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REPORT FOR THE GERMAN GUARD INITIATIVE

Breaking through the Wall

*Enhancing Research and Development of Antibiotics in Science
and Industry*

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CONTENTS

4 EXECUTIVE SUMMARY

8 1. OBJECTIVES OF THIS REPORT

10 2. ANTIBIOTIC RESISTANCE: A GLOBAL HUMANITARIAN CHALLENGE

- 10 2.1 Avoiding Clinical Failure in the Field of Antibiotics
- 14 2.2 Addressing the Greatest Public Health Threats Posed by Bacteria

17 3. MAIN CHALLENGES IN ANTIBIOTICS RESEARCH AND DEVELOPMENT

- 17 3.1 Challenges in Basic Research and Preclinical Development
- 22 3.2 Challenges in Clinical Development
- 25 3.3 Challenges in Market Approval
- 27 3.4 Challenges in Commercialization
- 32 3.5 Overview of Challenges Along the Value Chain

33 4. POTENTIAL LEVERS TO FOSTER RESEARCH AND DEVELOPMENT IN ANTIBIOTICS

- 34 4.1 Incentives Primarily Targeting Basic Research and Preclinical Development
- 39 4.2 Incentives Primarily Targeting Clinical Development
- 41 4.3 Incentives Targeting Market Approval
- 43 4.4 Incentives Targeting Commercialization
Potential Financing Options

49 5. RECOMMENDED LEVERS: STIMULATING R&D IN ANTIBIOTICS

- 50 5.1 Definition of Target Product Profiles (TPP)
- 51 5.2 Global Antibiotics Research Fund
- 53 5.3 Global Antibiotics Research Prize
- 54 5.4 Antibiotics Research and Development Database
- 56 5.5 Global Antibiotics Expert Network
- 57 5.6 Partnerships in Clinical Development
- 59 5.7 Global Antibiotics Trial Platform
- 60 5.8 Global Alignment of Regulatory Approval Processes
- 61 5.9 Market Entry Reward for Innovative Antibiotics
- 63 5.10 Reimbursement for Innovative Antibiotics in Hospitals
- 65 5.11 Timing and First Steps

66 6. THOUGHTS ON IMPLEMENTATION

- 66 6.1 Global Antibiotics Collaboration Platform
- 68 6.2 Conclusion

69 7. APPENDIX

- 69 7.1 Current Status of Global Political Context and Actions
- 72 7.2 Country Profiles

Explanation of abbreviations

AMR	Antimicrobial resistance
BARDA	Biomedical Advanced Research and Development Authority
CDC	US Centers for Disease Control and Prevention
COMBACTE	Combating Bacterial Resistance in Europe
DNA	Deoxyribonucleic Acid
DNDi	Drugs for Neglected Diseases initiative
DRG	Diagnosis-related group
DWPI	Derwent World Patent Index
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EMA/EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
FRG	Functional resistance groups
GAIN	Generating Antibiotic Incentives Now
GAVI	Global Alliance for Vaccines and Immunizations
GDP	Gross Domestic Product
HHS	US Department of Health and Human Services
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMI	Innovative Medicines Initiative
IP	Intellectual property
IV	Intravenously
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
ND4BB	New Drugs 4 Bad Bugs
NIAID	National Institute of Allergy and Infectious Diseases
NHS	National Health Service
NIH	National Institutes of Health
NPV	Net present value (current value of all cash flows)
OECD	Organization for Economic Co-operation and Development
P4P	Pay for performance
PDP	Product development partnership
PMDA	Japan Pharmaceuticals and Medical Devices Agency
POC	Point of care
PPP	Public-private partnership
PRV	Priority review voucher
QIDP	Qualified infectious disease product
R&D	Research and development
RoI	Return on investment (return relative to size of investment)

Explanation of abbreviations

SMEs	Small and medium-sized enterprises
TA	Therapeutic area
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TPP	Target Product Profile
TSR	Total shareholder return
UK	United Kingdom
UN	United Nations
USA	United States of America
WEF	World Economic Forum
WHA	World Health Assembly
WHO	World Health Organization

EXECUTIVE SUMMARY

IN 1967, IT WAS thought that medicine could “close the book on infectious diseases” and that we could “declare the war against pestilence won.”¹ Today, however, we know that this was a misconception. Growing resistance to antibiotics and a dramatic loss of research and development activities and capabilities present a severe public health challenge. The number of deaths directly caused by infections of drug-resistant bacteria is estimated at 48,000 patients per year in the United States and Europe alone; a toll that is assumed to increase substantially year by year. Estimates of the global death toll caused by antimicrobial resistance vary, but estimates of up to 700,000 annually have been brought forward.²

While the impact of antimicrobial resistance may still appear containable today, failure to address this challenge may lead to a serious and potentially uncontrollable global health threat, especially when considering that developing an antibiotic takes approximately 10 years. Progress in the field of antibiotic resistance is therefore a global imperative for a sustainable health-care system.

This report analyzes the reasons that have led to the decline in antibiotics research and development and proposes levers and measures to spark sustainable innovation in the area of antibiotics. Antibiotic approvals by the US Food and Drug Administration (FDA) have plummeted from 19 approvals in the years 1980–84 to only 1 in the years 2010–12. The analyses and recommendations are based on a review of the current literature, first-hand data analysis and interviews with experts from governments, public agencies, multi-lateral organizations, biotech companies, multinational pharmaceutical companies, and others.

The current value chain for antibiotic research and development is broken. In each phase, major challenges for public and private research and development have been identified:

- **“Discovery void” in basic research**
Major scientific challenges, especially in understanding ways to fight gram-negative bacteria, in combination with a lack of funding and a brain drain of antibiotics researchers, lead to scarcity of promising innovations.
- **“Valley of death” in preclinical development**
The exit of numerous important players results in difficulties in translating scientific ideas into clinical successes. The reduced activity in this area is not compensated by new players entering the field.

¹ WHO Report on Global Surveillance of Epidemic-Prone Infectious Diseases. World Health Organization. 2015.
² Figure includes drug-resistant HIV and drug-resistant malaria;
Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. December 2014.

- **High cost and difficult patient recruitment in clinical development**
While the clinical development of antibiotics is less expensive than that of many other therapeutic areas, developmental costs are still substantial (approximately €120 million) and are often prohibitive for small and medium-sized enterprises (SMEs). Additionally, recruiting patients for clinical trials is a challenge given the acute treatment setting and a lack of accessibility of potentially suitable patients for trials.
- **Insufficient alignment of regulatory requirements between leading regulatory agencies**
Remaining differences in regulatory approval requirements lead to additional cost and efforts for companies seeking market approval.
- **Low market attractiveness in commercialization**
Low revenue expectations driven by necessary stewardship efforts and low prices make investments in antibiotics commercially unattractive. The low commercial attractiveness trickles down the value chain, leading to limited activity across all phases of the value chain.

This report evaluates a range of possible solutions based on their potential to address the challenges described above. Based on the evaluation, we propose a bundle of the following ten levers, which are most effective when combined together but do not all have to be implemented at the same time:

- **Lever 1: Target Product Profiles**
Develop global Target Product Profiles (TPPs) in order to steer research and development into the areas of the highest public health need and in order to have a globally accepted metric for the value of a new antibiotic. The Target Product Profiles will be based on the most urgent bacterial threats.
- **Lever 2: Global Antibiotics Research Fund**
Create a fund that supports basic research at academic institutions and small and medium-sized enterprises (SMEs). The priorities of the fund will be based on a strategic research agenda in-line with the Target Product Profiles. Priorities of the fund could be research into gram-negative bacteria and point-of-care diagnostics.
- **Lever 3: Global Antibiotics Research Prize**
Establish an annual prize rewarding scientific advancements in antibacterial research in order to increase the attractiveness of the research area and awareness for certain research challenges.
- **Lever 4: Antibiotics Research and Development Database**
Implement a database of past and ongoing research projects that allows researchers to identify promising research approaches and avoid duplicating research efforts.
- **Lever 5: Global Antibiotics Expert Network**
Set up a network of global antibiotics experts that supports ongoing research and development projects, especially those supported by the Global Antibiotics Research Fund and the partnerships in clinical development.

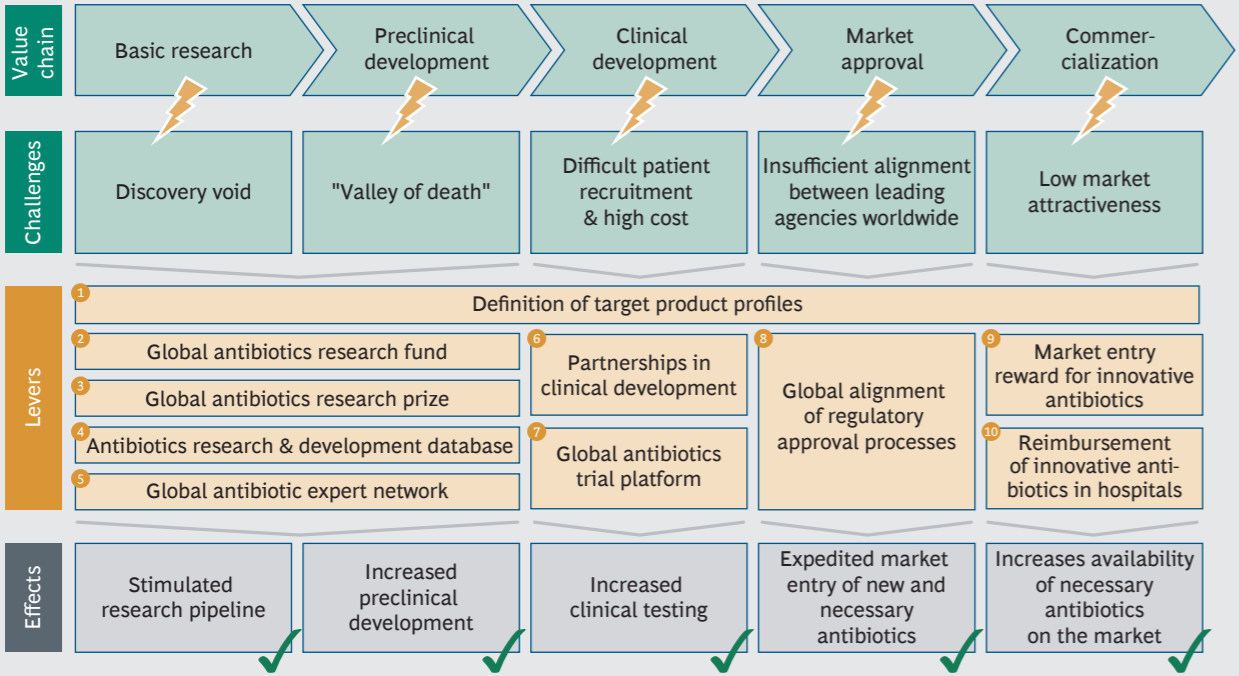
- Lever 6: Partnerships in Clinical Development**
 Establish partnerships in clinical development in order to support research institutions and small and medium-sized enterprises in advancing the clinical development of promising antibiotic candidates. Partnerships in clinical development include financial support as well as in-kind support (e.g., access to experts and laboratories).
- Lever 7: Global Antibiotics Trial Platform**
 Connect hospitals and developers through a global platform of antibiotics trials that allows matching suitable patients to ongoing antibiotics clinical trials.
- Lever 8: Global Alignment of Regulatory Approval Processes**
 Continue the alignment of regulatory approval processes for antibiotics, ultimately leading to a unified global regulatory pathway for antibiotics.
- Lever 9: Market Entry Reward for Innovative Antibiotics**
 Introduce a market entry reward for innovative antibiotics that meets the Target Product Profiles. The market entry reward has to be significant (i.e., in the order of €1,000 million) and will provide a reliable and predictable source of income that is delinked from sales volumes, thereby increasing the commercial attractiveness of antibiotics research and development.

- Lever 10: Reimbursement for Innovative Antibiotics in Hospitals**
 Ensure adequate reimbursement levels for innovative antibiotics, especially in a hospital setting.

Public and private actors share the responsibility to overcome the challenge of antimicrobial resistance. Therefore, we propose that market participants, e.g., pharmaceutical companies, contribute to financing the levers described above.

IMPLEMENTATION, COORDINATION, AND controlling across different initiatives have been major challenges within the last years. In order to advance the implementation of the levers proposed above, we recommend setting up a dedicated global antibiotics collaboration platform. The creation of such a collaboration platform will show a strong long-term commitment, which is essential given the magnitude of the challenge ahead of us.

FIGURE 1 | Overview of recommendations along the value chain



1. OBJECTIVES OF THIS REPORT

THE GERMAN FEDERAL MINISTRY of Health commissioned an advisory consortium consisting of ÖPP Deutschland AG (Partnerships Germany), The Boston Consulting Group (BCG), and the Healthcare Management Department of Berlin University of Technology (TU Berlin) to form an expert opinion entitled *Breaking through the Wall—Enhancing Research and Development of Antibiotics in Industry and Science*. This report is a summary of the expert opinion and its core statements. The report supports the German Global Union for Antibiotics Research and Development (GUARD) initiative.

Growing resistance to antibiotics and a lack of new, innovative antibiotics entering the market present a severe public health challenge. This public health challenge is exacerbated by a dramatic decrease in antibiotics research and development resources and capabilities. As the development of resistance to antibiotics is inevitable, a healthy pipeline of new antibiotics is essential. This requires investments into the development of new, innovative antibiotics. Experts agree that the current rate at which new, innovative antibiotics are developed is not sufficient to cover the requirements for new antibiotics. This has sparked a debate on a national and international level as to how an increased research and development (R&D) output can be encouraged.

The main objective of this report is to recommend a set of levers that stimulate research and development in antibiotics that address the most urgent public health needs on a global level.

Based on an analysis of the root causes behind the current situation and an assessment of potential incentive mechanisms, we propose sustainable levers to increase innovation in antibiotic research and development. A further central proposition of this report is to develop a framework for implementation to support, expand and refocus existing expertise and capacities.

This report is not a comprehensive review of all relevant aspects of antibiotic resistance. It rather seeks to propose a cohesive set of levers to enhance research and development of antibiotics in science and industry. Therefore, this report focuses on a single component of the antibiotic resistance—the lack of new antibiotics being developed and brought to market. We acknowledge that a successful response to this challenge will also need to address overuse, misuse, and premature resistance (conservation), as well as global access to antibiotics.

The findings and recommendations described in this report are based on multiple sources of information. These include, but are not limited to:

- Relevant scientific research and publications
- Firsthand data analysis of public and proprietary data
- Extensive expert interviews with diverse stakeholders (from research, industry, non-profit institutions, and the public sector)
- Experts from the working group “Antibiotics” of the German Pharma Dialog

WE ACKNOWLEDGE THAT the terms “antibiotics” and “antimicrobials” are often used interchangeably (though antimicrobials is a broader term) in the relevant literature. For clarity and readability we are using the term antibiotics in this report. In this report, this term will include natural and chemical compounds as well as targeted pathogens, such as fungi and bacteria.

2. ANTIBIOTIC RESISTANCE: A GLOBAL HUMANITARIAN CHALLENGE

ANTIBIOTICS ARE LIVE-SAVING DRUGS that need to be considered as a precious public good, as they are needed to cure and prevent the spread of bacterial infections. The use of antibiotics also constitutes a negative externality: Every time an antibiotic is used, there is a risk of bacteria developing resistance.³ Infections with antibiotic-resistant bacteria can lead to direct mortality, jeopardize the effectiveness of other standard medical procedures, and place a heavy cost burden on health-care systems. Antibiotics are used around the globe—in both human and animal health—and resistance can spread among bacteria. Thus, antibiotic resistance is a global problem.

2.1 Avoiding Clinical Failure in the Field of Antibiotics

2.1.1 The Global Impact of Antibiotic Resistance

While the impact of antibiotic resistance may still appear containable today, failure to address this challenge may lead to a serious and potentially uncontrollable global health threat, especially when considering that developing an antibiotic takes approximately 10 years.⁴ Therefore, it is critical that preventive action is taken now in order to avoid clinical failure in the coming decades.

In the European Union and United States alone, it has been estimated that 48,000 patients die per year as a direct consequence of infections caused by drug-resistant bacteria in both in- and outpatient settings.⁵ In many of these cases, an already weakened immune system is overpowered by the infection. Estimates of the global death toll caused by antimicrobial resistance vary, but estimates of up to 700,000 annually have been brought forward.⁶ While exact predictions of the future mortality caused by drug-resistant bacteria are very difficult, available forecasts, are as high as 10 million annual deaths worldwide by 2050. This illustrates the potential magnitude of the problem and the consequences of in action.⁷

Approximately 20,000 patients worldwide are estimated to die each year as a direct consequence of drug-resistant bacterial infections acquired during surgery.⁸ Both routine surgeries, such as hip and knee replacements, and emergency surgeries are becoming increasingly risky for patients. In addition to surgery, routine medical procedures such as using a catheter or intravenously administering fluids can potentially cause life-threatening bloodstream infections if resistance spreads further. Thus, antibiotic resistance threat-

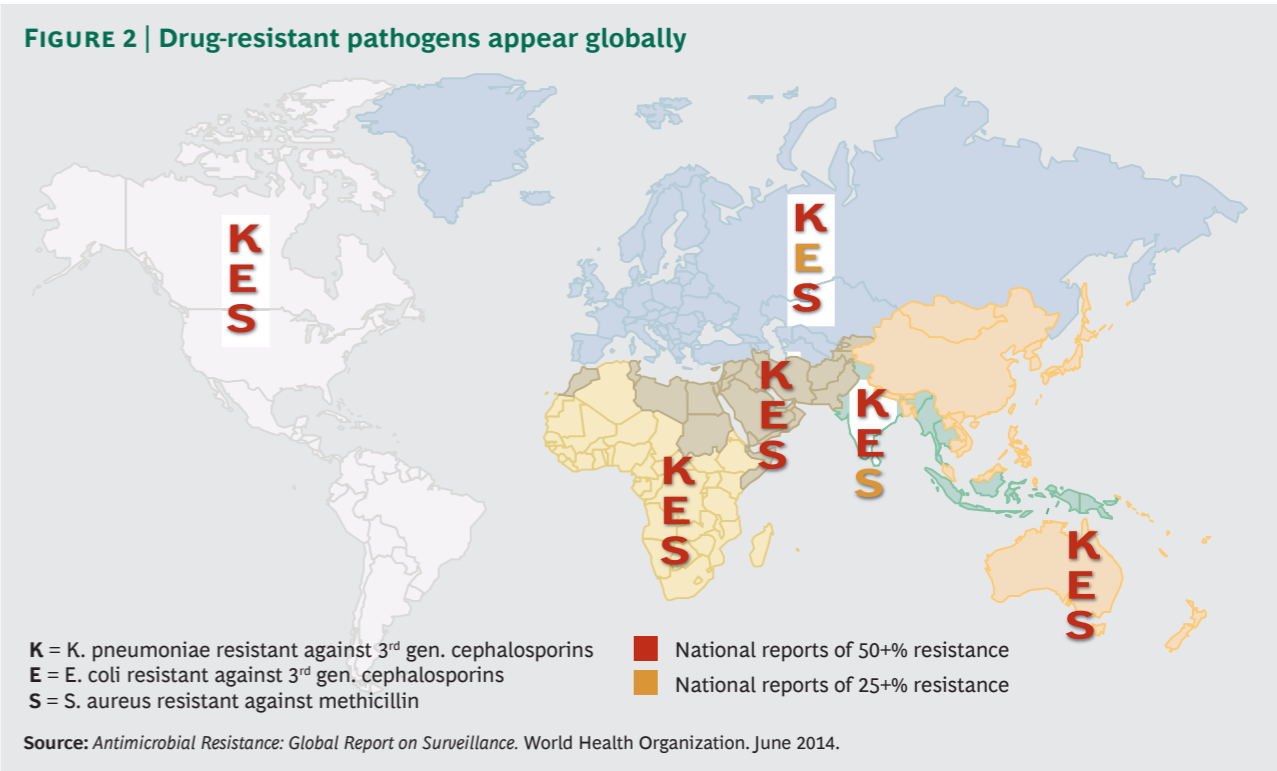
³Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. June 2014; Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention. April 2013; Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. December 2014.
⁴Trade & Innovation: Pharmaceuticals (OECD Trade Policy Working Paper No. 113). Organisation for Economic Co-operation and Development. March 2011.
⁵The bacterial challenge: time to react. ECDC/EMA. September 2009; Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention. April 2013.
⁶Figure includes drug-resistant HIV and drug-resistant malaria; Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. December 2014.
⁷Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. December 2014.
⁸Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, A Public Health Crisis Brews. Infectious Diseases Society of America. July 2004; Surgical Site Infection (SSI) Event. Centers for Disease Control and Prevention. January 2015.

ens the effectiveness of medical procedures that we have grown accustomed to, which, in a worst-case scenario, may catapult us into a “medical dark age”⁹.

