité. Cette partie de l'infrastructure, qui concerne spécifiquement le pipeline de développement des antibiotiques, considère cette filière sous l'angle de la nécessité de mettre en place des incitations financières pour réussir. Le système des PPP est une méthode qui permet d'assurer la fabrication de nouveaux médicaments mais c'est un processus lent. Cependant, lorsqu'on évalue l'infrastructure globale des antibiotiques, il apparaît clairement que les structures financières sont instables. Elles dépendent de l'intérêt de financeurs publics sans lesquels les entreprises privées refusent de se lancer directement dans la recherche et le développement de nouveaux antibiotiques. Cette incertitude et parfois une pénurie de fonds ralentissent nettement la production réelle. C'est particulièrement préoccupant parce que le retour sur investissement pour ces produits n'est pas suffisant. L'évaluation du pipeline, de sa santé financière et de son équilibre permet de clarifier la façon dont cette partie de l'infrastructure fonctionne, mais ce faisant, elle pointe également des fractures dans le potentiel de production continue de nouveaux antibiotiques à l'avenir.

Malheureusement, malgré l'avènement de plusieurs partenariats public-privé dans le secteur du développement des antibiotiques, aucun nouvel antibiotique issu de ces sociétés n'a encore reçu d'approbation réglementaire ni d'autorisation de mise sur le marché. Par conséquent, il est encore difficile de déterminer si la mise en place de la structure dans son état actuel, pour répondre aux soucis de développement des antibiotiques, est (ou sera) couronnée de succès. Le quatrième chapitre de cette thèse comble cette lacune par une étude de cas, en examinant l'action de *TB Alliance*, le partenariat public-privé consacré

spécifiquement à la recherche sur la tuberculose mis en place en 2002. Grâce à un accord conclu avec Johnson & Johnson, il s'agit du seul partenariat public-privé ayant contribué à mettre sur le marché un nouvel antibiotique : l'antituberculeux nommé bédaquiline. De toutes les bactéries, *Mycobacterium tuberculosis* est celle qui compte la plus grande population de patients présentant une résistance médicamenteuse. Leur produit aurait dû pouvoir atteindre des centaines de milliers de personnes à la fois et le cas de ce médicament constitue un bon exemple pour décrire la diversité et l'ampleur globales des problèmes de résistance.

La trajectoire médicamenteuse de la bédaquiline

Le seul PPP à avoir réussi à mettre sur le marché un nouvel antibiotique est celui qui a été conclu entre *TB Alliance* et Johnson & Johnson pour développer la bédaquiline contre la tuberculose multirésistante. L'analyse de la trajectoire et de l'impact de ce produit nous aide à mieux comprendre comment le seul candidat-médicament retenu a réussi à franchir les étapes du pipeline de recherche et développement. Elle révèle également dans quelle mesure l'infrastructure antibiotique dans son état actuel peut réellement garantir un accès concret des patients aux antibiotiques.

Les trajectoires des médicaments, ainsi que leur méthode de développement et de suivi, ont été décrites pour la première fois par Jean-Paul Gaudillière en 2005. Elles indiquent « les quatre points d'entrée dans le parcours des produits pharmaceutiques », à savoir les médicaments biologiques, la standardisation des médicaments, leur mise sur le marché réglementaire et l'expertise profane[1104]. Il suffit de prendre l'un de ces quatre angles comme point de départ pour étudier la trajectoire complète d'un médicament et son cycle de vie : d'où il est issu, où il repose actuellement, et son impact tout du long. En suivant la trajectoire médicamenteuse de la bédaquiline, on peut observer comment l'infrastructure antibiotique

[1104] Gaudillière, « Introduction: Drug Trajectories », 609-10.

destinée à développer de nouveaux médicaments au sein du pipeline est conçue et où se trouvent les sites de maintenance.

C'est Janssen, une filiale de Johnson & Johnson, qui a commencé à travailler sur la bédaquiline. Janssen a ensuite transmis ses travaux à Tibotec, une autre filiale de Johnson & Johnson, pour la suite des recherches[1105]. Tibotec n'avait aucune expérience préalable de recherches sur la tuberculose puisque ce laboratoires avait travaillé principalement sur des médicaments contre le VIH jusque-là. La molécule qu'ils ont découverte était prometteuse et est passée rapidement aux essais cliniques. Cependant, le mécanisme d'action de la bédaquiline était extraordinairement lent chez les humains par rapport aux souris de laboratoire. Lorsque le premier patient de l'essai clinique a reçu de la bédaquiline, le 6 juillet 2005, les cliniciens ont été stupéfaits de découvrir que la charge bactérienne après sept jours ne présentait qu'une amélioration minime par rapport à l'administration d'isoniazide et de rifampicine[1106]. Les chercheurs ont fini par comprendre que cela tenait à un problème de temporalité. *Mycobacterium tuberculosis* est présent dans le corps des patients dans trois états principaux : un état de réplication rapide (alpha), un état de métabolisme ralenti de moitié (bêta) et un état latent (gamma)[1107]. Par le passé, la plupart des médicaments contre la

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[1105] Johnson & Johnson, « 2004 Annual Report », (New Brunswick, United States: Johnson & Johnson, 2004), 33.
Johnson & Johnson, « Janssen Announces Expanded Collaboration with International Partnership for Microbicides for Development and Commercialization of Dapivirine for Prevention of Sexual Transmission of HIV », Media Center, May 8, 2014, https://www.jnj.com/media-center/press-releases/janssen-announces-expanded-collaboration-with-international-partnership-for-microbicides-for-development-and-commercialization-of-dapivirine-for-prevention-of-sexual-transmission-of-hiv.
Communiqué de presse de Johnson & Johnson, « Johnson & Johnson Completes Acquisition of Tibotec-Virco », News, April 18, 2002. https ://johnsonandjohnson.gcs-web.com/news-releases/news-release-details/johnson-johnson-completes-acquisition-tibotec-virco

[1106] Hui Guo, Gautier M. Courbon, Stephanie A. Bueler, Juntao Mai, Jun Liu et John L. Rubinstein, « Structure of Mycobacterial ATP Synthase Bound to the Tuberculosis Drug Bedaquiline », *Nature* 589, n°7840 (January 7, 2021): 143. https://doi.org/10.1038/s41586-020-3004-3.
Anil Koul, Luc Vranckx, Najoua Dendouga, Wendy Balemans, Ilse Van Den Wyngaert, Karen Vergauwen, Hinrich W.H. Göhlmann, *et al*, « Diarylquinolines Are Bactericidal for Dormant Mycobacteria as a Result of Disturbed ATP Homeostasis », *Journal of Biological Chemistry* 283, n°37 (September 2008) : 25273– 74. https://doi.org/10.1074/jbc.M803899200.