An additional aspect of the antibiotic resistance challenge is the economic burden of increased mortality and morbidity. For example, within the EU it is estimated that the current cost of antibiotic resistance amounts to €1.5 billion annually.¹⁰ This includes increased health-care costs caused by additional hospital stays, expensive treatment, isolation measures and loss of productivity. Cost associated with antibiotic resistance is expected to increase dramatically over the upcoming decades. Antibiotic resistance therefore stretches the capacity of health-care systems around the globe and impacts our social and economic system. Low-income regions in particular are expected to experience the greatest burden.¹¹

2.1.2 Use of Antibiotics Is Reducing Their Effectiveness

Some of the most common bacterial pathogens have been reported to exhibit 50% or more resistance against commonly used antibiotics (figure 2).¹² In all of the six World Health Organization (WHO) regions, these very high resistance rates have been found for three common bacteria strains, demonstrating that resistant bacteria are an increasing concern.



⁹BBC report. Antibiotic resistance: Cameron warns of medical 'dark ages'. <http://www.bbc.com/news/health-28098838>
¹⁰The bacterial challenge: time to react. ECDC/EMA. September 2009.
¹¹Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. December 2014.
¹²Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. June 2014; WHO regions: African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region, Western Pacific Region.

This includes bacteria such as *K. pneumoniae*, *E. coli*, and *S. aureus* all of which can cause bloodstream infections and other diseases. In all three examples, the drug-resistant bacterium was found to cause a statistically significant increase in mortality attributable to the infection when compared to the drug-susceptible form.¹³ The wide use of antibiotics will exacerbate this development.

Increased Global Use Is Causing Antibiotic Resistance

Global antibiotic consumption in human medicine has been reported to have increased by 36% between 2000 and 2010. This trend is largely driven by increased consumption in Brazil, Russia, India, China, and South Africa.¹⁴ Only in developed countries such as the US, Canada, Japan, France, Germany, Italy and many other EU countries, a slight decline in the use of antibiotics has been observed.¹⁵ In veterinary medicine, a global increase of antibiotic consumption of 67% between 2010 and 2030 has been forecasted if no additional measures are taken to restrict use.¹⁶ The use of antibiotics in food-producing animals can lead to resistance development, which can also affect humans through the environment or consumption of these animal products.¹⁷

Particularly worrying are estimates that up to half of all antibiotics are unnecessarily or incorrectly taken.¹⁸ For example, many patients demand antibiotics for the treatment of the common cold. Physicians could therefore be under pressure to prescribe antibiotics even though they are not needed.¹⁹ Efforts to reduce the inappropriate use of antibiotics have been made, with differing success rates across countries and between inpatient and outpatient settings.²⁰

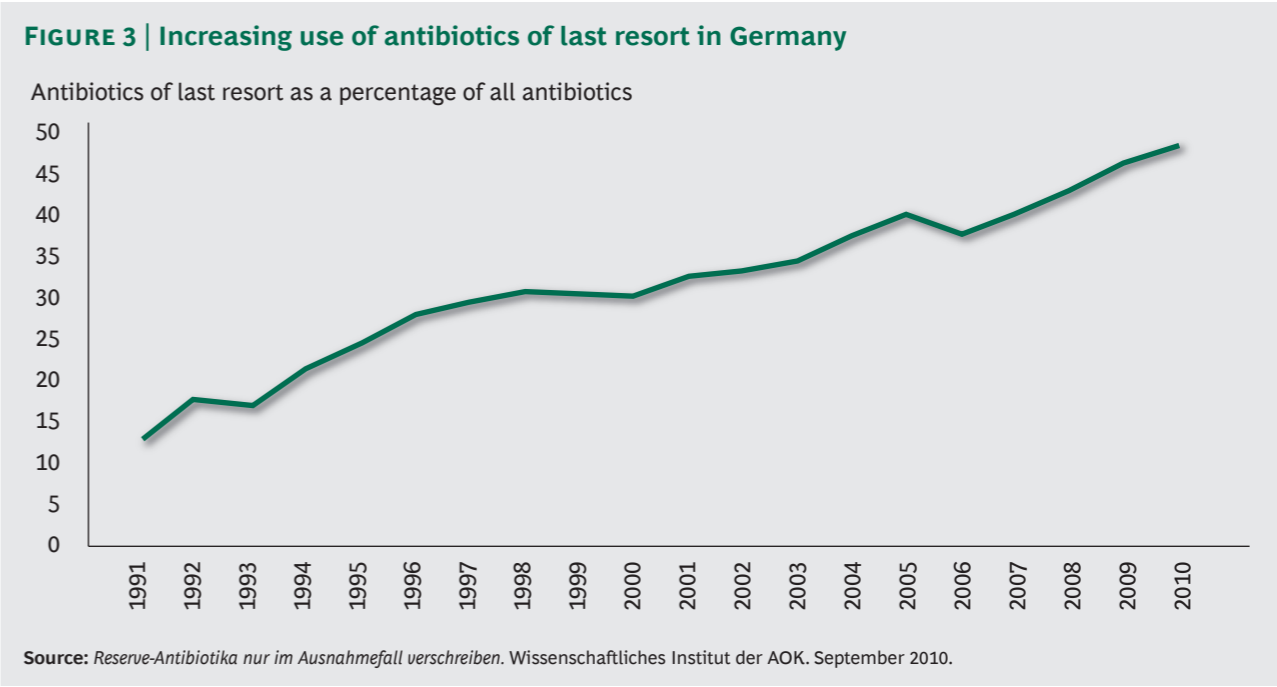
Lack of Point-of-Care Diagnostics Exacerbates the Problem

The lack of point-of-care diagnostic tools is a major obstacle that prevents physicians from prescribing antibiotics in a targeted manner. While promising innovations in rapid point-of-care diagnostics have been made, standard diagnostics often still require at least one day.²¹ Physicians therefore frequently prescribe antibiotics based on symptoms with no definitive diagnosis of the causative bacteria. This results in the prescription of antibiotics for nonbacterial infections as well as antibiotics which have no efficacy against the causative pathogen.

Increased Use of Antibiotics of Last Resort is not Sustainable

Antibiotic resistance is spreading, and so is the use of antibiotics of last resort. Between 2000 and 2010, global consumption of two classes of antibiotics of last resort rose significantly: *carbapenems* by 45% and *polymyxins* by 13%.²² This is a troubling development,

considering that, in order to preserve their efficacy against bacteria, antibiotics of last resort should only be used sparsely and only when other methods of treatment have failed. In Germany, for example, the share of antibiotics of last resort in all antibiotics prescriptions has risen steadily over the past 20 years reaching 46.5% in 2010 (figure 3).²³



2.1.3 Few New Treatment Options Coming to Market

As existing antibiotics of last resort slowly become a more common treatment and thus also lose their efficacy, new antibiotics are needed to serve as the next generation of antibiotics of last resort. Unfortunately, the market participants traditionally developing and launching new antibiotics have largely left the field. Of the 20 largest pharmaceutical companies worldwide which were active in antibiotics research in the 1990s, only four remain in this field in 2014.²⁴ Consequently, approvals of new antibiotics by the FDA have steadily declined, reaching an all-time low in 2010–2012 (figure 4).²⁵

2.1.4 Summary

Antibiotics save lives and prevent the spread of bacterial infections. However, the use of antibiotics also promotes the development of antibiotic resistance, which can lead to increased mortality, morbidity and cost. The consumption of antibiotics has increased worldwide, including use of antibiotics of last resort. Thus, new antibiotics are urgently needed to complement existing ones. However, the rate at which new antibiotics are approved is insufficient to satisfy the demand. This development can potentially have dramatic consequences if no action is taken.

¹³Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. June 2014.

¹⁴Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Van Boeckel TP, Gandra S, Ashok A, et al. Lancet Infect Dis. July 2014.

¹⁵Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Van Boeckel TP, Gandra S, Ashok A, et al. Lancet Infectious Diseases. July 2014.

¹⁶Global trends in antimicrobial use in food animals. Van Boeckel TP, Brower C, Gilbert M, et al. February 2015. Proc Natl Acad Sci U S A.

¹⁷Antimicrobial resistance in zoonotic enteric pathogens. Angulo, Nunnery, Bair. August 2004.

¹⁸Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention. April 2013.

¹⁹Patient demand drives antibiotic overuse. Healthline. 2014.

²⁰Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Van Boeckel TP, Gandra S, Ashok A et al. Lancet Infect Dis July 2014.

²¹New test system identifies 193 different yeasts and bacteria known to cause illness. U.S. Food and Drug Administration. August 2013.

²²Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Van Boeckel TP, Gandra S, Ashok A et al. Lancet Infect Dis July 2014.

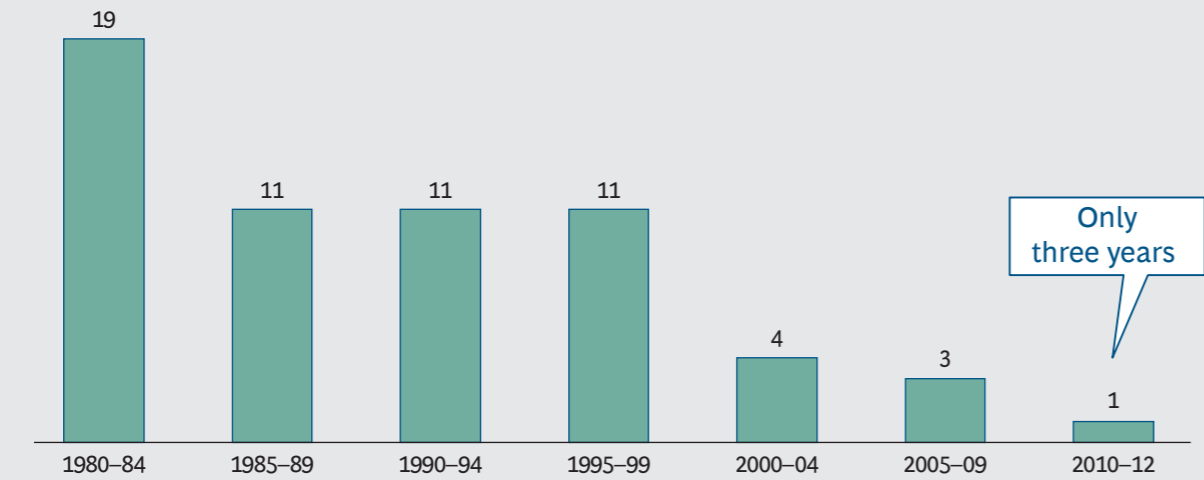
²³Reserve-Antibiotika nur im Ausnahmefall verschreiben. Wissenschaftliches Institut der AOK. September 2010.

²⁴Roche returns to antibiotic research as superbug threat grows. Reuters. June 2014; Despite superbug crisis, progress in antibiotic development 'alarmingly elusive'. Infectious Diseases Society of America. April 2013.

²⁵Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention. April 2013.

FIGURE 4 | Number of antibiotics being approved by the FDA is decreasing

FDA approvals of antibiotics NDAs
(new drug applications)



Source: Antibiotic Resistance Threats in the United States 2013. Centers for Disease Control and Prevention. 2013.

2.2 Addressing the Greatest Public Health Threats Posed by Bacteria

2.2.1 Not All Bacteria Equally Dangerous

Pathogenic bacteria vary in their infection rates, resistance levels, and morbidity and mortality rates. These factors can be used to estimate the public health threat that various bacteria pose. Different groups have developed lists of the most relevant bacterial threats, including the FDA (US Food and Drug Administration), and EMA (European Medicines Agency).²⁶ In a US-specific report published by the US Centers for Disease Control and Prevention (CDC), 17 groups of bacteria were classified into three threat levels: urgent, serious, and concerning. Three groups of bacteria were classified into the highest threat level of “urgent”: *C. difficile*, which is estimated to be responsible for 14,000 deaths annually in the United States, Carbapenem-resistant *Enterobacteriaceae*, which have become resistant to nearly all antibiotics and cause approximately 600 deaths per year, and drug-resistant *N. gonorrhoeae*, which is responsible for 246,000 infected patients per year.²⁷

Infection rates and resistance development vary across regions and comprehensive surveillance is often lacking.²⁸ At present, it is challenging to assess the global health threat that specific bacteria pose and what regions are most affected. In particular, assessments of the dynamic resistance development are dependent upon high-quality surveillance not yet established globally. Setting up and improving national surveillance systems is therefore essential to allow a targeted and specific approach to combating antibiotic resistance.

²⁶Antimicrobial Resistance: Global Report on Surveillance; WHO Report. FDA QIDP list of qualifying pathogens; The bacterial challenge: time to react. ECDC/EMA Report.

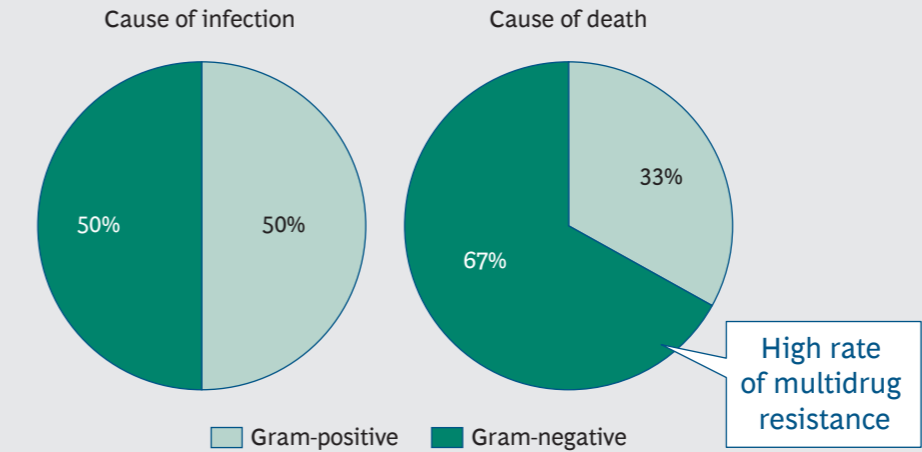
²⁷Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention. April 2013.

²⁸Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. June 2014.

2.2.2 Antibiotics Against Drug-Resistant Gram-Negative Bacteria Are Needed

Gram-negative bacteria are widely considered to be a greater clinical concern than gram-positive bacteria, especially when resistant strains are involved.²⁹ In Europe, a joint study by ECDC (European Centre for Disease Prevention and Control) and EMA has found that the analyzed drug-resistant gram-positive and gram-negative bacteria are approximately equally infectious.³⁰ However, the study has shown that infections with gram-negative bacteria are more often deadly: In 2007, the most recent year for which data is available, two-thirds of deaths caused by drug-resistant infections were attributable to gram-negative bacteria (figure 5).³¹

FIGURE 5 | Gram-negative bacteria cause more deaths (inpatient care)



Source: BCG analysis

A high rate of multidrug resistance is observed in gram-negative bacteria, in part due to the number of defense mechanisms these bacteria possess (figure 6).³² *K. pneumoniae*, for example, is a gram-negative bacterium frequently associated with pneumonia and bloodstream infections. Like other gram-negative bacteria, it has an outer membrane whose properties make it more challenging to design effective antibiotics.

Global levels of antibiotic resistance in *K. pneumoniae* have reached 40% thus far in 2015, and mortality rates in the range of 47–66% have been reported for patients infected with specific drug-resistant *K. pneumoniae* strains.³³ Similar trends are also observed with other drug-resistant gram-negative bacteria.³⁴

²⁹Securing New Drugs for Future Generations: The Pipeline of Antibiotics. Review on Antimicrobial Resistance. May 2015; Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention. April 2013.

³⁰Analyzed drug-resistant gram-positive bacteria: methicillin-resistant *S. aureus*, vancomycin-resistant *E. faecium*, penicillin-resistant *S. pneumoniae*.

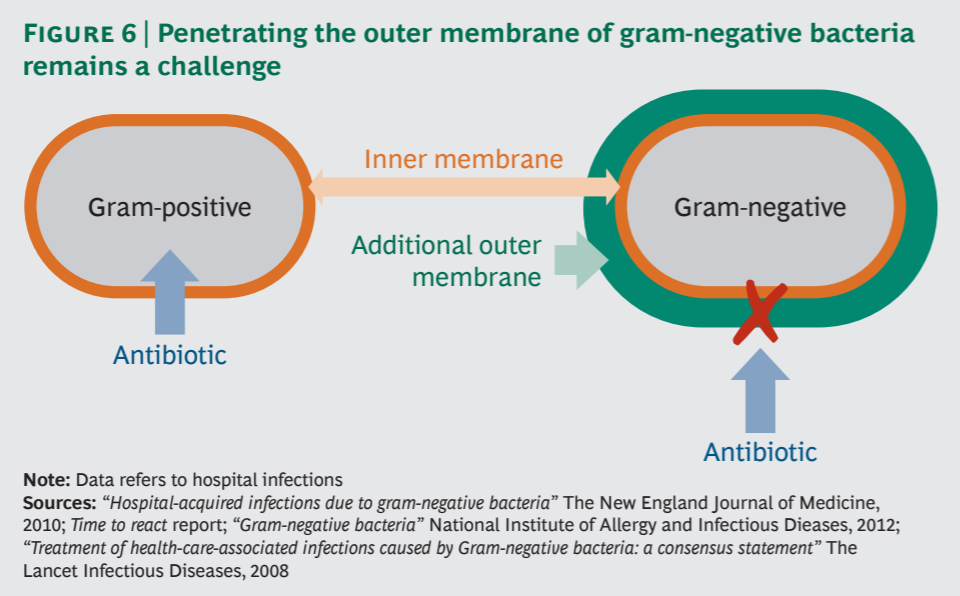
³¹Analyzed drug-resistant gram-negative bacteria: third-generation cephalosporin-resistant *E. coli*, third-generation cephalosporin-resistant *K. pneumoniae*, carbapenems-resistant *P. aeruginosa*; See The bacterial challenge: time to react. ECDC/EMA. September 2009.

³²The bacterial challenge: time to react. ECDC/EMA. September 2009.

³³Treatment of healthcare-associated infections caused by Gram-negative bacteria: a consensus statement. Chopra, Schofield, Everett et al. February 2008.

³⁴As measured by resistance to third-generation cephalosporins; data from the African Region, Region of the Americas, European Region and South East Asian Region was used; Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. June 2014; Emergence of *Klebsiella pneumoniae* Carbapenemase (KPC)-Producing Bacteria. Arnold, Thom, Sharma et al. January 2011; Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. June 2014. Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention. April 2013.

Basic research is needed to advance the understanding of gram-negative bacteria and to eventually design antibiotics that overcome the multiple defense mechanisms of gram-negative bacteria.



2.2.3 Diagnostics Are Required for Effective Use of Narrow-Spectrum Antibiotics

As described before, the lack of rapid point-of-care diagnostics makes it difficult for physicians to prescribe targeted treatments. Especially the use of narrow-spectrum antibiotics, which are effective only against one or few types of bacteria, is suffering from this challenge.

Therefore, it is essential to not only develop new drugs against bacteria but to also develop the diagnostics that allow rapid and targeted use of existing and potential new treatments.

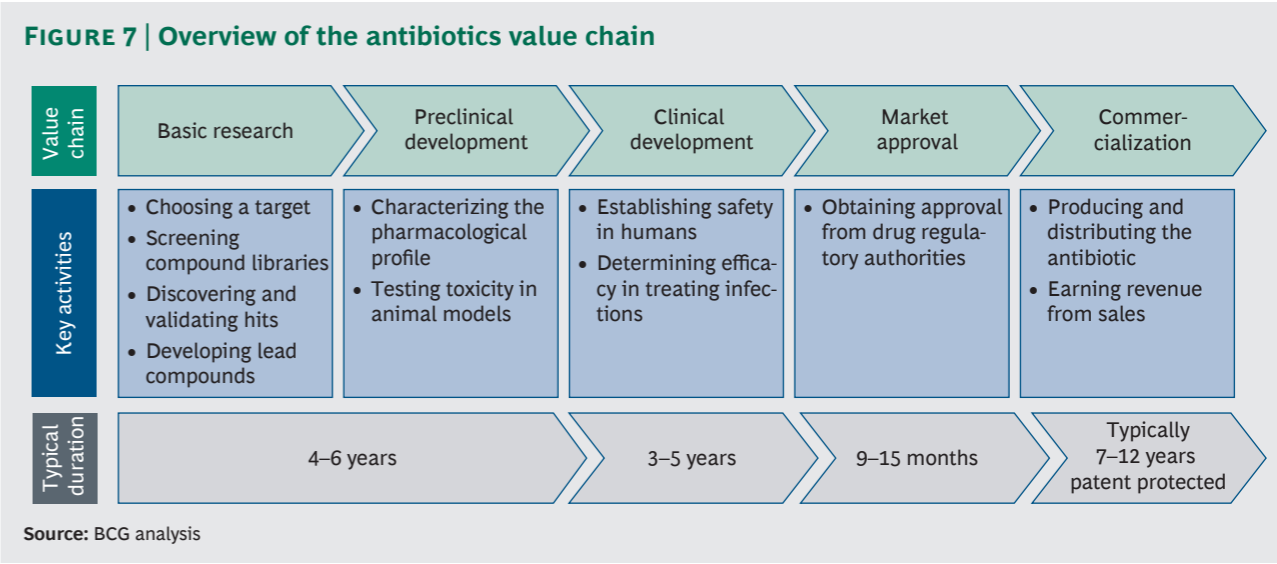
2.2.4 Summary

There are substantial variations in resistance levels among different bacteria, and not all drug-resistant bacterial infections are equally dangerous. It is therefore important to assess the potential health threat of different bacteria. Multidrug-resistant gram-negative bacteria are widely considered an urgent public health threat. Additionally, developing point-of-care diagnostics is important to ensure that antibiotics can be used in a targeted manner.

3. MAIN CHALLENGES IN ANTIBIOTICS RESEARCH AND DEVELOPMENT

THE DISCOVERY, DEVELOPMENT and marketing of an antibiotic can be segmented into five successive phases along a value chain (figure 7). This chapter provides an in-depth look into the challenges that exist along the value chain of antibiotic research and development. While challenges exist along the entire value chain for public and private players alike, the two major challenges are the low commercial attractiveness of antibiotics and a lack of promising leads in basic research. This combination is unique to antibiotics. While other therapeutic areas also face scientific challenges, the incentive to tackle these challenges is much higher if there is a commercially attractive market. This can be seen in therapeutic areas like Alzheimer’s disease, in which immense resources are mobilized because of the commercial attractiveness of a potential breakthrough drug even though the scientific problems are highly complex and challenging.

This chapter will take the reader through each step of the value chain, analyzing potential challenges from the perspectives of the main stakeholders involved.



3.1 Challenges in Basic Research and Preclinical Development

In this report, basic research refers to the general knowledge of biological processes and the discovery of potential targets for new antibiotics. Basic research is a main prerequisite for discovering new antibiotic candidates that could subsequently enter preclinical development.

3.1.1 Changing Landscape of Active Participants

The top patent filers in antibiotics research across all players between 2001 and 2013 have been pharmaceutical companies. However, the interest of large pharmaceutical

companies in antibiotics declined during that time, as an analysis of the patent application activity of the top 100 pharmaceutical companies shows (top 100 based on world-wide sales) (figure 8).³⁵

The number of antibiotic patents filed by the top five patent filers from the pharmaceutical industry decreased even more dramatically from over 40 patent families per year in 2001 to only ten in 2013 (figure 10). This is concerning, since the pharmaceutical industry has traditionally been a key contributor to antibiotic development, and its re-engagement into antibiotics research is urgently needed to reverse the loss of innovation in antibiotics.

The low interest of pharmaceutical companies in antibiotic research is exemplified by the following statistic: in the past 11 years, the world’s top 10 pharmaceutical companies based on global sales have filed significantly more patents in rare disease research and vaccines than antibiotics (figure 9). While there have been 1,195 patents filed in antibiotics between 2004 and 2015, that number is almost twice as high in vaccines (2,113 patents) and 7 times as high in rare diseases (8,689 patents).

Academic institutions traditionally play an important role in the early-stage discovery of drugs. The top 100 academic institutions in terms of patents filed related to antibiotics between 2001 and 2013 have increased their patent application activity. Despite this positive development, funding for antibiotics research from both governmental institutions and pharmaceutical companies is still insufficient. Nevertheless, the growing interest of

academic institutions is a promising development for the basic research of antibiotics. Interestingly, a similar trend can be observed for governmental institutions in the same time frame from 2001 to 2013.³⁶ Here too, the number of patent family applications has grown.

FIGURE 9 | Top 10 pharmaceutical companies focus on other areas

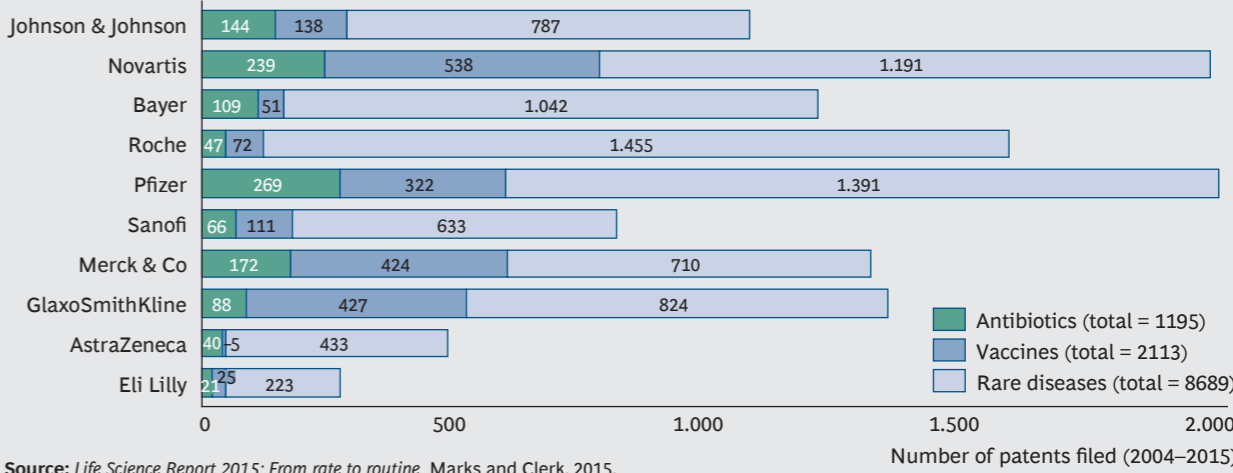


FIGURE 10 | Interest from the top 5 players is declining rapidly

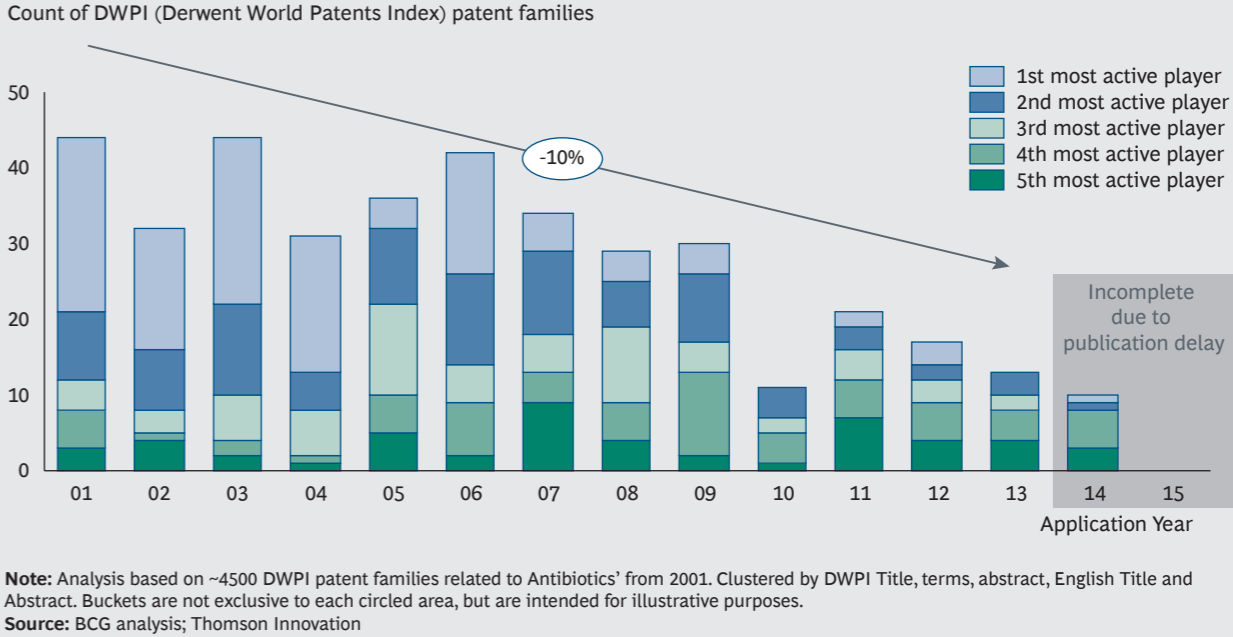
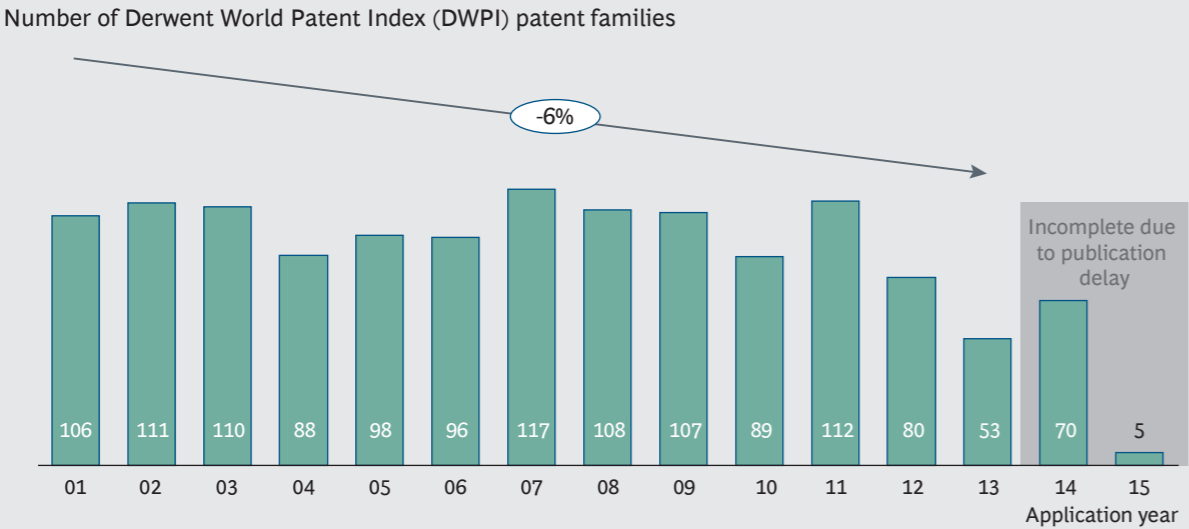


FIGURE 8 | Continuously decreasing activity of top 100 pharmaceutical companies in antibiotic research



³⁵Analysis based on about 4,500 Derwent World Patent Index (DWPI) patent families related to antibiotics from 2001. Clustered by DWPI title, terms, and abstract. Note that patent data is incomplete for 2014–2015 due to publication delays. Source: Thomson Innovation. BCG analysis. It should be noted that patent filing activity may be biased toward pharmaceutical companies, as these tend to have a greater interest in filing patents than academic institutions.

³⁶Analysis based on about 4,500 DWPI patent families related to antibiotics from 2001. Clustered by DWPI title, terms, and abstract. Note that patent data is incomplete for 2014–2015 due to publication delays. Source: Thomson Innovation; BCG analysis.

The development described above constitutes a significant change in the landscape of antibiotic research and discovery. Industry players are leaving research and public and academic institutions are slowly increasing their efforts without fully compensating for the industry’s exit.

3.1.2 Loss of Talent Threatening Research and Preclinical Development Activity

The closure of centers for antibiotics research and the steady exit of the pharmaceutical industry from antibiotics research have a direct effect on the researcher community. One of the greatest concerns in antibiotics research and development is the ongoing brain drain as researchers exit the area.³⁷ Multiple experts interviewed for this report have estimated that there are as few as 250–500 dedicated experts actively researching in the area of antibiotics, approximately half of those in academic and public institutions and half in pharmaceutical companies. This development has progressed so far that one interviewed stakeholder called antibiotics researchers “an endangered species.”

The steady exit of often older researchers is accompanied by difficulties in attracting new researchers for anti-infectives research. In the United States, for example, there are only 0.8 applicants per available fellowship and medical residency in this area. This is significantly lower than in other research areas, such as cardiovascular diseases (1.4 applicants per position) and neurology (2.5 applicants per position).³⁸

3.1.3 Traditional Research and Discovery Approaches Less Effective for Antibiotics

The “golden era of antibiotic discovery” lasted roughly from 1945 to 1960. Since then, there has been a strong decline in the number of novel antibiotic classes. One of the reasons for the “discovery void” in antibiotics is the failure of the dominant drug discovery strategies that have been applied in recent years. It was thought that the advance of bacterial genomics (the study of bacterial DNA) and modern in-vitro, target-based approaches would lead to many new antibiotic discoveries. Although such methods proved successful in other areas, they have not yet yielded the desired results in the area of antibiotics.

3.1.4 The Valley of Death in Preclinical Development

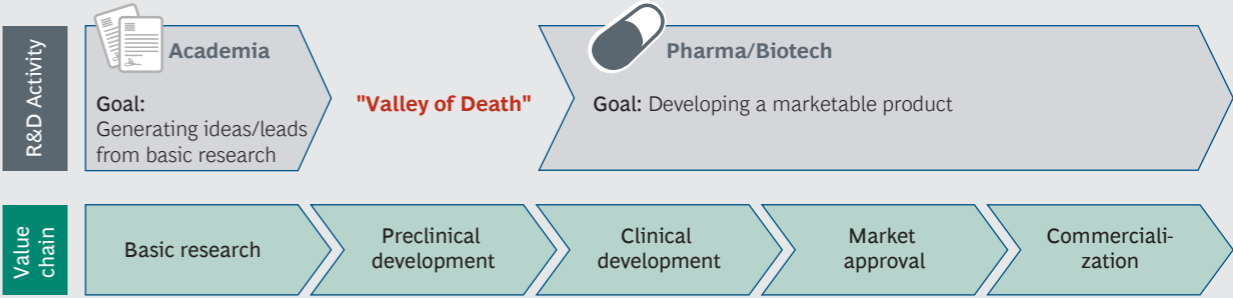
Experts from both academic institutions and the pharmaceutical industry frequently point out the gap that exists between basic research and clinical development. One interviewee described this gap as the “valley of death” (figure 11). The main problem is that preclinical development is more expensive than basic research on a per-compound basis. Preclinical development is primarily conducted in direct preparation for clinical development. If clinical development is not commercially attractive, there will be little activity in preclinical development as well. The consequence, in the words of another expert, is that “there is a cemetery of good ideas”.

3.1.5 Mostly Isolated Efforts in Preclinical Development

The “valley of death” mentioned above can be attributed in part to a lack of exchange between academic institutions and pharmaceutical companies, although good examples of cooperation exist. This effect is highlighted by an analysis of the patent citation network. In the following diagram, two players are connected with a line when the published

³⁷Combating Antimicrobial Resistance: Policy Recommendations to Save Lives. Robert Guidos, Infectious Diseases Society of America. May 2011.
³⁸Tackling a global health crisis: initial steps. The Review on Antimicrobial Resistance. February 2015.

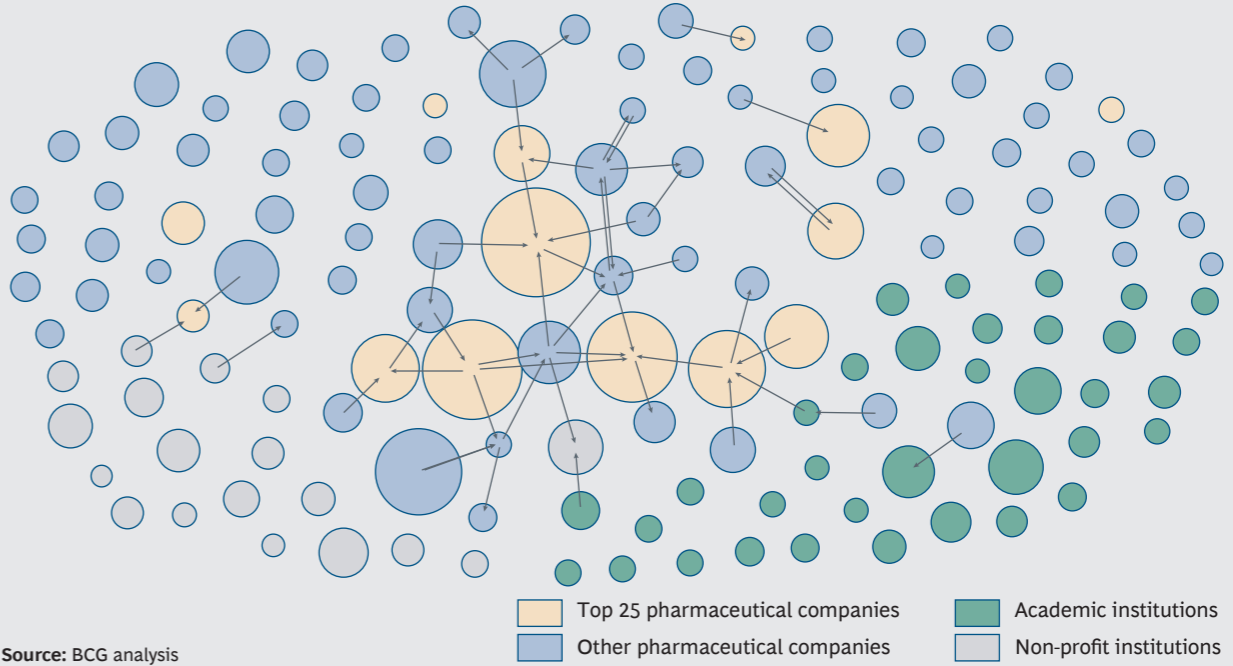
FIGURE 11 | The “valley of death” in antibiotics research and development



patent of one player references the patent of another player (the arrow points toward the cited player). Few patents published in the area of antibiotics cite existing patents (figure 12).³⁹ This low degree of connectedness indicates a potential area of improvement. Improving the connectedness of the most important organizations and individuals will be paramount to improve the effectiveness of preclinical development.