[1107] Anil Koul, « The Discovery of Bedaquiline – Innovation in Tuberculosis Discovery", Inaugural lecture, London School of Hygiene and Tropical Medicine, February 2, 2021, http://vimeo.com/508781243 (Consulté le 2 avril 2022).

tuberculose ciblaient les populations alpha et bêta et peinaient à cibler les états gamma. Or la bédaquiline s'est avérée beaucoup plus performante contre la population gamma de *M. tuberculosis* dont la culture dans l'hôte humain demande plus de temps[1108]. Même si les essais cliniques ont débuté en 2005, il a fallu attendre 2012 pour que la bédaquiline soit mise sur le marché, spécifiquement comme traitement de la tuberculose multirésistante, ce qui a nécessité l'assistance de plusieurs filières de développement d'antibiotiques.

Les négociations avec le partenariat public-privé *TB Alliance* qui ont eu lieu entre 2005 et 2009 ont abouti à un accord qui octroyait à *TB Alliance* une licence libre de droits pour le développement et l'accès mondial à la molécule qui allait être baptisée bédaquiline dans le secteur de la tuberculose *sensible* aux médicaments, Johnson & Johnson conservant les droits liés aux traitements contre la multirésistance aux médicaments. Le montant du soutien financier accordé par *TB Alliance* à Johnson & Johnson n'a pas été rendu public. Cependant, le directeur de *TB Alliance* a confirmé dans un entretien que « toute activité de haut niveau susceptible de bénéficier directement au développement de produits, à la fois dans le domaine de la tuberculose sensible aux médicaments et de la tuberculose résistante » a été incluse dans les négociations[1109]. Potentiellement, cela inclut tout essai clinique et toute recherche supplémentaire ou recherche à long terme (comme l'étude du mode d'action de la bédaquiline sur *Mycobacterium tuberculosis*).

Grâce à l'*Orphan Drug Act* (loi des États-Unis sur les médicaments orphelins), Johnson & Johnson a bénéficié d'une aide à la rédaction des normes relatives aux essais précliniques et cliniques, de crédits d'impôt égaux à 50 % des dépenses liées aux essais cliniques éligibles et d'une exonération de la taxe sur les demandes de mise sur le marché en vertu de la *Prescription Drug User Fee Act*, de subventions pour le développement de

[1108] Koul, *et al.*, « Diarylquinolines Are Bactericidal for Dormant Mycobacteria as a Result of Disturbed ATP Homeostasis », 25273–74.
[1109] Melvin Spigelman, entretien mené par Erin L. Paterson, 21 décembre 2023.

produits orphelins et d'une période de commercialisation exclusive d'une durée de sept ans après l'approbation du médicament par la FDA[1110]. L'entreprise a également participé au *Priority Review Voucher System* qui accorde un droit d'examen prioritaire à toute entreprise prouvant qu'elle travaille dans un secteur lié à une maladie négligée.

Une fois l'autorisation de commercialisation obtenue, le médicament a été lancé en 2012. Le laboratoire pharmaceutique a immédiatement demandé l'inclusion du médicaments dans la LME. L'OMS a refusé d'ajouter la bédaquiline à sa liste des médicaments essentiels à la première demande mais le produit a finalement intégré la liste en 2015 et était clairement considéré comme un médicament efficace contre la tuberculose multirésistante.

Cependant, malgré l'extraordinaire soutien financier de chacun des secteurs impliqués et le succès de la mise sur le marché de la bédaquiline, sept ans après son lancement, MSF a observé que seules 37 000 personnes s'étaient effectivement vu administrer ce médicament. La faute en a été largement imputée au coût du produit. Le prix de vente de la bédaquiline a été fixé sur la base de traitements de six mois, les pays à revenu élevé payant chaque traitement 30 000 dollars américain, les pays à revenu intermédiaire 3 000, et les pays à revenu faible seulement 900[1111]. Cette grille tarifaire a été jugée extrêmement prohibitive : dans les pays à revenu élevé, certaines compagnies d'assurance rechignaient à prendre ces frais en charge tandis que dans les pays à revenu faible ou intermédiaire, c'était tout simplement inenvisageable. *MSF Access Campaign* et d'autres ont alors pris à parti Johnson & Johnson pendant des années pour demander une baisse de prix, mais il a fallu attendre

[1110] Robert C. Griggs, *et al*, « Clinical Research for Rare Disease: Opportunities, Challenges, and Solutions », *Molecular Genetics and Metabolism*, vol. 96, n°1, Jan. 2009, 22. DOI.org (Crossref), https ://doi.org/10.1016/j.ymgme.2008.10.003.

[1111] Rapport du Comité d'experts de l'OMS, « La sélection des médicaments essentiels », Série de rapports techniques 994 (Genève, Suisse : Organisation mondiale de la santé, 2015), 29.

2020 pour que le traitement de six mois passe à 340 dollars américains (avec une réduction supplémentaire de 20 % pour l'achat de cinq traitements en même temps)[1112].