Inefficiency and duplication of efforts has also been repeatedly mentioned during expert interviews and in literature.⁴⁰ Especially failed and abandoned projects are not made available for the scientific community.

FIGURE 12 | Cooperation in patent application relatively low



³⁹Citation network of patents with application date 1.1.2001 to 1.8.2015. Only players with at least 4 patents published in this timeframe are shown. Circle area reflects number of patents published during this time period. Lines denote citations from one assignee's patent portfolio to the other. Arrows on the lines indicate the direction. Source: NCompassIP (TouchGraph); BCG Analysis
⁴⁰Strategic Research Agenda. Joint Programming Initiative on Antimicrobial Resistance. December 2013; Innovative public-private collaboration launches to tackle antibiotic research. AstraZeneca. May 2012.

There are examples of intensive cooperations between research institutions and pharmaceutical companies. For example, Sanofi and Fraunhofer Institute for Molecular Biology and Applied Ecology (Fraunhofer IME)⁴¹ have created an institute for research of natural compounds. It allows Sanofi to access Fraunhofer’s extensive database of microorganisms, while Fraunhofer IME can benefit from Sanofi’s expertise in developing anti-infectives.

3.1.6 Summary of Challenges in Basic Research and Preclinical Development

The top pharmaceutical companies are leaving basic research and preclinical development in antibiotics. Other players, notably academic institutions, are increasing their engagement in the area but do not compensate the lack of activity from large pharmaceutical companies, given insufficient funding and the low prestige of antibiotics research. The resulting brain drain from the area of antibiotic research leads to a loss of decades of valuable research experience; experience which is desperately needed to make progress on the scientific challenges of antibiotic development, especially for gram-negative bacteria, and refill the “discovery void” in basic research.

In basic research and preclinical development, the lack of exchange across active players leads to duplicated efforts and inefficient resource allocation. A revival of basic research and preclinical development must therefore address issues of coordination, funding and talent recruiting and retention.

3.2 Challenges in Clinical Development

Clinical development encompasses trials that test the safety and efficacy of an antibiotic in humans. As with other drugs, clinical trials are typically split into three main phases, which differ in duration, length, number of volunteers/patients, and objectives.⁴²

3.2.1 Cost of Developing for Antibiotics Lower Than for Other Drugs but still Significant

Antibiotics that pass through the “valley of death” in the preclinical phase (discussed in 3.1.5) and enter clinical development have relatively high rates of success (figure 13).⁴³

The high success rate in clinical development is partly driven by animal models being more reliable for antibiotics than for other therapeutic areas. This particularly applies to preclinical toxicity, where animals are used to estimate possible toxicity in humans. The guinea pig, for example, is frequently used to study antibiotics because it is highly sensitive to them.⁴⁴ The overall high success rates in later development phases and the good predictability of animal models allow for development programs to “fail early”, reducing the cost of developing antibiotics. The success rates for pharmaceuticals in general are significantly lower (e.g., phase II success rate: 30%; phase III success rate: 59%) These lower success rates increase the typical cost of clinical trials significantly.⁴⁵

⁴¹Fraunhofer Institut für Molekularbiologie und Angewandte Ökologie [Institute for Molecular Biology and Applied Ecology].

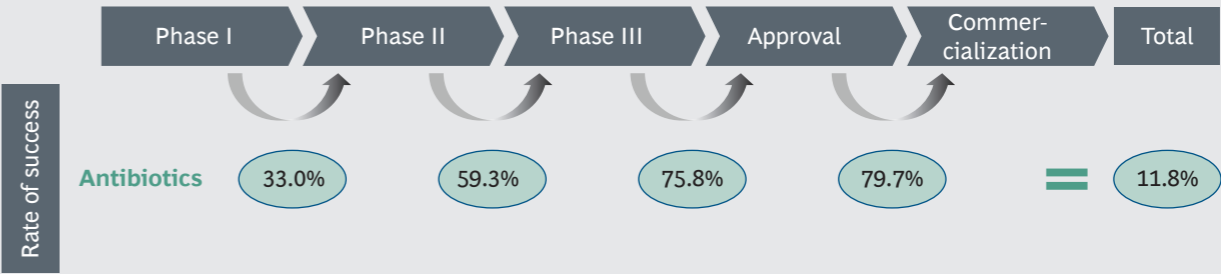
⁴²The FDA’s Drug Review Process: Ensuring Drugs Are Safe and Effective. Food and Drug Administration. June 2014; Overview of Clinical Trials. CenterWatch. 2015.

⁴³Antibiotics: An Analysis of Approved Drugs, Pipelines, and Approvability. BioMedTracker. 2014.

⁴⁴The Guinea Pig as a Model of Infectious Diseases. Padilla-Carlin, McMurray, Hickey. August 2008.

⁴⁵Antibiotics: An Analysis of Approved Drugs, Pipelines, and Approvability. BioMedTracker. 2014.

FIGURE 13 | Success rates in clinical development of antibiotics



Source: Securing New Drugs for Future Generations: The Pipeline of Antibiotics. The Review on Antimicrobial Resistance. May 2015.

Still, clinical development is an expensive endeavor that has been estimated to cost around €120 million on average per marketed antibiotic.⁴⁶ This excludes the cost of failure for compounds that did not make it to the market and the cost of marketing the antibiotic. Thus, total development cost of an antibiotic is significantly higher and is estimated to be about €700–1,100 million.⁴⁷ This includes the clinical costs described above and investments in basic and preclinical development where large investments are necessary to test many compounds in the hopes of finding a lead compound for further development. Seeking approval and marketing the product require further significant investments.

The resources required for clinical development are prohibitively high for small and medium-sized enterprises (SMEs) and academic institutions. This is reflected in the observation that only 4% of antibiotics in clinical development belong to academic institutions. Furthermore, academic institutions are not active in phase III trials of antibiotics, which are significantly more expensive than phase I and II trials).⁴⁸

3.2.2 Largest Pharmaceutical Companies Not Active Investors in Development

With the exit of the largest pharmaceutical companies from antibiotics research and development (R&D), their contribution to innovation is also declining. In 2014, only 15% of the antibiotics in clinical development belonged to one of the top 25 pharmaceutical companies (figure 14, right chart).⁴⁹ This signifies a substantial loss in investment potential in antibiotic research and development and stands in strong contrast to the fact that the top 25 pharmaceutical companies spend approximately two-thirds of the world’s pharmaceutical R&D budget (figure 14, left chart).⁵⁰

⁴⁶Securing New Drugs for Future Generations: The Pipeline of Antibiotics. The Review on Antimicrobial Resistance. May 2015.

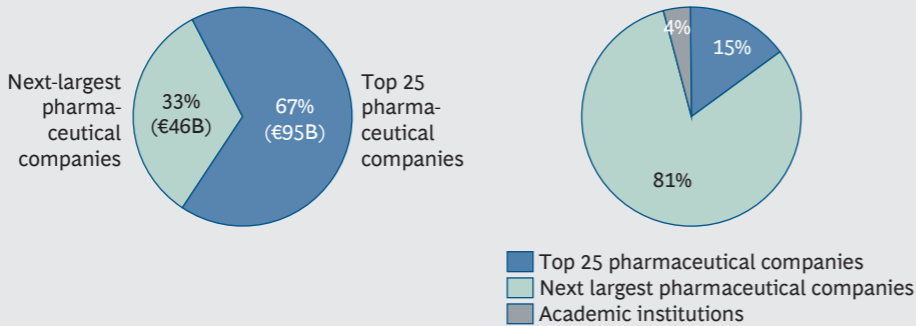
⁴⁷Securing New Drugs for Future Generations: The Pipeline of Antibiotics. The Review on Antimicrobial Resistance. May 2015; The fallacies of hope: will we discover new antibiotics to combat pathogenic bacteria in time?. Vicente, Hodgson, Massidda. July 2006. Report to the President on Combating Antibiotic Resistance. Executive Office of the President of the United States. September 2014; Policies and Incentives for Promoting Innovation in Antibiotic Research. Mossialos, Morel, Edwards et al. 2010.

⁴⁸EvaluatePharma. 2014.

⁴⁹Securing New Drugs for Future Generations: The Pipeline of Antibiotics. The Review on Antimicrobial Resistance. May 2015.

⁵⁰The “next largest pharmaceutical companies” is composed of the 2,033 next-largest pharmaceutical companies. EvaluatePharma. 2014.

FIGURE 14 | Worldwide R&D investments and clinical activity in antibiotics in 2014



¹ EvaluatePharma. 2014.

² The group "Remaining Pharma" is composed of the 2033 next-largest pharmaceutical firms

Smaller pharmaceutical companies and biotechnology firms specialized in anti-infectives (e.g., antibiotics, antimicrobials) are now the primary investors in antibiotics, along with selected academic institutions. Supporting these innovative small and medium-sized companies (SMEs) in financing the later stages of clinical development will have a positive impact on the antibiotics pipeline.

3.2.3 Operational Challenges in Running Clinical Trials

Clinical trials in antibiotics have the major advantage of being very short compared to other indications. For example, antibiotic treatment for urinary tract infections is typically limited to three days, for community-acquired pneumonia to five days, and for ventilator-associated pneumonia to eight days.⁵¹ The FDA, for example, requires endpoints as short as 48–72 hours after treatment initiation for acute bacterial skin and skin structure infections.⁵²

Unfortunately, the flip side to short treatment times is that many bacterial infections are acute.⁵³ The interviewed experts repeatedly emphasized the difficulty of recruiting patients with acute infections, as the time window to identify patients and initiate treatment is very narrow. The lack of unified patient databases leads to a significant logistical and administrative effort when trying to recruit a sufficient number of patients for clinical trials. The situation is further complicated by the lack of rapid point-of-care diagnostics, increasing the challenge of recruiting patients with infections caused by specific bacteria.

Within the EU, initial steps to address this issue have been initiated by the CLIN-Net (Clinical-Net) project of the COMBACTE (Combating Bacterial Resistance in Europe) program, which was initiated in 2013⁵⁴. CLIN-Net aims to support and coordinate clinical trials of antibiotics by developing a network of qualified clinical trial sites. While this is an

⁵¹ *General Principles of Antimicrobial Therapy*. Leekha, Terrell, Edson. February 2011.

⁵² *Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*. Food and Drug Administration. October 2013.

⁵³ *Chronic bacterial infections: living with unwanted guests*. Young, Hussell, Dougan. November 2002.

⁵⁴ The COMBACTE (Combating Bacterial Resistance in Europe) project, resulting from the sixth Call for proposals issued by the Innovative Medicines Initiative (IMI), is one of the projects that is part of the "New Drugs For Bad Bugs" (ND4BB) programme. CLIN-Net is the clinical trial network within COMBACTE.

important step forward, it is solely focused on the EU. Similar initiatives with a more global scope would be required to truly overcome the challenge of recruiting patients for clinical trials in antibiotics.

3.2.4 Lack of Practitioners with Required Skills

Because bacterial infections can occur in different tissues, clinical trials in antibiotics can require medical expertise ranging from dermatology to gynecology to internal medicine.⁵⁵ This wide range of expertise poses a challenge in training practitioners to carry out clinical trials for antibiotics according to necessary standards. Interviews with experts have revealed that the lack of practitioners experienced in antibiotics trials poses a challenge in conducting them appropriately. The lack of interest in fellowships and medical residencies in the area of anti-infectives (discussed in chapter 3.1.2) further exacerbates this problem.

3.2.5 Summary of Challenges in Clinical Development

Despite the relatively good success rates of antibiotic candidates in clinical development, the clinical development of antibiotics is still a costly endeavor. The high cost associated with clinical development often prevents SMEs and academic institutions from advancing antibiotics throughout the different development phases, thereby excluding important innovators. Across all phases, recruiting patients and finding medical practitioners that are experienced in clinical trials are challenges that particularly affect antibiotic development.

3.3 Challenges in Market Approval

A common challenge faced by drug developers is that approval processes between regulatory authorities are not aligned in all regards.⁵⁶ Persisting differences incur additional costs because clinical trials have to be designed to fulfill the different requirements of regulatory authorities around the globe. According to Elias Zerhouni, president of global R&D at Sanofi, the company spends "20% of [its] R&D budget trying to mix and match in order to do the convergence between different systems."⁵⁷ While this effect is not specific to antibiotics, it increases development cost and effort for antibiotics in a market that is already commercially unattractive (discussed in chapter 3.4.4).

The additional costs and delay of market entries resulting from remaining differences in the approval process have been recognized, and transnational efforts have been initiated to improve the alignment of approval processes.

TATFAR, the Transatlantic Taskforce on Antimicrobial Resistance, was established in 2009. Its goals are to improve cooperation between the United States and the EU in the appropriate therapeutic use of antimicrobial drugs, the prevention of infections, and strategies for promoting the development of antimicrobial drugs. Since the inception of TATFAR, both the EMA and FDA have published individual, detailed guidelines regarding the appropriate design of clinical trials for antibiotics.⁵⁸ TATFAR has already contrib-

⁵⁵ *Molecular basis of host specificity in human pathogenic bacteria*. Pan, Yan, Zhang. March 2014.

⁵⁶ *A comprehensive study on regulatory requirements for development and filing of generic drugs globally*. Handoo, Arora, Khera et al. September 2012.

⁵⁷ *Sanofi R&D head bemoans divergence in global drug regulation*. Reuters. March 2015.

⁵⁸ *Transatlantic Taskforce on Antimicrobial Resistance: Progress report*. TATFAR. May 2014.

uted to advancing the alignment of the approval , but differences still exist. These include, but are not limited to:

- **Selection criteria for patients in clinical trials.** From the expert interviews conducted for this report, we have gathered that patient recruitment is more restrictively regulated by the FDA than by its European counterpart, the EMA.⁵⁹ Regulation regarding prior exposure to antibiotic treatments excludes some patients for FDA trials that could be included according to EMA regulation.⁶⁰
- **Definition of clinical endpoints.** An example of a different definition of clinical endpoints is the phase III trials of the antibiotic of Cemptra Pharmaceuticals *solithromycin* (to treat community acquired pneumonia). The FDA capped measurement of the primary endpoint for non-inferiority at 72 hours after treatment was initiated. In contrast, the EMA allowed primary endpoint measurements to be conducted 5–10 days after the end of therapy.⁶¹ In interviews conducted for this report, public-sector officials who are engaged in current antibacterial approval processes stated that the FDA and EMA are already working together for antibiotic approvals.
- **Specification of statistical parameters.** The parameters defined for specific statistics can differ between agencies. This can be a challenge for trial design. An example is the recent phase III trials for the broad-spectrum antibiotic *eravacycline*.⁶² While the FDA required a 10% noninferiority margin, the EMA accepted a 12.5% noninferiority margin.
- **Expedited approval for antibiotics.** From 2010 to 2014, the US Food and Drug Administration (FDA) granted priority review to 71% of anti-infectives, while the EMA used accelerated assessment for 38% of anti-infectives.⁶³

Greater differences can be observed among regulatory authorities not included in TATFAR efforts.⁶⁴ The practical impact of different approval pathways and regulations across major regulatory agencies becomes visible when comparing approval timelines for anti-infectives and the share of anti-infectives that receive an expedited review (figure 15).⁶⁵ A globally unified approval process could potentially reduce those differences and is called for by both interviewed experts and the literature, though significant legal challenges exist.⁶⁶

⁵⁹New Antibiotic Development: Barriers and Opportunities in 2012. Brad Spellberg. 2012.

⁶⁰FDA Guidance for ABSSSI Trials: Implications for Conducting and Interpreting Clinical Trials. Itani, Shorr. 2014.

⁶¹Cemptra Presenting Additional Data From the Phase 3 Oral Solithromycin Study in Community Acquired Bacterial Pneumonia at the American Thoracic Society Conference. Cemptra Pharmaceuticals. May 2015.

⁶²Eravacycline. Tetrphase Pharmaceuticals. 2015.

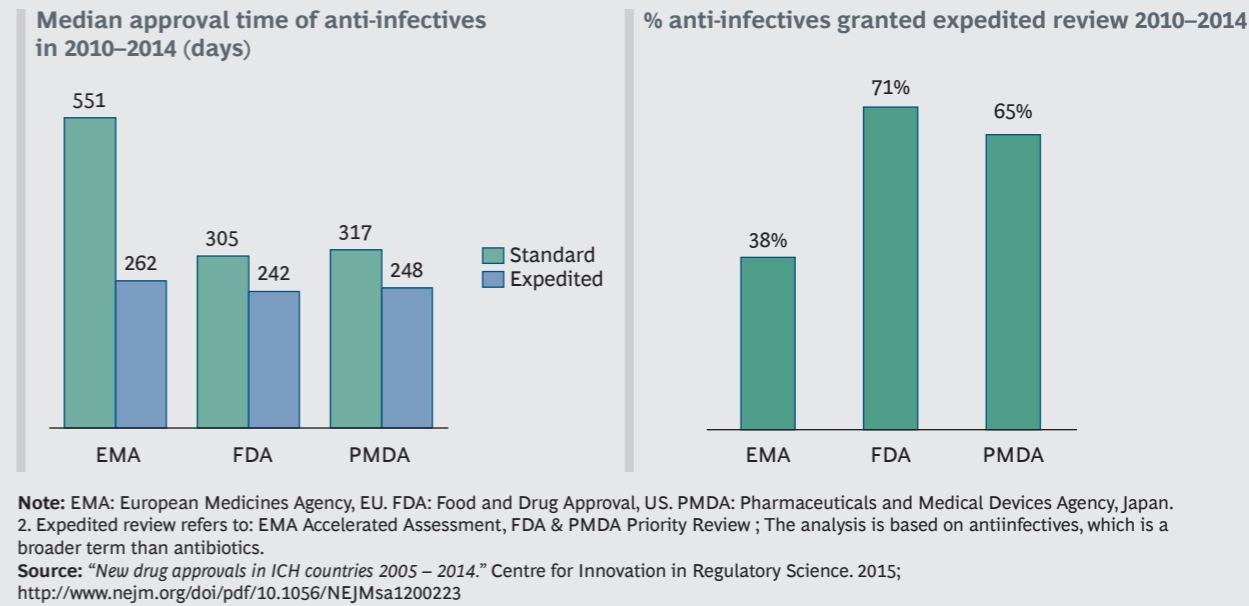
⁶³Anti-infectives include antiviral, antifungal, and antiparasitics; New drug approvals in ICH countries 2005 – 2014: Focus on facilitated regulatory pathways and orphan designations. Centre for Innovation in Regulatory Science. July 2015.

⁶⁴A comprehensive study on regulatory requirements for development and filing of generic drugs globally. Handoo, Arora, Khera et al. September 2012.

⁶⁵New drug approvals in ICH countries 2005 – 2014: Focus on facilitated regulatory pathways and orphan designations. Centre for Innovation in Regulatory Science. July 2015.

⁶⁶A comprehensive study on regulatory requirements for development and filing of generic drugs globally. Handoo, Arora, Khera et al. September 2012; International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary. Forum on Drug Discovery, Development, and Translation; Institute of Medicine. October 2013.

FIGURE 15 | Comparison of expedited approval for anti-infectives and standard review times



3.3.1 Summary of Challenges in Market Approval

Much work has been done to align approval processes among major regulatory authorities. Still, the remaining differences result in higher complexity in trial design and result in increased resource investments (e.g., time, planning, and direct cost of trials) for the players conducting the clinical trials.

3.4 Challenges in Commercialization

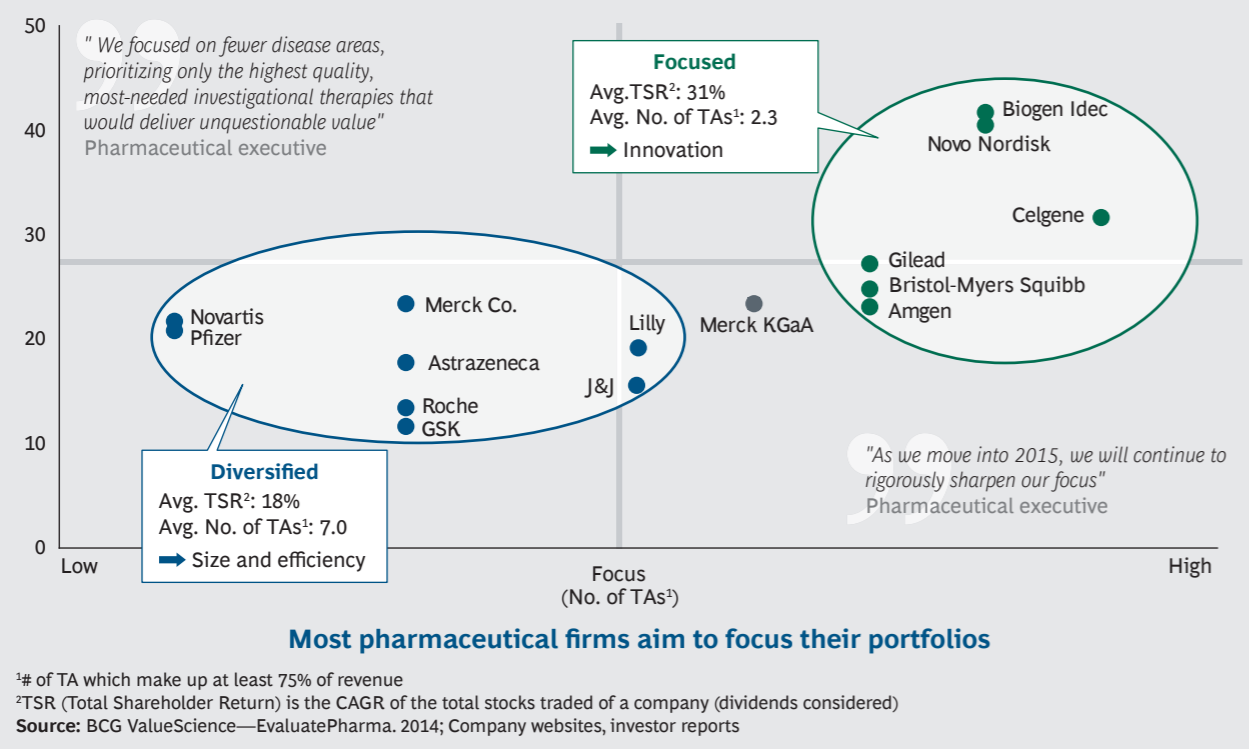
The market for antibiotics has massively lost attractiveness over the last decades. From around 20 of the largest pharmaceutical companies worldwide being active in antibiotics research in the 1990s, only four remained in 2014.⁶⁷ Many of the major pharmaceutical companies have scaled back efforts, carved out antibiotics departments into separate companies, or left the area entirely.⁶⁸ Roche reentering the area is an exception to this overall trend and does not likely reflect a turnaround of the pharmaceutical industry’s view on the attractiveness of the antibiotics market. These developments cannot be explained with any single reason; they are the result of multiple factors and trends acting together.

The commercialization of antibiotics is a market which is attractive for other players besides the largest pharmaceutical companies. Small and medium sized biotech companies for example (see chapter 3.2.2) are considered important innovators in the field.

⁶⁷Roche returns to antibiotic research as superbug threat grows. Reuters. June 2014; Despite Superbug Crisis, Progress in Antibiotic Development ‘Alarmingly Elusive’. Infectious Diseases Society of America. April 2013.

⁶⁸AstraZeneca to carve out antibiotic R&D into separate firm. Business Insider. February 2015; Whittled down to biotech size, AstraZeneca’s antibiotics crew starts over as Entasis. FierceBiotech. July 2015.

FIGURE 16 | Pharmaceutical companies with focused portfolios rewarded by the financial market



3.4.1 Increased Focus on Most Profitable Therapeutic Areas

An analysis of the shareholder returns (the financial performance of a company's stock over time) shows that an increased focus on a small number of therapeutic areas has been rewarded by the capital markets. Pharmaceutical companies with fewer therapeutic areas were able to achieve a substantially higher total shareholder return (TSR)—31% vs. 18% on average (see figure 16). In figure 16, focus is measured by therapeutic areas (TAs), which account for at least 75% of revenue. Success on the financial market is measured by TSR: The total return of a stock to an investor (capital gain plus dividends).

Under pressure from the financial markets, publicly traded pharmaceutical companies evaluate their portfolio with increased scrutiny to identify the areas that promise the highest return on investment. Unprofitable or marginally profitable therapeutic areas are sold or terminated to increase focus on the most profitable areas.

This trend adds to the challenge of turning around the past developments in the therapeutic area of antibiotics. Achieving marginal profitability for the therapeutic area will not be sufficient enough to reignite the interest of pharmaceutical companies, as the area of antibiotics is in direct competition with other, more profitable therapeutic areas. An effective bundle of levers will have to make sure that the attractiveness of the antibiotics market can compete with other therapeutic areas.

3.4.2 Low Expected Sales Volume

The low expected sales volume of antibiotics is one of the biggest inherent challenges of this therapeutic area. It is a significant deterring factor for pharmaceutical companies. Revenue estimations for antibiotics are low and volatile for multiple reasons:

- New antibiotics entering the market can be designated as antibiotics of last resort. Paradoxically, the more innovative a product is, the less it might be used, as more novel and innovative treatments are rightfully more restrictively used. The designation of a new antibiotic as an antibiotic of last resort means that it is only to be used as a last method of treatment when all other attempts have failed. These restrictions can reduce sales volumes significantly and thus makes the development commercially more risky and less attractive.
- The appearance of resistance within the relevant bacterial strains has been detected increasingly quickly (see chapter 2.1.2). The detection of resistance does not render an antibiotic useless, but it can still significantly impact how often it will be prescribed and sold.
- Most innovative antibiotics are initially used in the hospital setting. Hospitals are usually, at least implicitly, expected to pay for these from their regular budget or income from DRG-like (diagnosis related group) reimbursement. The use of innovative antibiotics may be limited by inadequate reimbursement.

3.4.3 Prices for Antibiotics Mostly Low Compared to Other Lifesaving Medicine

The prices for antibiotics in the ambulatory care setting (i.e. those which are prescribed by physicians and distributed via community pharmacies) have been relatively low compared to other potentially lifesaving medicines. While this enables widespread access, the downside of low prices is the lack of commercial attractiveness for the developer. Antibiotics are often seen as a commodity. The willingness to pay a high price for, e.g., a hepatitis C treatment is significantly larger than for antibiotics. *Sofosbuvir* (Sovaldi®), a new treatment for hepatitis C, entered the US market in 2014 with a price tag of €900 per pill. A 12-week course of Sovaldi® costs €75,500. Cancer treatments typically achieve prices over €90,000 over the course of treatment lasting a year.⁶⁹ In contrast, many antibiotics treatments are often less than €40 over the course of a treatment lasting a week.⁷⁰ In some cases, higher prices can be achieved for antibiotics (see below). These prices are still significantly lower than for treatments for hepatitis C and/or cancer.

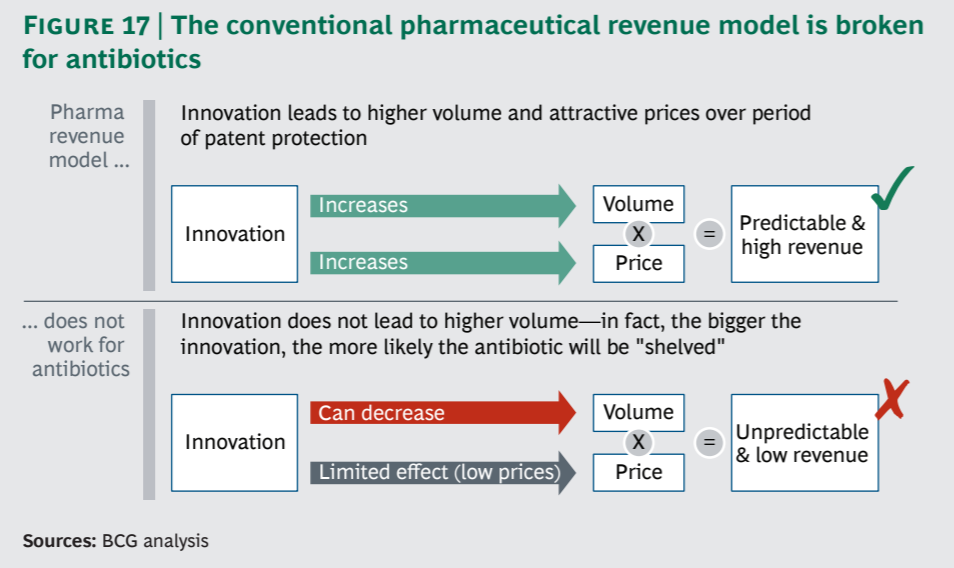
Reimbursability of new pharmaceuticals (i.e. that third-party payers cover the costs) is in many countries based on an assessment of additional benefit to patients vs. existing alternatives and/or its cost-effectiveness. The degree of additional benefit will be crucially dependent on what is considered to be the appropriate comparator. Since most antibiotic classes were invented decades ago, patent protection has expired and generics dominate the market. In Germany, for example, generics maintain over 95% of market share for the most popular antibiotic products.⁷¹

⁶⁹Investors Bet \$100,000 Cancer Drug Prices are Here to Stay. Bloomberg. March 2015.

⁷⁰Anzahl der Verordnungen, Veränderungen im Vergleich zum Vorjahr und Höhe der Nettokosten von Antibiotika in Deutschland nach Wirkstoff im Jahr 2013 (Change in number of prescriptions in comparison to the preceding year and total cost of antibiotics in Germany per active ingredient in the year 2013). Statista. 2015.

⁷¹Zahl des Monats (number of the month). Pro Generika http://www.progenerika.de/wp-content/uploads/2015/06/Zahl-des-Monats-Juni_038-%E2%82%AC.pdf accessed 24 September, 2015

However, innovative antibiotics that treat urgent health threats and are new-in-class can command high prices. *Fidaxomicin* (Difcid®), a first-in-class narrow-spectrum antibiotic to treat *C. difficile* associated diarrhea (CDAD) that was approved in 2011,⁷² has an average wholesale price of \$3,360 for a 10-day treatment regimen. In comparison, *vancomycin*, which treats the same type of infection, costs \$1,392.80 for a 10-day treatment plan. The third treatment option for the infection is a generic drug, metronidazole, which costs a mere \$20.70 for a 10-day treatment program.⁷³ This illustrates that truly innovative antibiotics can achieve relatively high prices on the market.



3.4.4 Current Business Model Does Not Work for Antibiotics

In a conventional pharmaceutical business model, revenue is determined by the volume sold and the price of a product. Innovative drugs add significant benefit compared to existing treatments, therefore they often achieve higher prices and larger volumes (figure 17).

Low volumes for antibiotics, low prices (or higher prices in combination with highly limited use), and the high cost of development make an unattractive business case for antibiotics. For an example calculation, the following assumptions were used:

- Total development costs of around €800 million (estimation based on literature⁷⁴)
- Peak sales of €300 million as a base for calculating total sales (in-line with recent antibiotic launches)
- Discount rate of 10% (based on cost of capital for pharmaceutical companies)
- Development time of eight years (in-line with recent antibiotic launches)
- 12-year patent protection on the market (in-line with recent antibiotic launches)

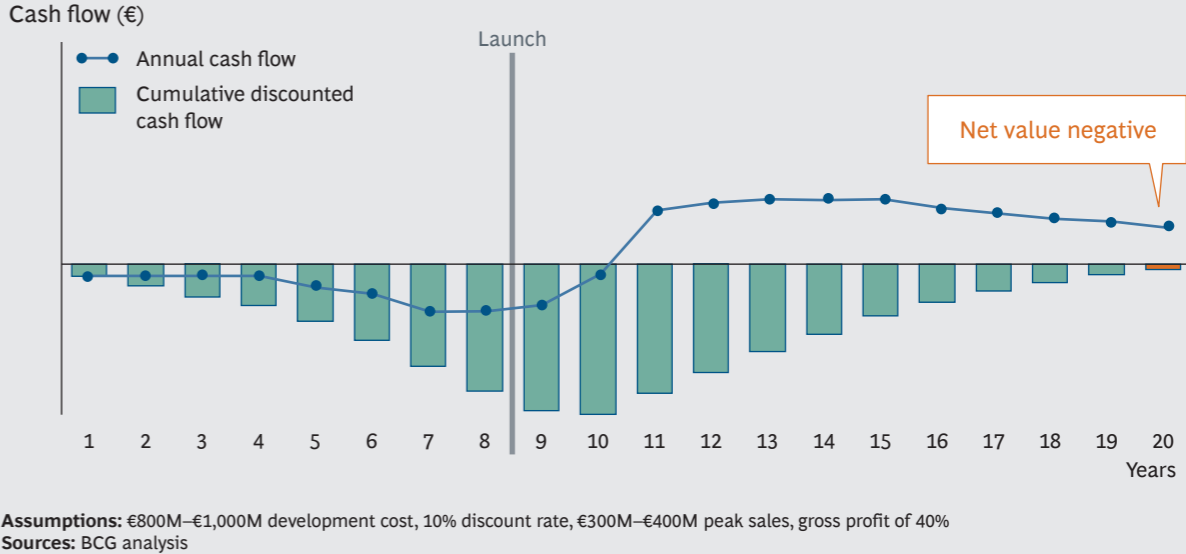
Based on the above assumptions, the net present value (NPV), for the development and commercialization of a new antibiotic is actually negative (see figure 18).

⁷²Press release: FDA approves treatment for Clostridium difficile infection. US Food and Drug Administration. May 2011.

⁷³Fidaxomicin (Difcid®), a Novel Oral Macrocyclic Antibacterial Agent for the Treatment of Clostridium difficile-Associated Diarrhea in Adults. Cruz. May 2012.

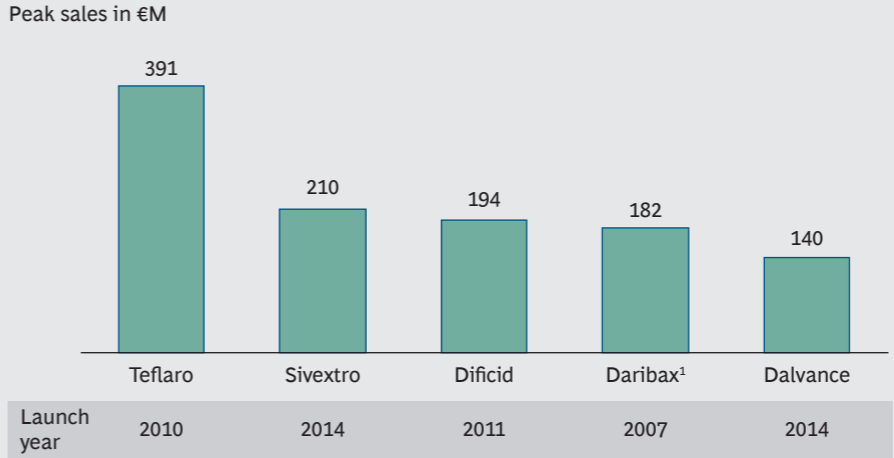
⁷⁴UK Review on Antimicrobial Resistanc. The Review is commissioned by, and will report to, the UK Prime Minister. The Chair of the Review, Jim O'Neill. <http://amr-review.org/>

FIGURE 18 | Development of antibiotics results in negative net present value



For comparison, figure 19 shows antibiotics peak sales and peak sales forecasts for recent launches.

FIGURE 19 | Recent antibiotics peak sales forecasts showing low revenue potential



¹Actual sales numbers from 2013

Notes: adjusted for inflation; Telavancin is not included because of lack of reliable revenue data (estimate: under 10 m EUR Peak Sales)

Sources: EvaluatePharma; FDA; BCG analysis. "Report to the president on combating antibiotic resistance." President's Council of Advisors on Science and Technology. 2014.

"We need new policies to tackle antimicrobial resistance." London School of Economics and Political Science.

"The fallacies of hope: will we discover new antibiotics to combat pathogenic bacteria in time?" Federation of European Microbiological Societies, Microbiology Review, 2006.

Achieving a positive net present value (NPV), defined as a net profit of a multi-year investment, is a necessary first step toward making the market for antibiotic attractive again. A barely positive return on investment (RoI), meaning the benefit of an investment, however, will not be enough to have a significant impact on pharmaceutical companies feeling intense market pressure and being under scrutiny from capital markets.

3.4.5 Summary of Challenges in Commercialization

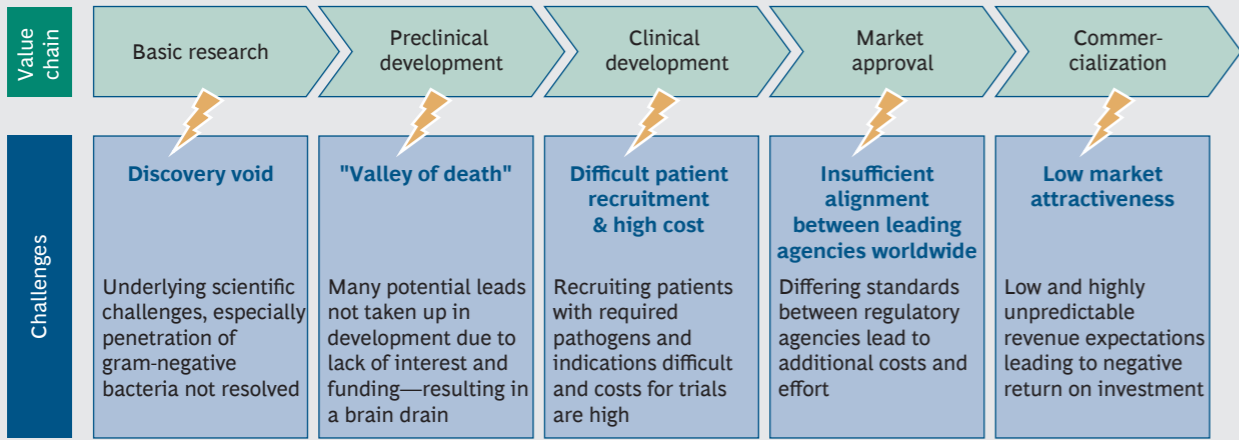
The market for antibiotics is commercially unattractive because of low expected sales volumes and prices. The necessary financial investments in development are so large that a relevant business opportunity in the form of a significantly positive net present value is a prerequisite for interest and investments in this therapeutic area. This is true for big pharmaceutical companies and small biotech start-ups alike.