Ainsi, comme le montre ce chapitre de manière éloquente, même si un médicament manifestement prometteur est mis sur le marché, son acheminement jusqu'aux patients est une tout autre affaire. L'infrastructure antibiotique dont l'objectif est de favoriser l'accès à des antibiotiques efficaces vacille du fait des mêmes enjeux financiers qui entravent la création de nouveaux médicaments dans les premières phases de recherche et développement du pipeline. Certes, ces enjeux financiers entre les entreprises pharmaceutiques et les consommateurs ne sont pas nouveaux, et l'inaccessibilité de la bédaquiline en raison de son prix élevé n'est que l'une des dimensions des contraintes financières en présence. En dépit de la variété des soutiens financiers révélée par le cas de la bédaquiline, pour soutenir l'investissement des firmes pharmaceutiques dans le domaine délaissé des antibiotiques, il ne suffit pas de réussir la mise au point d'un médicament, ni même d'obtenir sa mise sur le marché. Les mesures visant à garantir aux patients l'accès effectif à de nouveaux médicaments constituent une composante encore très sous-développée de l'infrastructure à l'heure actuelle – *surtout* si ce patient vient d'un pays à revenu faible ou intermédiaire, dont les fonds limités entravent l'accès à des médicaments hors de prix. Même si d'autres PPP tels que GARDP et CARB-X ont abordé les questions d'accès dans leurs actions, ils n'ont pas indiqué clairement comment ils s'y prendraient pour rendre de nouveaux médicaments accessibles après leur autorisation de mise sur le marché. Pour la bédaquiline, il n'y avait strictement rien de prévu, et ses chiffres de vente et d'accessibilité ont diminué en conséquence. Le désintérêt pour cette partie du pipeline affecte donc fortement la façon dont

[1112] STOP TB Partnerships, "Bedaquiline Is Accessible through GDF at a Price of US$ 340 for a Bottle of 188 Tablets," Access Bedaquiline, 2019, https://www.stoptb.org/new-tools/access-bedaquiline. (Consulté le 2 avril 2022.)

ce dernier peut prêter assistance à l'infrastructure globale des antibiotiques et à l'accessibilité à ces médicaments dans le monde entier.

La question de l'accès à ce qui manque : les anciens et les nouveaux antibiotiques

Le dernier chapitre analytique de cette thèse explore la façon dont l'offre mondiale d'antibiotiques s'est progressivement précarisée à partir des années 1980 cependant que les mesures de réduction des coûts et la course au prix le plus bas entraînaient la diminution du nombre de fabricants d'ingrédients pharmaceutiques actifs (IPA) et suscitaient de l'insécurité autour de la création et la réception réelles d'un antibiotique efficace.

Les pénuries d'antibiotiques à l'échelle mondiale augmentent depuis les années 1980 mais leur suivi pose problème, d'une part parce qu'il n'existe pas de définition fixe de ce qui constitue une pénurie, et d'autre part parce que la communication entre les pays et les fournisseurs eux-mêmes est souvent opaque. Toutefois, au cours des 30 dernières années, la fréquence et le taux des pénuries d'antibiotiques résultant de défaillances de la chaîne d'approvisionnement ont augmenté non seulement dans les pays à revenu faible mais également dans les pays à revenu élevé[1113]. Ce chapitre fait valoir que non seulement l'infrastructure de la chaîne d'approvisionnement qui permet la production physique des antibiotiques et leur transport a été fragilisée pour les pays à revenu faible en raison de la pression financière croissante, mais que les pays à revenu élevé souffrent également de ce défaut de « maintenance » de la chaîne d'approvisionnement.

Ces pénuries peuvent être dues au manque de matières premières, à la fermeture de certains sites de production (pour cause de maintenance, catastrophes écologiques ou décisions commerciales, entre autres) ou à des perturbations effectives des transports (là

[1113] L'annexe 6 de cette thèse présente davantage d'informations sur les pénuries de médicaments aux États-Unis.

encore, en raison de problèmes écologiques mais aussi de décisions politiques ou réglementaires et de l'état dans lequel se trouvent les pays eux-mêmes [exemple : les zones de guerre peuvent perturber le transport de marchandises vers ceux qui en ont besoin]). À titre d'exemple de l'impact que ces pénuries peuvent avoir pour les pays à revenu élevé : depuis 2001, il y a eu 345 pénuries d'antibiotiques aux États-Unis, soit un total de 163 278 jours où un produit était en rupture. Trente médicaments représentent 72 % de ce total (soit 117 875 jours sur 163 278) ; 70 d'entre eux figuraient sur la liste des médicaments essentiels de l'OMS. Ces chiffres ne concernent qu'un seul pays à revenu élevé mais ils sont un indice de ce que vivent d'autres pays de même niveau économique. Ils servent également d'avertissement dans la mesure où on peut supposer que ceux qui ont moins de moyens connaissent des pénuries encore plus importantes.

Même s'il n'existe pas de définition standard mondiale de la « pénurie de médicaments », il y a des similitudes entre les différentes définitions utilisées. En revanche, chaque variante s'accompagne de particularités qui empêchent une comparaison réglée entre les pays. Pour la *Food and Drug Administration* aux États-Unis, une « pénurie de médicaments » se réfère à « une période dans le temps où la demande (prévisionnelle ou non) pour un médicament aux États-Unis dépasse l'offre »[1114]. Pour l'Agence européenne des médicaments, les pénuries sont définies et déclarées au niveau national. Par exemple, la France utilise deux termes : « tension d'approvisionnement » et « rupture de stock »[1115]. La tension survient lorsque des marchandises sont disponibles mais pas en quantité suffisante pour répondre aux besoins de la collectivité[1116]. Il y a rupture de stock lorsqu'une

[1114] United States FDA, « Frequently Asked Questions about Drug Shortages », Government, Food and Drug Administration, October 11, 2023. https://www.fda.gov/drugs/drug-shortages/frequently-asked-questions-about-drug-shortages.
[1115] Agence nationale de sécurité du médicament et des produits de santé, « Disponibilité des produits de santé », Gouvernement, https://ansm.sante.fr/disponibilites-des-produits-de-sante/medicaments (Consulté le 2 avril 2025.)
[1116] Santé Publique France, « Ruptures de stock et tensions d'approvisionnement des vaccins », Gouvernement, https://vaccination-info-service.fr/Generalites-sur-les-vaccinations/Qualite-securite-et-efficacite-des-

« pharmacie de ville ou pharmacie à usage interne dans un établissement (sanitaire ou médico-social) [est incapable] de fournir un médicament à un patient dans les 72 heures »[1117]. Les deux situations sont déclarées au registre de l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) à des fins de sensibilisation du public[1118]. De son côté, le Canada référence les pénuries au cas par cas en fonction du code de la liste des médicaments, ce qui peut donner l'impression qu'il y a des centaines de pénuries sur un produit pour lequel les États-Unis ne comptabiliseraient qu'une seule pénurie[1119]. Dans toutes les définitions ci-dessus, il y a une difficulté supplémentaire puisqu'il peut arriver qu'un patient ignore qu'il y a pénurie quand une solution de rechange existe et lui est fournie sans commentaire. Néanmoins, cette situation comporte également des risques concernant l'augmentation potentielle de la résistance aux antimicrobiens[1120]. Les raisons de procéder ainsi sont diverses mais le raisonnement est essentiellement le suivant : quand un patient demande un traitement pour lequel il a une ordonnance, il est fort probable qu'il ne se soucie pas du médicament spécifique qu'on lui fournit, du moment que ce dernier soulage les symptômes pour lesquels il a consulté son médecin ou son pharmacien au départ.