To turn this trend around, any set of levers will be judged by the “business case” it creates for pharmaceutical and biotech companies. This business case must also consider the necessary investments into capabilities (hiring/maintaining/training staff and cost for facilities) that are prerequisites for any meaningful investment into an antibiotic candidate.

3.5 Overview of Challenges Along the Value Chain

The negative trend in research and development for antibiotics is not due to a singular reason. Multiple challenges appear along the value chain. Figure 20 presents an overview.

FIGURE 20 | Overview of challenges of antibiotics along the value chain

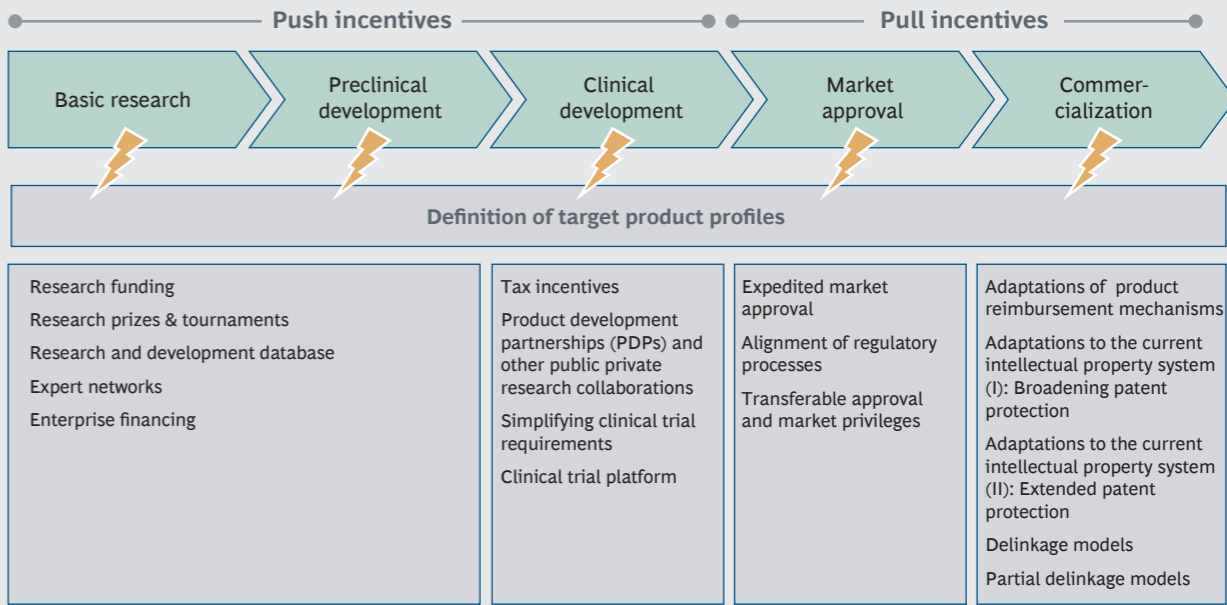


Source: BCG analysis

4. POTENTIAL LEVERS TO FOSTER RESEARCH AND DEVELOPMENT IN ANTIBIOTICS

THERE IS A WIDE range of potential levers available to policy makers. Figure 21 illustrates a list of levers discussed in this section. These levers are potential options for resolving the identified challenges along the value chain. They can be divided into levers that target the early phases of the value chain (including basic research and preclinical and clinical development) and levers that are applied later in the value chain (market approval and commercialization). Levers employed early in the value chain are referred to as “push” incentives, lowering the barriers of market entry for developers by reducing the costs of research and development (R&D). Complementary to more conventional levers, such as directly subsidizing research and specific tax incentives, newer tools and concepts have been developed. Their aims are to increase access to knowledge, speed up its diffusion, and foster new constellations of expertise and more collaborative solutions. Levers applied later in the value chain are referred to as “pull” incentives, tending to target the removal of regulatory inefficiencies or increase the attractiveness of the market and the return on investment for pharmaceutical developers and manufacturers. These “pull” incentives include refinements to the existing patent-driven system intellectual property (IP) extensions, reimbursement top-ups), decoupling the innovation from the volume of sales (delinkage models) and hybrid models which lie in between (partial delinkage).

FIGURE 21 | List of existing levers discussed in this section



Notes: Incentives have been placed along the value chain for illustrative purposes. In reality most incentives target phase transitions or multiple phases along the value chain (e.g., milestone prizes and tournaments are incentives used in basic research, preclinical, and clinical development). Sources: TUB analysis, BCG analysis

The following chapter discusses a comprehensive list of levers, including examples and main advantages and challenges. The levers which are most suited to help overcome the challenges are combined into a comprehensive bundle. In order to make sure that the chosen levers work together and complement each other by ideally developing synergetic effects, possible interactions between the levers were considered during the selection process as well.

The result of this process is a comprehensive combination of levers that has the potential to reverse the trend in antibiotic research and development and lead to the development of innovative antibiotics in high-need areas. The recommended levers are further detailed in chapter 5.

4.1 Incentives Primarily Targeting Basic Research and Preclinical Development

Definition of Target Product Profile (TPP)

Examples of specific tools: lists of most urgent threats, lists of high priority agents.

The public health threat resulting from different bacteria varies greatly. TPPs specify desired optimal and minimum required characteristics of a product, e.g., the pathogens that a product should be effective against.⁷⁵ A TPP could define the most urgent threats based on global unmet medical need. The Centers for Disease Control and Prevention (CDC), for example, has developed a list of the most urgent bacterial threats in the United States. Similar efforts are underway in Europe.

The TPPs would provide the basis for any support in research, development, and commercialization in that only products meeting the requirements specified in the TPPs being eligible for (full) support. In order to account for the changing resistance pattern of bacteria, TPPs would have to be periodically updated.

Main advantages

- + Allows for focus to be on the most-needed antibiotics according to public health priorities
- + Avoids funding of nonpriority antibiotics
- + Supports strategic research agenda for antibiotics

Main challenges

- Changes in threat level of bacteria uncertain
- Current surveillance capability limits understanding of bacterial threat dynamics

Research funding

Examples of specific tools: project grants, subsidies, fellowships, career establishment grants.

⁷⁵Towards new business models for R&D for novel antibiotics. So, Gupta, Brahmachari et al., 2011.

Funding to boost basic research and preclinical development can be targeted at different levels: 1) individuals 2) research groups, or 3) institutions. Increasingly, there is a shift away from traditional approaches to more complex funding instruments. These new instruments incorporate all three levels in project-based, problem-orientated research. There is a trend towards more cluster-oriented policy to foster spatial concentration and networking effects by incorporating partners from universities, public research institutes, and the private sector.⁷⁶

For example, at a project level the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)⁷⁷ aims at coordinating research on antimicrobial resistance (AMR) in the EU plus Israel and Canada and has a strategic research agenda (2014) that provides a framework for future investment and research priorities. At an individual level, direct support to individuals include the United State's National Institute of Health (NIH) directors program (career-establishment grants)⁷⁸ and the EU's Marie Skłodowska-Curie actions (MSCA)⁷⁹ (fellowships) and the Nobel Prize for Medicine (a recognition prize).

Main advantages

- + Funding can be specifically targeted to overcome particular technical challenges/priorities
- + Lowers barriers to developer entry, facilitating participation of diverse developers

Main challenges

- Sponsor bares all (or most) of the cost and risk, as a large amount of the funding may not facilitate later product development
- Problems with transparency and information asymmetries can inhibit access to, and quality of the resulting knowledge
- Dependent upon changing public research priorities

Research Prizes and Tournaments

Examples of specific tools: optional reward system, milestone prizes, best entry tournaments.

Research prizes can be designed to stimulate competitive, outcomes-based solutions. Prizes can be helpful to encourage smaller developers and to overcome specific, technical challenges. There is a huge heterogeneity of designs, but main types include milestone prizes that reward researchers for reaching certain milestones and best-entry tournaments that reward those achieving the most progress toward a specified research goal by a specified date. Other options include rewards that enable researchers to choose between a monetary prize and a patent.⁸⁰

⁷⁶Policies and incentives for promoting innovation in antibiotic research. Mossialos, Morel, Edwards et al., 2010.

⁷⁷The strategic research agenda. Joint Programme Initiative on Antimicrobial Resistance.

⁷⁸Programs. National Institute of Health. 2015. The National Institutes of Health NIH Common Fund is managed by the Office of Strategic Coordination, part of the Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), USA

⁷⁹Marie Skłodowska-Curie actions. European Commission. 2015. Marie Skłodowska-Curie actions (MSCA) is a part of the Horizon 2020. Horizon 2020 is the biggest EU Research and Innovation programme.

⁸⁰Policies and incentives for promoting innovation in antibiotic research. Mossialos, Morel, Edwards et al., 2010.

For example, the Breakthrough Prize in Life Science started in 2013 and is funded by the founders of Facebook and Google (among others).⁸¹ Each year, up to six \$3 million prizes are awarded, and in 2015 a researcher at the Institute for Molecular Medicine Finland (FIMM) was one of the winners based on her discoveries regarding an ancient defense mechanism in bacteria (CRISPR/CAS9).

Main advantages

- + Enables recouping of investment costs earlier and increases participation of smaller developers
- + Attracts those who feel they have a competitive advantage
- + Attracts public and community attention to the cause and rewards active research community members
- + Overcomes the pitfalls of information asymmetries

Main challenges

- Potentially rewarding research that never reaches market
- Risk of collusion between participants
- Confidentiality concerns could deter those with breakthrough leads

Research and Development Databases

Examples of specific tools: open-access platforms, data exchange portals.

Open access and data exchange aim to foster innovation by increasing the efficiency of research and removing barriers to knowledge access, participation, and generation. Very few tools and very little knowledge generated from basic research are currently in the public domain. Knowledge generation can figure a proprietary (private ownership) nature, even at “precompetitive” development phases. The ability of these platforms to increase transparency and reduce a duplication of efforts is garnering increasing attention.

For example, the WHO Global Observatory on Health Research and Development—a platform collating information on health research and development (R&D), identifying gaps and opportunities for health R&D, and helping to define priorities for new R&D investments based on public health needs, especially in emerging countries.⁸² Other examples are InnoCentive⁸³ a crowdsourcing platform for innovative solutions. The open access, peer-reviewed Public Library of Science (PLOS⁸⁴), the WHO International Clinical Trials Registry Platform (ICTRP),⁸⁵ or the European Clinical Trials Database (Eudra CT),⁸⁶ as well as the Open Source Drug Discovery Initiative (OSDD⁸⁷) in India.

⁸¹Life sciences breakthrough prize. Breakthrough Prize, accessed 23 September 2015.

⁸²Global Observatory on Health Research and Development. World Health Organization, accessed 23 September 2015.

⁸³At a Glance. InnoCentive, accessed 23 September 2015.

InnoCentive is an online enterprise that brings the scientific research and development community together.

⁸⁴Public Library of Science (PLOS). <https://www.plos.org/about/>, accessed 23 September 2015.

PLOS is a nonprofit publisher and advocacy organization founded 2001 to accelerate progress in science and medicine by leading a transformation in research communication.

⁸⁵International Clinical Trials Registry Platform. World Health Organization, accessed 23 September 2015.

⁸⁶EudraCT. European Clinical Trials Database (EudraCT), accessed 23 September 2015.

EudraCT is a database of all clinical trials which commenced in the Community from 1 May 2004, and also includes clinical trials linked to European paediatric drug development.

⁸⁷Open source drug discovery. Open source drug discovery (OSDD), accessed 23 September 2015.

OSDD (India) is a translational platform for drug discovery, bringing together informaticians, wet lab scientists, contract research organizations, clinicians, hospitals and others who are willing to adhere to the affordable healthcare philosophy agreeing to the OSDD license.

Main advantages

- + Increases efficiency of knowledge generation and dissemination
- + Reduces costs and wasteful duplication of research

Main challenges

- Relies on goodwill of participants (proprietary culture may inhibit submission of most valuable information)
- Problems with transparency and informational asymmetries can inhibit access to and quality of the resulting knowledge

Expert Networks

Examples of specific tools: bridging organizations, expert networks.

Expert networks aim at increasing the efficiency of research by removing barriers between different experts. They can support in gathering knowledge in specific areas. These networks can engage members of a research community and increase cohesiveness and effectiveness.

Main advantages

- + Increases efficiency of knowledge generation and dissemination
- + Removes barriers to participation and collaboration, beyond traditional players
- + Can be used as a tool to keep formerly active researchers involved in the cause

Main challenges

- Relies on goodwill of participants
- Success dependent upon specific and continuous engagement of the members of expert networks

Enterprise Financing

Examples of specific tools: angel financing, venture capital, risk-sharing instruments, guaranteed loans, refundable tax credits.

Small and medium-sized enterprises (SMEs) have much smaller capital reserves than large pharmaceutical companies and smaller portfolio’s across which they can spread their risks.⁸⁸ Innovative financing tools for small and medium-sized enterprises are increasingly common as countries try to boost their knowledge and innovation economies and acknowledge the role small and medium-sized enterprises can play in addressing societal challenges.

For example, the European Investment Bank (EIB)⁸⁹ and the European Investment Fund (EIF) in cooperation with the European Commission’s Horizon 2020 have three relevant

⁸⁸Policies and incentives for promoting innovation in antibiotic research. Mossialos, Morel, Edwards et al., 2010.

⁸⁹About EIB. European Investment Bank (EIB).

financing streams available through their joint initiative “InnovFin-EU Finance for Innovators”. The three streams include SME venture capital, SME guarantor, and InnovFin Infectious Diseases—the latter being aimed specifically at financing €7.5–75 million for the clinical validation of AMR-related technologies.⁹⁰ Similar programs can be found in the United States and in some countries at national level.

Main advantages

- + Maximizes participation by all developers
- + Relatively small sums can make a difference

Main challenges

- Sponsor bares some/all of the risk
- Challenges in identifying promising SMEs/ideas to finance based off limited early-stage data

Recommended Levers for Basic Research and Preclinical Development

Due to the interlinked nature of the challenges identified in these steps, levers for the first two phases of the value chain were considered together. The following challenges were identified in chapter 3:

- “Discovery Void” in basic research
- “Valley of death” in preclinical development

Results of evaluation

The following levers were identified to be the most effective to combat these challenges.

Defining **Target Product Profiles** allows for a strategic and focused agenda for developing antibiotics most urgently needed from a global health perspective. The careful specification of Target Product Profiles will be essential to the success of an effective comprehensive antibiotics strategy.

Providing additional sources of **research funding** is essential to increasing research activity in antibiotics. Without direct financial support, the challenges in basic research and preclinical development are unlikely to be resolved. In order to spark research activity, a significant investment is likely to be necessary. Funding for basic research should seek to support individual, promising projects via direct financing and lighthouse institutions via enterprise financing and institutional financing.

A **research and development database** will be needed to facilitate a strategic funding approach and to avoid duplication of efforts. An **expert network** can slow down the brain drain currently underway in the field of antibiotics and support a turnaround. It can provide valuable input into ongoing research and development efforts. Finally, a **research prize** can inspire members of the research community and serve as a visible sign of a new dynamic in the field. The research prize will also increase the prestige associated with antibiotics research.

⁹⁰InnovFin. Infectious Diseases. European Investment Bank (EIB). http://www.eib.org/attachments/documents/innovfin_infectious_diseases_flysheet_en.pdf, accessed 23 September 2015.

InnovFin - EU Finance for Innovators is a joint initiative by the EIB Group and the European Commission under Horizon 2020.

4.2 Incentives Primarily Targeting Clinical Development

Tax Incentives

Examples of specific tools: tax deferrals, tax allowances, tax credits, refundable tax credits.

Tax incentives for research and development (R&D) can be in the form of adjustments to taxable income (deductions), lower tax rates, and adjustments to tax payments (tax credits). Enhanced deductions over 100% are referred to as allowances and a deferral is a tax liability that can be carried forward to a future point in time.

For example, the USA’s 1983 Orphan Drug Tax Credit (ODTC) and the UK’s Vaccine Research Relief Programme⁹¹. The ODTC allows developers to claim a tax credit for up to 50% of qualified PI-III clinical testing expenses.⁹² The UK Vaccine Research Relief allows for a further 40% reduction against corporation tax for relevant R&D cost.

Main advantages

- + More flexible than grants; priorities and approach remain in the hands of the developers

Main challenges

- Incentive tied to the country where the R&D conducted
- Little evidence of cost effectiveness relative to alternatives

Product Development Partnerships (PDPs) and Other Public Private Research Collaborations

Examples of specific tools: PDPs, multidisciplinary engagement initiatives, research excellence initiatives (REI’s).

Partnerships that combine different skills and resources from multiple sectors have been used to address research or development challenges in other areas. Independent legal entities have been formed to address disease-specific challenges. They attract funding, manage the R&D process (potentially including intellectual property management) and facilitate collaborative working. PDPs became a frequent model in the last 15 years to address specific product needs for patients in the developing world. They lower the cost of development through more efficient use of resources by pulling in expertise only as it is required at each step or through securing pro bono expert input.

For example, the Drugs for Neglected Diseases initiative (DNDi) is one of the earliest (inception in 2003) and is currently advocating the creation of an antibiotic-specific product development partnership (PDP)⁹³, a proposal echoed many times but also by Chatham House’s Global Antibiotic PDP (GAPPP). Some PDPs operate at national level such as the USA’s Biomedical Advanced Research and Development Authority (BARDA). BARDA provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies.⁹⁴ In

⁹¹UK Research and Development Tax Relief https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/192107/randd_tax_relief.pdf

⁹²Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases. EY Building a better working world, 2015.

⁹³Drugs for Neglected Diseases initiative (DNDi) is a collaborative, patients’ needs-driven, non-profit drug research and development (R&D) organization that is developing new treatments for Neglected Diseases

⁹⁴Office of the Assistant Secretary for Preparedness and Response (ASPR). Biomedical Advanced Research and Development Authority (BARDA).

the EU—although frequently global in its collaboration—the Innovative Medicines Initiative (IMI) has a number of initiatives under the New Drugs for Bad Bugs (ND4BB) program but only some are directed specifically at product development⁹⁵.

Main advantages

- + Appeal to both large (when market too small or risky) and small (lower costs) developers
- + Potentially easier to align with public health goals (access considerations often a precondition for participation)
- + High efficiency of development process

Main challenges

- Managing different objectives of different partners (especially with respect to IP rights)
- Risk and cost is spread between developers (but sponsor takes on most)
- Challenges with monitoring and accountability

Simplifying Clinical Trial Requirements

For example: changing trial requirement guidelines.