Les différentes définitions nationales de la pénurie suivent globalement les mêmes principes généraux mais les nuances qui existent entre elles rendent les comparaisons directes de pays à pays plus difficiles. La formulation la plus cohérente tend à évoquer, d'une façon ou d'une autre, une offre qui ne répond pas à la demande présente (ou prévisionnelle)[1121]. Les

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vaccins/Gestion-des-stocks-des-vaccins/Ruptures-de-stock-et-tensions-d-approvisionnement-des-vaccins (Consulté le 2 avril 2025.)

[1117] Ministère du Travail, de la Santé et des Solidarités, « Rupture d'approvisionnement d'un médicament », Gouvernement, https ://sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/prescription-et-dispensation/article/rupture-d-approvisionnement-d-un-medicament. (Consulté le 2 avril 2025.)

[1118] L'ANSM ne recense que les pénuries françaises et ces rapports ne sont destinés qu'aux personnes qui connaissent des pénuries en France.

[1119] Erin Fox, entretien mené par Erin L. Paterson, 31 mars 2023.

[1120] Mingyuan Zhang, « In Shortage: Understanding Global Antibiotic Supply Chains through Pharmaceutical Trade Fairs », *Anthropologica* 65, n°1 (September 28, 2023), 2-3, https ://doi.org/10.18357/anthropologica65120232605.

[1121] S. Shukar, F. Zahoor, K. Hayat, A. Saeed, A. H. Gillani, S. Omer, S. Hu, ZUD Babar, Y. Fang et C. Yang, « Drug Shortage: Causes, Impact, and Mitigation Strategies », *Frontiers in Pharmacology,* 12 n°693426, (2021), 3, https ://doi.org/10.3389/fphar.2021.693426

causes de ce défaut d'approvisionnement peuvent être résumées en sept catégories clés que l'administrateur de pharmacie et expert en pénuries médicales Sundus Shukar (*et al.*) appelle des problèmes d'approvisionnement, de demande ou de réglementation[1122].

Problèmes d'approvisionnement	Problèmes de demande	Problèmes de réglementation
Problèmes de fabrication : problèmes de qualité sur les produits	**Inventaire à flux tendu :** création et stockage de matériaux en fonction d'un achat prévisionnel, sans stockage supplémentaire de marchandises	La législation empêche ou interdit la distribution de médicaments en dépit des besoins
Indisponibilité des matières premières : pénuries d'IPA	**Marketing renforcé :** attire l'attention sur un produit, ce qui peut entraîner une augmentation de la demande que l'offre n'arrive pas à suivre	
Enjeux commerciaux : considérations de profit et intérêts financiers, dont le fait que le prix du médicament soit trop élevé pour le consommateur	**Système d'appel d'offres :** soumission d'une offre pour un montant déterminé, avec fermeture du marché à d'autres fournisseurs, ce qui entraîne une perte d'entreprises sur le marché	
Problèmes logistiques : retards dus à des catastrophes naturelles		

Tableau 2 Informations tirées de S. Shukar, F. Zahoor, K. Hayat, A. Saeed, AH Gillani, S. Omer, S. Hu, ZUD Babar, Y. Fang, et C. Yang. « Drug Shortage: Causes, Impact, and Mitigation Strategies », Frontiers in Pharmacology, 12 n°693426, (2021), 6- 9, doi: https://doi.org/10.3389/fphar.2021.693426.

Ces trois points peuvent être regroupés sous la thématique globale de la surveillance et de la gestion des politiques. Il s'ensuit que les pénuries de médicaments sont représentatives de ces conflits car elles indiquent un échec de la politique, de la gestion et de la livraison des produits.

Pour réussir la maintenance de ces chaînes d'approvisionnement et garantir qu'elles ne connaissent pas de rupture, l'infrastructure doit être considérée comme un tout. Il est d'autant plus difficile de savoir quels fabricants d'ingrédients pharmaceutiques actifs produisent quels médicaments et quels tarifs d'expédition ils appliquent que ces informations sont souvent protégées par des accords de non-divulgation. Il est d'ailleurs tout aussi compliqué de suivre les voies d'expédition et les dispositions en matière de transport.

[1122] Shukar, *et al.*, « Drug Shortage », 6-9

Les données les plus complètes sur les pénuries d'antibiotiques proviennent des États-Unis. Erin Fox, professeure de pharmacothérapie chargée de la collecte et du traitement des données sur les pénuries de médicaments, et la *Utah University* ont recensé ces pénuries à l'échelle nationale depuis les années 1990. Nous avons entrepris une analyse de la base de données de Fox, en prêtant une attention particulière aux antibiotiques qu'elle avait répertoriés[1123].

Sur les 345 pénuries d'antibiotiques apparues depuis 2001, 146 concernaient des antibiotiques oraux/topiques (42 % de toutes les pénuries) tandis que pour 199 d'entre elles, il s'agissait d'antibiotiques injectables/administrés par perfusion (58 % de toutes les pénuries). La durée moyenne d'une pénurie est de 474 jours, bien que nous ayons parfois des valeurs aberrantes avec des pénuries auxquelles a été attribuée une durée de 0 jour (le médicament n'était plus commercialisé et n'aurait donc pas continué à être produit de toute façon), ainsi qu'à des médicaments qui ont fait défaut pendant plus de dix ans sans interruption[1124]. L'ampicilline sulbactam, le céfotaxime injectable, la ceftazidime, la clindamycine injectable et la vancomycine injectable ont tous été répertoriés comme faisant défaut depuis 10 à 14 ans, ce qui a fait l'objet d'une mention particulière dans le rapport de la *Homeland Security and Government Affairs Majority Staff* (Commission de la sécurité intérieure et des affaires gouvernementales) de 2023 qui a accompagné l'audition au Sénat[1125] [1126].

Les données que nous avons analysées confirment que 21 médicaments manquants étaient la seule source de cet antibiotique alors que des alternatives existaient pour 64 autres antibiotiques manquants. Il reste 260 antibiotiques pour lesquels on ignore s'ils étaient la

[1123] Erin Fox, Small File Data Shortage Through 2022 (Petit dossier sur les données concernant les pénuries jusqu'en 2022), reçu le 31 mars 2023, transmis par Erin Fox de la *Utah University.*
[1124] Fox, Small File Data Shortage Through 2022.
[1125] Gary Peters, « Short Supply: The Health and National Security Risks of Drug Shortages », Majority Report, Washington DC: Homeland Security and Government Affairs, March 2023, 9.
[1126] United States Congress, Senate, Committee on Homeland Security and Governmental Affairs, *Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms*, 118th Cong., 2023.

seule source ou non. Cent vingt-neuf antibiotiques différents étaient à l'origine des 345 pénuries constatées aux États-Unis. Cinquante-trois antibiotiques avaient connu une seule pénurie tandis que 76 d'entre eux avaient connu chacun deux pénuries ou plus. Soixante-dix médicaments étaient présents sur la LME[1127]. Pour garantir la précision de notre travail, nous avons examiné les données de Fox de plus près, non seulement pour identifier les médicaments qui figuraient sur la LME, mais aussi pour savoir quelle formulation exacte était recommandée par la LME et quelle pénurie était en vigueur à ce moment-là. Nous avons enregistré la quantité du médicament, le croisement éventuel avec la LME et les dates de pénurie en particulier. À partir de ces informations, nous avons enquêté sur les distributeurs connus du médicament et sur tous les laboratoires connus qui avaient reçu une autorisation de mise sur le marché auparavant mais n'étaient plus en activité, pour identifier clairement les entreprises associées aux pénuries en question.

Compte tenu des différences énormes de durée des pénuries et afin de mieux comprendre où se trouvent les principaux facteurs de complication pour tel ou tel antibiotique, nous avons isolé les 30 antibiotiques qui ont connu les pénuries les plus longues et nous les avons classés en fonction de la durée de la pénurie et des facteurs connus ayant contribué à sa longueur. Comme il en résulte un très grand tableau malgré ces restrictions, cette reprise des travaux de Fox est présentée dans l'annexe 6 de cette thèse. En tout cas, ce que ce tableau révèle, c'est que seules quelques raisons ont été invoquées pour expliquer les pénuries. En effet, en tenant compte des recoupements (car différentes pénuries peuvent avoir plus d'une cause répertoriée), des retards de fabrication/pénuries de matières premières sont à l'origine de quatorze pénuries tandis que des raisons inconnues (10), des décisions commerciales (7) et l'offre et la demande (6) ont déterminé le reste. Les retards de fabrication correspondent à un problème spécifique avec le fabricant d'ingrédients pharmaceutiques

[1127] Fox, Small File Data Shortage Through 2022.

actifs. Pour ce qui est de l'infrastructure, cela souligne le fait que la fragilité se manifeste essentiellement au point de production. Bien entendu, cela ne tient pas compte des autres raisons présentes en aval : les décisions commerciales et l'offre et la demande se recoupent de façon très significative. En effet, le choix que font les entreprises de la quantité de médicaments à produire par rapport à la quantité requise donne lieu à de mauvaises estimations et fait apparaître un besoin d'accroissement de leur production.

Quoi qu'il en soit, le plus frappant au sujet de ces 30 médicaments est peut-être précisément *la durée* de ces pénuries. La période la plus courte sur la liste était de 4,7 ans tandis que la plus longue (pour la ciprofloxacine) s'est étendue sur *24 ans*[1128]. Ces traitements sont censés être des médicaments essentiels, capables de répondre aux problèmes de la population, mais leur indisponibilité persistante dans ce contexte pointe de façon très précise l'endroit où une maintenance structurée devrait être appliquée à l'infrastructure antibiotique. Si ce sont les matières premières et les difficultés de fabrication qui provoquent les retards les plus extrêmes, c'est là qu'une intervention ciblée devrait être mise en œuvre. Toutefois, jusqu'à présent, ces mesures ciblées n'ont pas été prises.

Les formulaires pharmaceutiques des hôpitaux du monde entier doivent acheter une quantité précise de médicaments avec un budget limité. Au départ, la LME a été conçue comme une aide dans ce domaine mais, en fin de compte, la question du coût économique reste incontournable. S'ils sont en présence de 100 fournisseurs d'amoxicilline, les acheteurs choisiront systématiquement celui dont le prix est le plus bas pour être en mesure d'acheter une plus grande quantité des autres médicaments dont ils pourraient avoir besoin. Dès lors, les laboratoires pharmaceutiques actifs qui ont perdu l'appel d'offres font faillite ou se tournent vers d'autres médicaments avec lesquels ils peuvent encore réaliser une vente. Il

[1128] Ces pénuries n'étaient pas continues. La durée moyenne d'une pénurie de ciprofloxacine aux États-Unis se situait entre 1 à 6 ans mais cela montre avec une régularité surprenante que cette formulation particulière n'est ni stable ni fiable. Dans le cas de la ciprofloxacine, le manque de matières premières et les problèmes d'offre et de demande consécutifs à la crise de l'anthrax ont été en grande partie à l'origine de la persistance des retards.

s'ensuit une raréfaction des fabricants qui travaillent sur un même médicament à un moment donné. Par conséquent, en cas de problème avec l'unité qui fabrique effectivement le produit en question, personne d'autre n'est capable de prendre le relai. L'infrastructure qui gère le développement et le transport des antibiotiques se fragilise alors de plus en plus. Si l'on veut bien filer la métaphore, cette fragilité nécessite une maintenance pour pouvoir s'adapter. En effet, les mises à jour constantes et la rotation des appels d'offres sont peut-être le seul moyen de garantir un écosystème florissant de « pièces » disponibles, pour ainsi dire. Mais il faudrait que ces mises à jour puissent d'une part, réagir aux véritables causes des problèmes et d'autre part, avoir une dimension prédictive pour anticiper d'éventuels problèmes supplémentaires.