The European Medicines Agency (EMA) has recently changed its guidelines for clinical antibiotic trials to facilitate patient recruitment, enable organism-specific (rather than disease-specific) studies, and accept smaller studies.⁹⁶ Additionally, it has developed “adaptive pathways”, whereby the authorization starts with one indication (most likely a “niche” indication) for a given drug, and through iterative phases of evidence gathering the licensing may be widened to potential further therapeutic uses.⁹⁷ The FDA is also considering and implementing more flexible arrangements specifically for antibiotic approvals. Despite these recent changes, the clinical trial phases remain costly and risky for developers. Therefore, streamlining this phase of the process could make antibiotics more attractive to developers.

Main advantages

- + Reduced time for antibiotic to reach market at significantly lower developer costs

Main challenges

- Lower trial requirements increase risk for insufficient patient safety and efficacy of antibiotics

⁹⁵The Innovative Medicines Initiative. Innovative medicines initiative. The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative. The program is based on a collaborative approach engaging public, academic and private institutions in joint research projects. Among other goals it seeks to develop effective treatments against gram-negative bacteria.

⁹⁶Antibiotic resistance-the need for global solutions. Laxminarayan R, Duse A, Wattal C, et al. 2013.

⁹⁷Adaptive pathways. European Medicines Agency.

Clinical Trial Platform

For example: developing clinical trial platform.

Clinical trials regarding antibiotics face the challenge of recruiting patients. Trial platform indirectly reduce the time and financial investments necessary by facilitating the recruitment of patients and clinical trials.

Main advantages

- + Reduces time for antibiotic to reach market at lower developer costs
- + Decreases barriers to non-pharmaceutical industry participation

Main challenges

- Data protection of participants needs to be carefully implemented

Recommended Levers for Clinical Development

The following major challenge was identified in chapter 3:

- High cost in clinical development and difficult patient recruitment

Results of Evaluation

The following levers were identified to be the most effective to combat these challenges.

Product development partnerships (PDPs) can provide valuable support for companies, especially small and medium-sized enterprises (SMEs), with promising antibiotic candidates. Companies owning a suitable antibiotic candidate would be supported financially and with expert advice during the costly clinical development – and potentially also during marketing of the medicine.

An clinical trial platform for antibiotics could help facilitate clinical trials and address a major issue along the value chain: the challenge of recruiting sufficient numbers of suitable patients. The platform could include all ongoing clinical trials, relevant hospitals and clinics, which are likely to be able to include potential trial participants. Establishing a database for trials patients can participate in, would furthermore support surveillance efforts.

4.3 Incentives Targeting Market Approval

Expedited Market Approval

Examples of specific tools: special designation, expedited/priority review, and regulatory harmonization.

Regulatory agencies such as the EMA and FDA approve pharmaceuticals in their respective geographies. For a “global antibiotic”, a developer would need to secure approval in many different countries (or groups of countries such as the EU). Although the requirements are broadly similar, they vary in detail among differing jurisdictions. On a national or regional level, priority antibiotics could receive a special designation making them eligible for some form of expedited regulatory review. Both the EMA and FDA have four such designations. The FDA has a specified antibiotic designation.

For example, Qualified Infectious Disease Products (QIDP) in the USA is the first jurisdiction to have an antibiotic-specific expedited review pathway, approving four new antibiotics this way in 2014. A drug that receives QIDP designation is eligible under the statute for fast track designation and priority review.⁹⁸

Main advantages

- + Products are available to patients faster (public health gain)
- + Increased revenues to developer as effective patent-life extended

Main challenges

- Could potentially compromise patient safety only if used in conjunction with simplified requirements
- Maybe of limited/insufficient financial value to the developer
- May require increasing resources/staffing for regulatory agencies

Alignment of Regulatory Processes

On a global level, alignment (or some level of mutual recognition) between jurisdictions would ensure priority antibiotics were most rapidly available to patients, lessen the administrative burden on developers, and enable developers to capitalize more effectively on the patent term.

For example, since 1990 the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has brought together developers and regulatory agencies from the USA, Japan, and Europe to work on this issue.⁹⁹

Main advantages

- + Promotes quicker access to needed antibiotics
- + Reduce resources (time and money) required for antibiotic development and approval for both developer and payer

Main challenges

- Regulatory systems subject to different national/regional interests
- Limited advantages for antibiotics because “low-hanging fruits” already implemented and cooperation already advanced in most areas

Transferable Approval and Market Privileges

Example of specific tools: wildcard patent extensions, transferable regulatory reviews, and vouchers.

By making the privileges of expedited review or prolonged patent protection (see also chapter 4.4) transferable to another drug in a developer’s portfolio (partial) or even another company (full—via a sale), the incentive can be greatly strengthened and advantages broadened.

⁹⁸Guidance for Industry. Expedited Programs for Serious Conditions – Drugs and Biologics <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>
⁹⁹International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) <http://www.ich.org>

For example, legislation exists in the USA for wildcard priority review vouchers (PRV) for developers of treatments for neglected (2008) or rare pediatric (2014) diseases. For the latter the “pediatric PRV” was created by section 908 of the 2012 FDA Safety and Innovation Act (“FDASIA”) the most recently rewarded PRV was sold for \$245 million by the company Retrophin to Sanofi.¹⁰⁰

Main advantages

- + Off-budget, i.e., payers incur no direct costs
- + Potentially strong incentive (ability to monetize them, pull-in blockbuster returns, issue multiple vouchers)
- + Transfers attractiveness of other therapeutic areas to field of antibiotics

Main challenges

- Distorts market signals by attaching an award to an unrelated drug
- Would be an uncertain and nontransparent economic benefit to developers
- Potentially large social costs from market distortion in other therapeutic areas

Recommended Levers for Market Approval

The following major challenge was identified in chapter 3:
Insufficient alignment between leading agencies worldwide in market approval

Results of Evaluation

The following levers were identified to be the most effective to address these challenges.

A further **alignment of approval processes** for antibiotics across major regulatory agencies could build on existing efforts and decrease the necessary investment in financial resources and time to develop a new antibiotic.

Transferable approval and market privileges provide a potentially attractive financing mechanism for the levers recommended in this report.

4.4 Incentives Targeting Commercialization Adaptations to Product Reimbursement Mechanisms

Examples of specific tools: reimbursement top-ups/add-on payments, conditional reimbursement, pay-for-performance (P4P).

Higher or broader reimbursement increases the commercial attractiveness of a given market. Payers have used conditional reimbursement or pay-for-performance agreements to reimburse products while additional evidence on the value of the product is still being gathered. In the case of antibiotics, it has to be noted that a more generous reimbursement may facilitate overuse and/or misuse.

For example, the United States has experience implementing add-on payments for selected new technologies (50% over the DRG) through Medicare’s New Technology Add-on

¹⁰⁰Regulatory Explainer: Everything You Need to Know About FDA’s Priority Review Vouchers. Gaffney and Mezher, 2015.

Payment (NTAP) and the creation of extra-budgetary payments through Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM).¹⁰¹ Additional ‘pay-for-performance (P4P) contracts could be introduced in either case to further incentivize keeping with conservation goals.

Main advantages

- + Feasible within current system—seen as the “natural incentive” for R&D into novel/high-priority antibiotics
- + Increases net present value and revenue certainty for developers
- + Society pays for what it benefits from and values and reimbursement could be adjusted as antibiotic effectiveness changes

Main challenges

- Would require a substantial increase in reimbursement rates—perhaps beyond what is feasible
- Requires an agreement on how to conduct a health technology assessment across countries (or one uniform assessment)
- Does not delink revenues from sales volume so incentive remains for intense marketing with potential impact on overuse and/or misuse

Adaptations to the Current Intellectual Property System (I): Broadening Patent Protection

Examples of specific tools: broadening or extending patent protection.

Two adaptations to the existing intellectual property (IP) system have been proposed: broadening patents so they cover whole resistance groups (known as functional resistance groups (FRG) or extending the patent duration.¹⁰² For the former, increasing the breadth of patents in this way would dampen the incentives for marketing (internalizing the costs of resistance). Broad patents could stop companies competing for the same pool of effectiveness within a functional resistance group, but maintain incentives for developers outside of the patented classes.

For example, academic proposal put forward by by Prof. Ramanan Laxminarayan¹⁰³ not yet implemented.

Main advantages

- + The developer would have strong conservation incentives
- + Slows down the development of resistance by addressing the “tragedy of the commons”

Main challenges

- Implementation challenging regarding how to define the groups and design the system—especially groups where patents exist already
- Need to relax antitrust laws and consider sui generis rights

¹⁰¹Reinvigorating the Oral Antibacterial Drug Development Pipeline. Engelberg Center for Health Care Reform at Brookings, 2014.
¹⁰²Preserving a Precious Resource: Rationalizing the Use of Antibiotics. Kades, 2005.
¹⁰³How broad should the scope of antibiotic patents be? Laxminarayan, 2002. Professor Laxminarayan is Vice-President for Research and Policy at the Public Health Foundation of India. Laxminarayan is also directing the Center for Disease Dynamics, Economics & Policy in Washington.

Adaptations to the Current Intellectual Property System (II): Extended Patent Protection

Extending the patent protection period and/or strengthening data exclusivity provisions would delay the entry of lower-cost generic competitors and increase the profitability of the product for the originator. Besides the profitability aspect, it is much debated if this would increase or decrease¹⁰⁴ the development of resistance. While an increase can result from deterring the follow-on products and further stifling innovation, a decrease might be due to reducing incentives for marketing.

For example, *dalbavancin* (Dalvance®) an antibacterial drug used to treat adults with skin infections approval by the FDA in 2014 received an additional 5 years of exclusivity (2–3 years effectively), until 2024 as opposed to 2019, as part of the US Generating Antibiotic Incentives Now (GAIN) Act. Dalvance® is the first drug designated as a Qualified Infectious Disease Product (QIDP) to receive FDA approval.¹⁰⁵

Main advantages

- + Potential to suppress overconsumption
- + Increased revenue expectations
- + Potential to delay development of resistan

Main challenges

- Unlikely to spur additional investment because the impact on net present value is limited due to the fact that later years in the product lifecycle are heavily discounted. Could exacerbate resistance by stifling further innovation beyond the first mover, deterring follow-on products and promoting over-utilization for a longer period

Delinkage Models

Examples of specific tools: advanced market commitments, patent buyouts

Incentives to stimulate research and development (R&D) for antibiotics that involve uncoupling the developers’ return on investments (RoI) from the volume of antibiotics sold on the market are referred to as delinkage models. Delinkage models usually comprise value-based lump sum payments at certain milestones (e.g., market approval). Such models are popular because an increase of antibiotics prizes risks increasing marketing and sales activity, thereby counteracting stewardship efforts.

When designing the lump sum payment, a balance between being large enough to attract researchers with the necessary skill set while avoiding overpayment that wastes scarce public (or donated) resources has to be found. A number of delinkage models exist, and they are fundamentally based on different ways by which the lump sum payment is calculated. The main ones are listed as follows:

¹⁰⁴Extending the Cure: Policy responses to the growing threat of antibiotic resistance. Laxminarayan and Malani, 2007. Washington, DC, Resources for the Future (Resources for the Future /RFF Report). http://www.rff.org/files/sharepoint/WorkImages/Download/ETC_full-report.pdf, accessed 23 September 2015.
Laxminarayan and Malani argue that resistance might accelerate a few years before the exhaustion of IP protection as companies have an incentive to maximize sales before the arrival of generic competition, otherwise known as patent holder waste.
¹⁰⁵Press release: FDA approves Dalvance to treat skin infections. U.S. Food and Drug Administration. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm398724.htm>, accessed 23 September 2015.



- **Prize funds:** An umbrella term for a lump sum reward to developers of a successful new antibiotic, in exchange to forgo their intellectual property rights. The size of the prize can be determined by estimating what the market value might have been, what the private value is (auction), or a calculation of the social value (using health economics or the Health Impact Fund (HIF) proposal).
For example, *three prizes* targeting antimicrobial diagnostics were announced in 2015, the UK’s €14 million *Longitude Prize*¹⁰⁶, the EU €1 million *Horizon Prize*¹⁰⁷, and the *United States €18 million prize* from the National Institutes of Health (NIH)¹⁰⁸.
- **Advanced market commitments (AMCs):** A type of purchase guarantee scheme, whereby a third-party agrees to subsidize the purchase of an antibiotic at a pre-agreed price and volume.
For example, currently being piloted for GlaxoSmithKline’s/Pfizer’s pneumococcal conjugate vaccines (PCV) by the Global Alliance for Vaccines and Immunisation (GAVI).
- **License agreements based on social value:** Upfront contracts drawn up between public bodies (payers) and private developers (company) to agree on an upfront lump sum payment for a newly developed innovative antibiotic without further unit payments on market release.

When designing delinkage levers, the ownership of intellectual property (IP) needs to be considered as well. Depending on the design of the delinkage model, the intellectual property could either remain with the developer or be transferred to a public body (patent buy-out). A coordinating mechanism that aggregates licensing agreements or patent rights is a patent pool. This mechanism enables collective acquisition and management of intellectual property for use by third parties.

Main advantages

- + Delinks commercial attractiveness from low volume expectations
- + Could facilitate achieving global conservation goals (the slowing of resistance) and achieve access goals
- + Could facilitate the allocation of costs of innovation fairly among parties/countries

Main challenges

- Requires a third-party (extra-market) determination of value
- Lack of trust/credibility/predictability of reward for developers when development is longer than political and budgetary cycles

¹⁰⁶ *Longitude Prize 2014-2019*. Nesta.

¹⁰⁷ Press release: *European Commission launches €1m prize for a diagnostic test to combat antibiotic resistance*. European Commission. <http://ec.europa.eu/research/index.cfm?pg=newsalert&year=2015&na=na-260215>, accessed 23 September 2015.

¹⁰⁸ Statement on *Prize for Diagnostic Devices to Identify Antimicrobial Resistant Bacterial Infections*. National Institutes of Health. http://www.nih.gov/about/director/09182014_statement_brain-amr.htm, accessed 23 September 2015.

Partial Delinkage Models

In partial delinkage models, patent holders retain their intellectual property rights (IP) over the new antibiotic. They can manufacture, sell, and distribute the products as normal or agree on licencing agreements; two such concepts reoccur in the literature. The first involves licensing the intellectual property rights to a public body, which pays a (reduced) lump sum in exchange for the company agreeing to supply the product on defined markets at marginal costs. The second involves companies receiving a full reward and then reimbursing the sponsor with a share of profit from sales. The latter model has recently been proposed by the Jim O’Neill review and is similar to Rempex Pharmaceuticals Rewarding Antibiotic Development and Responsible Stewardship (RADARS) proposal.

For example, Rempex Pharmaceuticals has proposed the RADARS model whereby a public body guarantees to purchase a product for 5 years. Under this model, a revenue guarantee would climb each year as per-patient pricing would fall. Any discrepancy between hospital reimbursement would be fulfilled by guarantor (US Department of Health and Human Services/ HHS). The prize is reduced by company sales invoices. It includes eligibility criteria and conditional ties for patient, hospital, and innovator.¹⁰⁹

Recommended Levers for Commercialization

The following major challenge was identified in chapter 3:

Low market attractiveness in commercialization

Results of evaluation

The following levers were identified to be the most effective to combat this challenge.

We propose a **partial delinkage model** which bases the reward for an innovative antibiotic on value for public health. This partial delinkage would be designed as a “market entry reward” (detailed in chapter 5), which companies can receive upon approval of the product. Under the proposed model, the developer would still possess the intellectual property rights. The recipient of the market entry reward must agree to a profit sharing agreement with the sponsor to receive the reward.

In addition to the market entry rewards, selective adaptations to the reimbursement of antibiotics in the hospital setting could be made (detailed in chapter 5). Reimbursement of innovative antibiotics in the hospital should compensate for only the marginal costs arising from the use of those innovative antibiotics, so that hospitals have no incentives regarding overuse or misuse of certain high-priced antibiotics.

Potential Financing Options

Some, even though not all, of the levers discussed above will require – partially substantial – additional financial resources. Many proposals exist how the additional resources could be raised:

- National-contribution on a voluntary or legally-mandated basis, normally proposed as a % of Gross Domestic Product (GDP)
For example, as proposed in Global Health Innovative Technology Fund (GHIT Fund), Medical R&D Treaty¹¹⁰

¹⁰⁹ Press release: *HHS funds drug for antimicrobial-resistant*. U.S. Department of Health & Human Services (HHS). <http://www.hhs.gov/news/press/2014pres/02/20140205b.html>, accessed 23 September 2015.

¹¹⁰ *Our Motivation*. GHIT Fund. <https://www.ghitfund.org/motivation/motivation3> accessed 23 September 2015.

5. RECOMMENDED LEVERS: STIMULATING RESEARCH AND DEVELOPMENT IN ANTIBIOTICS

- Taxes or user fees on antibiotic use, including human and agricultural uses. For example, as proposed by the Antibiotics Innovation Funding Mechanism (AIFM)¹¹¹
- Fees flatly charged against the wholesale purchase of antibiotics for all uses. For example, as proposed by the Antimicrobial Innovation and Conservation (AIC) Fee¹¹²
- A fee on each insured person or – for Europe – a government insurance levy. For example, similar to US Patient-Centred Outcome Research Institute Trust Fund (PCORITF) which mandates a \$2 fee for each person covered on a group plan.
- An auction of priority-review vouchers (PRVs) or patent term extensions to developers¹¹³
- Issuance of 10-year government-guaranteed (antibiotic) corporate bonds, repaid from the sale of patent-extension certificates. For example, Corporate Bond Funding Model¹¹⁴
- Merging of existing (national-level) funds – creation of a global fund

¹¹¹ *Antibiotics innovation funding mechanism (AIFM)*. World Health Organization. http://www.who.int/phi/implementation/7_summary_EN.pdf, accessed 23 September 2015.

¹¹² *Combating Antimicrobial Resistance: Policy Recommendations to Save Lives*. Infectious Diseases Society of America (IDSA). http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Statements/IDSA%20Combating%20Antimicrobial%20Resistance%20Policy%20Paper%20Summary.pdf, accessed 23 September 2015.

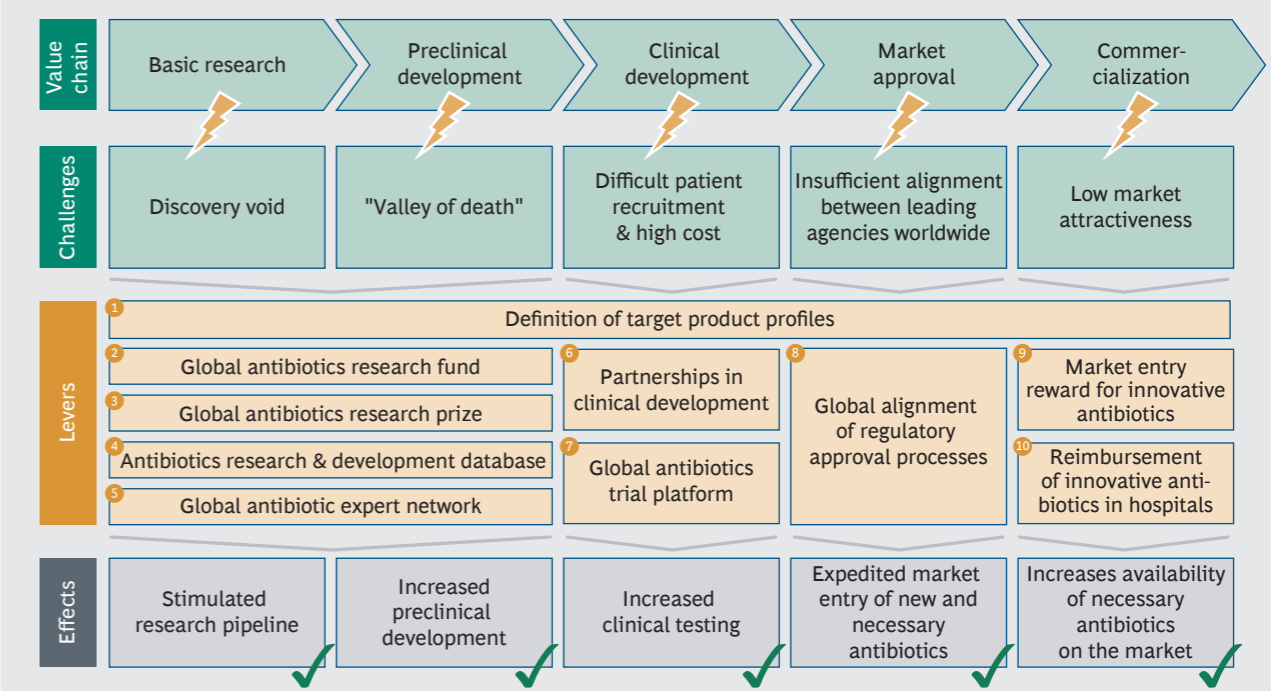
¹¹³ *Retrophin Closes Sale of Priority Review Voucher*. Market Watch. <http://www.marketwatch.com/story/retrophin-closes-sale-of-priority-review-voucher-2015-07-06>, accessed 23 September 2015.