Même si ce sont les États-Unis qui disposent des données de suivi national les plus complètes, nos recherches ont révélé des convergences à travers le monde, quel que soit le niveau de revenu national. Les antibiotiques génériques injectables bon marché étaient les plus menacés mais toutes les classes d'antibiotiques avaient connu une pénurie due à la fragilité de la chaîne d'approvisionnement. Parallèlement, il semble que les taux de résistance aux antimicrobiens correspondent en partie aux taux de pénurie parce qu'un antibiotique est « sur-utilisé », faute de disposer d'une solution de remplacement appropriée et efficace. On peut le constater à travers les expériences d'un hôpital suisse qui a suivi activement les taux de résistance de *Pseudomonas aeruginosa* à la suite d'une pénurie de céfépime *et* de pipéracilline/tazobactam survenue en 2011[1129]. L'hôpital a indiqué que le taux d'échec des traitements était beaucoup plus élevé à cause de la pénurie, du fait de l'absence de traitements rapides et efficaces. D'autres hôpitaux, des laboratoires pharmaceutiques[1130] et des chercheurs, ainsi que des particuliers, ont également commencé à remarquer et à se plaindre

[1129] C. Plüss-Suard, A. Pannatier, C. Ruffieux, A. Kronenberg, K. Mühlemann et G. Zanetti, « Changes in the Use of Broad-Spectrum Antibiotics after Cefepime Shortage: A Time Series Analysis », *Antimicrobial Agents and Chemotherapy* 56, n°2 (February 2012): 990, https://doi.org/10.1128/AAC.05560-11.
[1130] Kim Pauwels, Steven Simoens, Minne Casteels et Isabelle Huys, « Insights into European Drug Shortages: A Survey of Hospital Pharmacists », John Conly (dir.), *PLOS ONE* 10, n°3 (March 16, 2015) : e0119322, https ://doi.org/10.1371/journal.pone.0119322.

de l'absence d'une chaîne d'approvisionnement en antibiotiques stable et fiable pendant cette période, dénonçant le fait que la situation paraissait devenir de plus en plus instable[1131].

Ainsi, le prix exorbitant d'un nouveau produit en limite l'accès pour les consommateurs, et les mesures extrêmes de réduction de prix des anciens antibiotiques rendent ces derniers indisponibles également. Quant à la résistance aux antimicrobiens, elle ne fait que croître.

L'infrastructure destinée à garantir la distribution aux patients des antibiotiques après leur passage dans le pipeline est défectueuse. Même si, dans certains cas, la mise en place de l'infrastructure n'a jamais été complètement finalisée et que la question de la disponibilité et celle du coût n'ont jamais cessé de se poser, le fait que même dans les zones à revenu élevé, l'accessibilité soit devenue un problème montre bien la nécessité accrue d'une maintenance holistique mondiale.

Conclusion

Cette thèse est consacrée à la compréhension du développement et des faiblesses d'une composante clé des soins de santé mondiaux : l'infrastructure qui soutient l'accès aux antibiotiques. Dans le tableau ci-dessous, nous analysons la façon dont trois piliers de l'infrastructure antibiotique (la LME, le pipeline de développement des antibiotiques, et la chaîne d'approvisionnement des antibiotiques) se rapportent et se conforment aux neuf paramètres d'une infrastructure identifiés et décrits par Susan Leigh Star.

	La LME de l'OMS (section antibactérienne)	**Le pipeline de développement des antibiotiques**	**La chaîne d'approvisionnement des antibiotiques**
Intégration	S'appuie sur l'infrastructure existante de l'OMS ; dépend des réseaux internationaux de communication et de soutien de l'OMS.	S'appuie sur le pipeline pharmaceutique standard en vigueur dans tous les domaines de la médecine depuis le milieu du XXe siècle.	S'appuie sur des normes préexistantes en matière de transport et de contrôle, ainsi que sur l'utilisation d'accords avec les fabricants et les transporteurs.
Transparence	Mise à jour tous les deux ans ; ne nécessite donc pas beaucoup d'attention	On n'a commencé à prêter attention au pipeline des antibiotiques seulement quand on a constaté que	La fabrication et l'expédition d'un produit sont souvent ignorées tant que le produit atteint sa destination

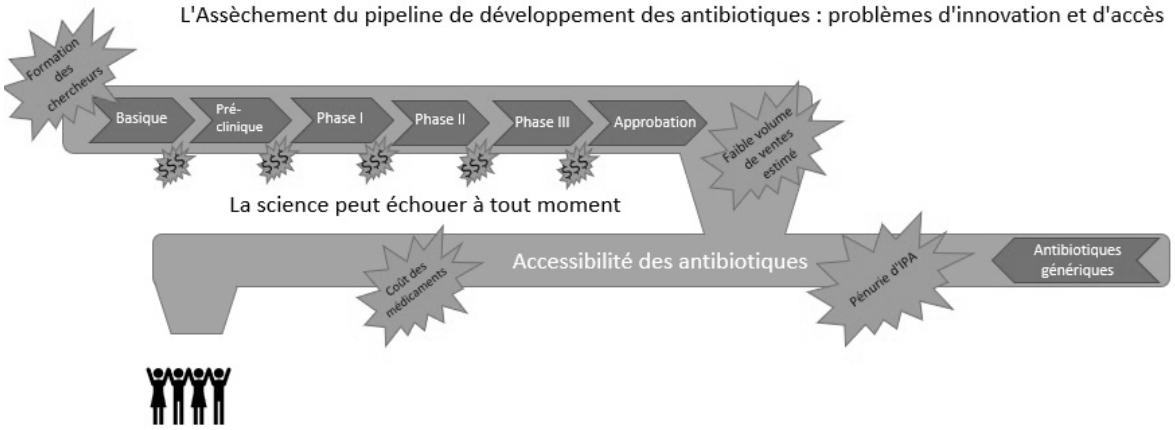
[1131] Pauwels, *et al.*, « Insights into European Drug Shortages », e0119322.

	supplémentaire de la part du pays qui l'utilise.	le développement de nouveaux antibiotiques ralentissait et que la résistance aux antimicrobiens ne pourrait pas être maîtrisée.	finale.
Portée	De portée mondiale, même si elle recommande (et a conduit à) la création de listes nationales de médicaments essentiels gérées par chaque pays. Ses recommandations et son travail visant à encourager un accès plus large aux antibiotiques restent néanmoins une initiative mondiale.	Toutes les entreprises produisant des antibiotiques travaillent dans le cadre de l'infrastructure du pipeline de développement des antibiotiques mais l'accès aux différents marchés nationaux est soumis aux réglementations nationales .	Chaîne d'approvisionnement mondiale qui garantit que les produits parviennent aux personnes qui en ont besoin, quel que soit leur niveau de revenu ou leur lieu de résidence. Elle est remise en question par cette portée même dans la mesure où des pays différents avec des niveaux de revenu différents n'ont pas tous la même capacité à alimenter et soutenir la chaîne d'approvisionnement.
Apprentissage à travers l'appartenance	Considérée comme une composante allant de soi du soutien de l'OMS aux pays ; son efficacité est tenue pour acquise.	Toutes les entreprises du secteur du développement des antibiotiques sont conscientes des étapes nécessaires pour amener un médicament à traverser le pipeline de développement des antibiotiques.	Les personnes impliquées dans l'approvisionnement sont activement conscientes des besoins et des exigences de la chaîne. En revanche, les personnes extérieures peuvent ne pas en être conscientes ou ne pas saisir ses complexités.
Liens avec les conventions de pratique	Ses recommandations et son suivi sont fortement associés aux lignes directrices et aux dispositions de l'OMS, ainsi qu'à ses idées, politiques et orientations contemporaines car les conventions changent au fil du temps.	Toutes les entreprises qui développent des antibiotiques utilisent le pipeline de la même façon et suivent les mêmes étapes et conventions de pratique que leurs pairs, en raison du développement graduel d'une régulation nationale et internationale.	La chaîne d'approvisionnement est soutenue par une grande variété d'autres chaînes d'approvisionnement et de normes industrielles similaires qui ne sont pas uniquement dédiées aux antibiotiques. Son fonctionnement n'est donc pas unique.
Intégration de normes	Standardisée en fonction de paramètres et de prescriptions antérieures de l'OMS ; les mises à jour suivent les nouvelles normes au fur et à mesure de leur apparition.	Les bonnes pratiques de fabrication (BPF) et les normes réglementaires s'appliquent à toutes les entreprises productrices d'antibiotiques qui espèrent réussir à commercialiser leur médicament.	La chaîne d'approvisionnement doit respecter des conditions standardisées pour s'assurer que le produit atteindra sa destination finale dans des conditions optimales.
Construit sur une base existante	Issue d'autres départements de l'OMS ; ses recommandations sont suivies en raison des travaux qui ont précédé.	Le pipeline de développement des antibiotiques suit les mêmes étapes que les autres pipelines de développement de médicaments. Lorsque des composantes supplémentaires sont incluses (comme le développement de PPP), les autres entreprises engagées dans ces travaux partagent ces modèles.	Pour garantir le succès des opérations, le fonctionnement de la chaîne d'approvisionnement fait appel à la même base que les autres, avec des itinéraires d'expédition similaires et des unités de fabrication de format similaire.
Devient visible en cas de défaillance	L'attention se porte sur elle quand il devient clair que les médicaments figurant sur la liste ne peuvent pas résoudre les problèmes qu'ils étaient censés résoudre (exemple : augmentation de la résistance aux antimicrobiens). Voir chapitre 2.	Le manque d'antibiotiques efficaces a spécifiquement attiré l'attention sur l'« assèchement du pipeline de développement des antibiotiques », ce qui rend visible ce dernier. Voir chapitres 3 et 4.	Lorsque les produits ne parviennent pas aux patients à temps, l'attention se concentre sur la chaîne d'approvisionnement et ses défaillances dans les domaines de la fabrication et du transport. Voir chapitre 5.
Remise en état graduelle	Sur le principe, la liste est mise à jour tous les deux ans mais lorsque des ajustements majeurs sont nécessaires, il faut du temps pour les mettre en place et le calendrier peut être modifié en conséquence.	La remise en état du pipeline a fait l'objet d'une grande attention, notamment en ce qui concerne l'affectation des fonds, la mise en place d'incitations financières, et la manière de répondre au mieux aux préoccupations les plus urgentes. Il s'agit de corrections modulaires et graduelles.	La remise en état de la chaîne d'approvisionnement doit se faire progressivement en raison de son impact et de ses effets à l'échelle mondiale. Les ajustements portent en priorité sur les unités de production ou les entrepôts de stockage, les itinéraires de transport, etc., plutôt que de procéder à de vastes changements de haut en bas.

Tableau 3 Analyse de la LME, du pipeline et de la chaîne d'approvisionnement à partir des théories de Susan Leigh Star sur l'ethnographie des infrastructures.

D'autres graphiques et d'autres interprétations peuvent s'appliquer à d'autres composantes de cette recherche. Par exemple, le pipeline des antibiotiques est axé

directement sur le développement d'un nouveau produit. Toutefois, si ce produit ne peut pas parvenir à un patient (c'est-à-dire devenir accessible), il échoue. Alors que la plupart des représentations du pipeline de développement des antibiotiques sont linéaires, nous en proposons une représentation actualisée (cf. schéma suivant) qui permet de replacer dans son contexte la façon dont il remplit réellement sa fonction de composante de l'infrastructure antibiotique, ainsi que les endroits où diverses défaillances et pannes se produisent.



Cette évaluation de l'histoire et de la trajectoire de l'infrastructure antibiotique et de son fonctionnement dans la pratique révèle qu'il ne suffit pas d'injecter de l'argent dans le pipeline pour développer un nouveau médicament et solutionner la résistance aux antimicrobiens ou les problèmes d'accès à des antibiotiques efficaces. La recherche d'une solution unique à ce problème relève de l'idéalisme et ne tient pas compte de la complexité de la crise dans son ensemble. L'infrastructure qui permet la diffusion des antibiotiques est devenue trop limitée au cours des 40 dernières années et a donc besoin de maintenance.

Les travaux de Mark Thomas Young, Mark Coeckelbergh, Jérôme Denis et David Pontille traitent tous des modalités d'application d'une philosophie de la maintenance. Les infrastructures connaissent des défaillances ; elles rencontrent des problèmes qui nécessitent des corrections. La maintenance préventive vise à traiter ces difficultés avant qu'elles ne deviennent des problèmes réels tandis que la maintenance corrective est mise en œuvre après

coup[1132]. Or une maintenance continue est indispensable pour assurer la pérennité d'une infrastructure ou d'un investissement[1133]. Pour l'infrastructure antibiotique, cette maintenance prend plusieurs formes. Les mises à jour continues de la LME concentrent l'attention sur les médicaments les plus efficaces et favorisent l'accès à ces médicaments. Les préoccupations financières du pipeline ont été compensées par les effets de maintenance des nouvelles stratégies PPP/PDP visant à augmenter l'intérêt des entreprises pour ce secteur. Pour la chaîne d'approvisionnement, l'ouverture de la boîte noire de Latour sur les modalités de délocalisation et d'assemblage multisite des médicaments, l'ajustement de la fabrication à flux tendu et la rotation des appels d'offres, ainsi que l'amélioration de la diversité des fabricants et de la façon dont ils sont payés, sont susceptibles d'augmenter la fiabilité de la chaîne d'approvisionnement. Ces initiatives constituent à la fois des actions de maintenance continue et de maintenance corrective pour des problèmes qui ont continué à se manifester au fil du temps. Et ce besoin de maintenance ne fait que croître.

Comme Clare Chandler l'a clairement exposé lorsqu'elle a abordé pour la première fois la conceptualisation des antibiotiques comme infrastructure, il s'agit de médicaments dont l'ère moderne ne peut pas se passer[1134]. Chaque opération chirurgicale, chaque traitement du cancer, chaque intervention risquée est mise en œuvre en sachant que des antibiotiques sont disponibles. Comme l'ont exprimé les États-Unis, l'accès mondial aux antibiotiques représente une menace sécuritaire [1135]. Mais il ne s'agit pas que des États-Unis, tous les pays du monde sont concernés. Cette menace existe réellement, comme de nombreux pays à revenu faible ou intermédiaire peuvent en témoigner : c'est une situation que vivent aujourd'hui des millions de personnes qui ont besoin de soins.

[1132] Young et Coeckelbergh, *Maintenance and Philosophy of Technology*, 19-20.
[1133] Denis et Pontille, *Le Soin des Choses,* 56.
[1134] Chandler, « Current Accounts of Antimicrobial Resistance », 9.
[1135] United States Congress, Senate, Committee on Homeland Security and Governmental Affairs, *Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms*, 118th Cong., 2023.

Si la métaphore de l'assèchement du pipeline des antibiotiques porte avant tout sur le développement de médicaments, c'est parce qu'il paraît simple de trouver les meilleures façons d'investir dans la création d'un médicament afin qu'il finisse par être vendu (et engendrer un retour sur investissement). La question d'un changement réel qui assurerait le développement de nouveaux antibiotiques et la continuité de la distribution des médicaments à ceux qui en ont besoin est beaucoup plus complexe. Il est si difficile de répondre à cette préoccupation que la résolution de la question de l'accès aux antibiotiques est reléguée à un avenir plus ou moins lointain. Mais l'avenir, c'est maintenant, et des mesures sont nécessaires pour s'assurer que les nouveaux antibiotiques en préparation parviennent finalement aux patients qui en ont besoin, même si la situation financière et matérielle des entreprises pharmaceutiques est loin d'être idéale pour ce qui concerne le retour sur investissement.

L'accès aux antibiotiques est un problème d'infrastructure. Les interventions qui ont été réalisées pour y remédier (sensibilisation à la nécessité de nouveaux antibiotiques, débats au Congrès sur la modification de la chaîne d'approvisionnement, développement de partenariats public-privé ou production physique d'antibiotiques dans le cadre de ces partenariats) n'ont encore rapporté ni profits ni contreparties fiscales d'importance. En outre, l'impact de chaque intervention peut être difficile à évaluer à court terme. L'infrastructure se doit d'être développée et maintenue à cet endroit également car ni la question de l'accès aux médicaments ni celle de la prévention et du contrôle des infections ne sont destinées à disparaître à l'avenir. Dans les deux cas, l'important est d'avoir un effet durable et continu. Il s'agit de favoriser l'accès aux médicaments maintenant et à l'avenir. Le développement de produits a beau être un élément de cette infrastructure, il doit s'accompagner de mesures favorisant l'accessibilité post-développement, sans quoi ses effets sont perdus. Il ne suffit pas de concevoir un nouveau produit au nom de la science. Il faut également prévoir un plan de production et de distribution continu et durable. Cela implique notamment de comprendre

que le retour sur investissement ne viendra pas d'une augmentation des prix mais qu'il vaut mieux parier sur des revenus durables à long terme.

Les laboratoires pharmaceutiques qui créaient un nouvel antibiotique après l'autre ont disparu. Les fonds qui ont permis à ces scientifiques et à ces magnats d'entreprise de mener leurs travaux ont été affectés à d'autres projets. Les chaînes d'approvisionnement sont menacées. Les listes de médicaments essentiels, autrefois considérées comme un moyen de faire la part des choses face à un trop grand nombre de médicaments, peinent désormais à inclure de nouveaux médicaments efficaces contre les souches résistantes. Cette thèse présente l'histoire de ces infrastructures, certaines d'entre elles depuis leur origine et d'autres jusqu'à leur mise en œuvre comme solutions de maintenance appliquées à un écosystème pharmaceutique déjà établi. Cependant, la conclusion de notre travail montre que cette histoire révèle une infrastructure actuellement en péril et en train de s'effriter. Si l'on considère les antibiotiques comme une composante indispensable des soins de santé dans le monde, il est indispensable de remettre cette infrastructure en état.