¹¹⁴ *Business Model Options for Antibiotics Learning from Other Industries*. The Royal Institute of International Affairs and the Big Innovation Centre, 2015.

THIS REPORT RECOMMENDS IMPLEMENTING a set of 10 levers that address the multiple challenges along the value chain. While the levers are designed to work together as a package, they do not all have to be implemented at the same time. The complexity of the existing challenges requires a multipronged approach (figure 22). The recommendations made in this chapter were validated with players from the scientific and research community, the pharmaceutical and biotech industry, as well as health and regulatory organizations.

In our view, the most important and effective levers are additional funding for basic research, Partnerships in Clinical Development, and a market entry reward for new, innovative antibiotics, i.e., a volume-independent reward for companies launching a novel antibiotic that is effective against one or more of the most urgent bacterial threats—as defined by a list of Target Product Profiles.

FIGURE 22 | Overview of a multipronged approach along the value chain



Source: BCG; TU Berlin

Financing Recommended Levers and Contribution of the Pharmaceutical Industry
Significant financial resources will be required in order to implement the recommended levers. In addition to funding from states, public entities and donors, we recommend having the pharmaceutical industry participate in financing these measures. The pharmaceutical industry has benefitted and benefits from the use of antibiotics in both humans and animals that inevitably leads to the development of resistance. Therefore, it is only logical to ask the pharmaceutical industry to contribute to the financing of levers that will ensure a sustainable supply of new antibiotics. The following models should be considered:

- **Contribution based on antibiotics sales:** The worldwide antibiotics market is estimated at around €40 billion. A sales-based contribution of up to 5% of sales could provide significant resources to fund activities in antibiotics research and development. This way, companies benefiting from the sale of antibiotics would contribute to the development of new and innovative antibiotics. Such a contribution could be limited to animal health antibiotics and would also have the additional effect of deterring irresponsible use.
Alternatively, such a contribution could be limited to companies that are not active in the research and development of new antibiotics.
- **Profit-sharing mechanism:** In cases where funding is provided for profit-oriented activities (for example late-stage clinical development) profit-sharing agreements should be used to at least partially recoup the investments made. These profit-sharing agreements would be based on the sales revenue generated from the antibiotics in question. Usually, the sponsor would receive a fixed percentage of profits (or revenues) over the entire lifecycle of the product.
- **Alternative funding sources:** A range of alternative sources of funding could be considered. One such source is the sale of transferable priority review vouchers (PRVs) that are already awarded in the area of neglected tropical diseases.¹¹⁵ PRVs have achieved prices of €220–320 million when sold on the open market. Regulatory approval agencies such as the EMA or FDA could alternate in selling such vouchers. This could create significant funds without placing a financial burden on governments or international organizations. Nevertheless, it should be noted that indirect societal costs (namely higher health care expenditure) can be incurred by this instrument, as it potentially distorts other pharmaceutical markets.

As shown in figure 22, each of the 10 recommended levers will have an impact on in different phases along the value chain.



5.1 Definition of Target Product Profiles (TPP)

5.1.1 Objectives

In order to steer research and development (R&D) toward the areas with the highest public health need, we recommend developing Target Product Profiles for the most urgently needed antibiotics. Such a definition will help all following levers to guide R&D efforts into areas of highest need. For example, the Target Product Profiles will be used to assess

¹¹⁵ *United Therapeutics Sells Priority-Review Voucher to AbbVie for \$350 Million*. The Wall Street Journal. <http://www.wsj.com/articles/united-therapeutics-sells-priority-review-voucher-to-abbvie-for-350-million-1439981104>, accessed 23 September 2015

the value and innovativeness of an antibiotic that qualifies for the market entry reward (see chapter 5.9).

5.1.2 Proposed Approach

The Target Product Profiles would be based on a classification of pathogens by threat level. National efforts have already been undertaken to classify bacterial threats and could serve as a basis for the development of global Target Product Profiles. The Centers for Disease Control and Prevention (CDC), for example, has developed a list of the most urgent microbial threats in the United States (see chapter 2.2.1).

5.1.3 Targeted Stakeholders

This lever will require the participation of the following stakeholders:

- **National health ministries and agencies:** National public bodies can help finding the most urgent areas of R&D. Including public agencies from developed and developing countries will help to create a comprehensive list of Target Product Profiles.
- **Researchers from science and industry:** It is essential to engage the scientific and research community to include topic experts in the definition process for the Target Product Profiles.
- **Non-governmental organizations:** Non-governmental organizations have proved successful in attracting attention to previously unattractive areas of research. Their expertise and support can increase the likelihood of a widely accepted list of Target Product Profiles

5.1.4 Financial Implications

The list of TPPs will serve as a guiding instrument for the other levers recommended in this report. A participatory process of identifying the most urgent global threats needs to include stakeholders from all fields. Direct funding necessary for this lever is limited to the cost of coordination of the participating stakeholders.

5.2 Global Antibiotics Research Fund

5.2.1 Objectives

The aim of a research fund is to substantially increase activity in basic research and pre-clinical development through project-based and institutional funding of academic institutions and small and medium-sized enterprises (SMEs). Basic research is often pre-competitive and dependent on funding by public actors, this is also true for antibiotics. Establishing a fund will signal long-term commitment to potential researchers. This will be important to enhance the activities in basic research and pre-clinical development. While there are already several initiatives on national or supra-national level, we recommend bundling these efforts in a global fund. The global antibiotics research fund will address two of the major challenges:

- “*Discovery void*” in basic research
- “*Valley of death*” in preclinical development



5.2.2 Proposed Approach

Defining a Strategic Focus

Following a strategic research agenda informed by the Target Product Profiles (lever 1), the research fund will support research projects of academic institutions and small and medium-sized enterprises (SMEs) with a focus on the biggest challenges in antibacterial research. From today’s perspective, these challenges could be:

- Advancing the understanding of multidrug-resistant gram-negative bacteria and identifying new compounds active against them
- Promoting the development of point-of-care diagnostic tools
- Additionally, the fund should selectively invest into blue sky research(the exploration of new and innovative research fields) that has the potential to open completely new avenues for antibacterial research

Funding Public and Private Entities

Funding will be available for research institutions and for small and medium-sized enterprises (enterprise funding). Interested parties can apply for funding on a project basis. Project funding can run for multiple years, depending on the nature of the projects. However, project progress will be tracked on a regular basis. The application process will be peer-reviewed by experts from the field. The financial support will be structured differently for basic research and preclinical development:

- **Basic research:** Supported organizations will receive grants which do not have to be repaid as projects in this precompetitive phase rarely generate revenues. Research institutions may furthermore apply for longer term institutional funding for PhD, post-doctoral positions or professorships. These mid- to long-term funding agreements are intended to create certainty and stability for antibiotics research and to allow for the institutionalization of knowledge.
- **Preclinical development:** In preclinical development, the opportunities of developing results with commercial value are already higher than in basic research. Therefore, as a condition for receiving a grant, the fund will put in place profit-sharing agreements with the institutions. These agreements require recipients to share a certain percentage of the resulting profits with the fund. If no profits are generated, the recipients have no financial obligations to the fund. The fund will seek to achieve an equivalent internal rate of return with the funded private entity.

Entities receiving funding are encouraged to share the results and data of funded projects with the research community (see lever 4 below).

5.2.3 Targeted Stakeholders

The following stakeholders will be eligible for funding from the global antibiotics research fund:

- **Academic institutions:** These institutions should be encouraged to apply for funding in both basic and preclinical development.
- **Small and medium-sized enterprises:** As big pharmaceutical companies have largely withdrawn from this phase in the value chain, it is essential to encourage other

commercial actors to continue and increase participation. Additionally, these smaller companies are more agile and able to change strategy in light of such funding opportunities.

5.2.4 Financial Implications

In order to turn around the decline in antibiotics research activity and to tackle the existing scientific challenges, significant funds will have to be provided. We estimate that total funding has to amount to a similar order of magnitude as the New Drugs 4 Bad Bugs (ND4BB)¹¹⁶ program (around €100 million per year). The fund could be financed by the public, by the contributions of the pharmaceutical industry (as discussed above) and with potential proceeds from profit-sharing agreements reached with participating entities.

5.3 Global Antibiotics Research Prize

5.3.1 Objectives

The prize will attract public attention to current challenges in antibiotics research. The prize will increase the visibility associated with antibacterial research and also create a platform for exchange among researchers. The public attention drawn by similar efforts in related areas, such as the UK Longitude Prize, is very high compared to the necessary investment. The announcement of such a prize itself can be used to create positive momentum for antibiotics R&D.

The global antibiotics research prize will have a positive impact on two major challenges of the value chain:

- “Discovery void” in basic research
- “Valley of death” in preclinical development

5.3.2 Proposed Approach

Awarding Innovation in Basic Research

Prizes will be awarded to the institution or researcher that presents the most promising or innovative concept regarding an announced theme. The awarded amounts should be in-line with similar research prizes, such as the UK Longitude Prize, which promises €10 million for a rapid point-of-care diagnostic for bacteria. Research projects from all over the world would be eligible for the prize.

To ensure that the prize winners are legitimate, the following requirements have to be met:

- Studies must be peer-reviewed
- Relevant data must be made available to ensure transparency

Potential First Focus: Gram-Negative Bacteria

As discussed before, gram-negative bacteria pose an exceptional challenge to the scientific progress in antibacterial research. Thus, we recommend focusing the first prize on achievements that have the potential to contribute to the development of effective treatments against gram-negative bacteria.

¹¹⁶New Drugs for Bad Bugs. <http://www.nd4bb.eu/>



An Conference as a Platform for Exchange

The award will be presented at a conference focusing on antibiotics. The conference will serve as a forum for exchange and community building for active researchers and experts in the field. The price will be awarded every 5 years. The conference, however, will serve as a yearly opportunity to network and advance R&D in antibiotics.

5.3.3 Targeted Stakeholders

Academic institutions conducting research on antibiotics are invited to compete for the prize. Beyond such research institutions, other stakeholders will also benefit from the research prize:

- **Active and former researchers:** The prize is expected to facilitate communication about research and knowledge concerning bacteria and antibiotics.
- **The wider public:** The prize is intended to attract attention to the cause of antibiotics research. Attracting journalists or interested citizens to the yearly conference will further increase the reach of the lever.
- **Sponsors:** The prize and the yearly conference are suitable sponsorship opportunities. Pharmaceutical companies or charitable organizations can play active roles in the organization of the research prize.

5.3.4 Financial Implications

The required investment for the global antibiotics price is estimated as follows:

- One-time establishment costs: approximately €1 million
- Total prize money (every 5 years): approximately €13 million
- Funds required for yearly conference: approximately €1 million

The estimations are based on comparable events and their required budgets.

5.4 Antibiotics Research and Development Database

5.4.1 Objectives

We recommend creating a database that will serve as a central information repository for researchers in the field of antibiotics. The database will bundle information on past and ongoing research projects from academia and commercial players. Allowing access to research results would be a condition for receiving financial support of any kind, e.g., from the research fund.

The database will help improve the allocation of research efforts and funds through more informed decision making. It will also facilitate the exchange of ideas between researchers working on similar problems. The antibiotics research and development database will have a positive impact on two major challenges:

- “*Discovery void*” in basic research
- “*Valley of death*” in preclinical development

5.4.2 Proposed Approach

Scope of the Global Antibiotic Research and Development Database

The database will have multiple functions which can be used by active researchers, policy makers and experts in antibiotics:

- Increased access to existing studies/research projects
- Increased ability to identify and communicate with relevant researchers in the field

Beyond Peer-Reviewed Articles

Essential knowledge about the behavior of bacteria and the mechanisms of antibacterial agents resides with different players in the field. It is important to engage these players to share project insights through the database. This includes information from past and current projects, successful as well as failed, as these are equally important to improving coordination and communication.

Motivating Open Sharing of Information

Achieving participation from all parties actively involved in antibiotics research is challenging. Especially pharmaceutical companies have had little motivation to share information on their antibiotics programs. However, recent efforts to enhance transparency (e.g., opening up compound libraries by big pharmaceutical institutions) have been increasingly successful and show that given sufficient positive public attention, the release of noncompetitive information can become attractive for pharmaceutical companies. Companies which have exited antibiotics research may be more likely to share information because there is no immediate risk of a competitive disadvantage.

Parties that actively share information could be rewarded with privileged access to the database. Clear guardrails for the treatment of intellectual property (IP) will have to be agreed upon with all participating stakeholders to ensure that the most valuable information is disclosed.

5.4.3 Targeted Stakeholders

The following stakeholders will have to be successfully engaged to establish a comprehensive and effective database:

- **Academic institutions:** These institutions should be encouraged to provide both peer reviewed studies and information on current research projects.
- **Pharmaceutical companies:** Often relevant research projects were conducted 10–15 years ago, when the commercial field was more active (see chapter 2.1.3). This knowledge is often not shared with the public or the scientific community at risk of being lost permanently, as research units are continuously being shut down. Achieving access to these studies will be challenging but critical for the success and usefulness of the database.
- **Scientific journals:** Targeting scientific journals directly can increase the comprehensiveness of the database. Creating a central repository for relevant information will require an active engagement with the scientific publishing community.

5.4.4 Financial Implications

Integration with Current Efforts

The database should seek to coordinate with current efforts already under way. In Europe, a project within the New Drugs for Bad Bugs (ND4BB) initiative has started to compile studies to improve decision making.¹¹⁷ Other efforts around the world should be considered as cooperation partners as well.

¹¹⁷ COMPACTE Program. Innovative Medicines Initiative.

The required investment for the global antibiotics R&D database could be in the following range (estimations based on expert interviews):

- One-time establishment costs: approximately €1–2 million
- Yearly running cost: Less than €1 million

The necessary investment for the establishment will vary substantially depending on the setup (independent or as part of existing structures) and the functions that the database will include.



5.5 Global Antibiotics Expert Network

5.5.1 Objectives

Addressing Current Inefficiencies in the Antibiotics Research and Development Community

We recommend establishing a network of antibiotics experts in order to preserve existing knowledge and support research and development projects.

Identifying these experts and securing their future support can significantly improve the chances of success for antibiotic research and development. The members of the expert network would advise research projects (in particular those funded by the research fund) and partnerships for clinical development, based on their extensive experience in the field.

This is essential in addressing the challenges:

- “*Discovery void*” in basic research
- “*Valley of death*” in preclinical development

5.5.2 Proposed Approach

Strengthening Connections within the Antibiotics R&D Community

The network would include active researchers but also former members of the antibiotics community who used to work in the field but have ended their active engagement in antibiotics research.

The expert network will also play a crucial role in supporting the other levers described in this chapter, especially the research prize (by serving as a panel selecting the winning entries), partnerships for clinical development (by providing expert advice) and the research fund (by evaluating and supporting research projects).

The network is intended as a targeted approach to identify and connect the leading active and former researchers. The members will form a panel, which could be approached when scientific advice is required.

Specifying Interaction Formats

The success of an expert network relies on regular in-person communication, which helps maintain a significant level of activity and productivity. This could be achieved through the following formats:

- Regular network events (such as the global antibiotic research prize and conference)
- Use of the expertise in allocating funding in basic research and preclinical development
- Placement of the experts as advisors on funded research and development projects

5.5.3 Targeted Stakeholders

The following stakeholders will have to be engaged to identify leading active and retired researchers and establish an effective global antibiotics expert network:

- **Academic institutions:** A significant part of basic research in antibiotics and related fields is conducted in academic settings. Institutions and individuals should be engaged to provide information on relevant researchers for the expert network.
- **Pharmaceutical companies:** A large part of basic research and preclinical development was conducted in the industrial setting. These organizations need to be engaged to provide details and serve as an introducer to active and retired researchers.

Practitioners with relevant expertise: In order to advise scientists on topics that are highly relevant for patient care, the consideration of practical expertise associated with antibiotics research and development (R&D) is important.

Multiple fields of expertise should be engaged to establish a comprehensive panel of researchers. These fields include pharmacology, microbiology, medicinal chemistry and others.

5.5.4 Financial Implications

The required investment for the global antibiotics expert network could be in the following range (based on expert interviews):

- One-time establishment costs: approximately €1–2 million
- Yearly maintenance: less than €500,000

5.6 Partnerships in Clinical Development



5.6.1 Objectives

We recommend establishing partnerships in clinical development for promising antibiotics that meet one (or several) of the Target Product Profiles (see chapter 5.1). Partnerships in clinical development will help small and medium-sized enterprises (SMEs) and research institutions in conducting clinical trials.

Although relatively low compared to other therapeutic areas, costs for clinical trials of antibiotics are still significant (around €120 million for the clinical development of an antibiotic, see chapter 3.2.1) and potentially prohibitive for small and medium-sized enterprises. Providing SMEs with financial and non-financial support (e.g., expert advice through the expert network) at this stage could increase the number of antibiotics in clinical trials.

The Partnerships in Clinical Development will address one of the major identified challenges:

- High cost in clinical development

5.6.2 Proposed Approach

Supporting Clinical Development

To foster increased activity in clinical development of antibiotics, partnerships in clinical development will be established. The partnerships will provide support along the clinical

development. Companies and research institutions can apply for support of clinical trials for promising candidates.

Providing Support Until Market Approval

Partnerships in clinical development can be formed for each phase of clinical development. If a clinical trial phase is successfully passed, funding for the next clinical phase is not automatically granted. Interested parties must apply for funding for each clinical phase. This is intended to ensure that the most promising candidates with the largest potential for societal benefit are identified and funded at each step.

Providing Financial and Organizational Support

If a candidate is evaluated as suitable, the partnership in clinical development will support the clinical trial in multiple ways:

- Financial support for the relevant trial phase (can cover up to 50% of the clinical trial costs)
- In-kind resources (e.g., laboratories and patient databases)
- Expert advice via the global antibiotic expert network (see chapter 5.4)

When small and medium-sized enterprises (SMEs) are funded, the cash flow requirements of these entities should be taken into consideration (increased reliance on continuous provision of funds in smaller increments).

Establishing a Profit-Sharing System

Companies accepting support must agree to a profit-sharing agreement, which is activated in case of market entry or sale of intellectual property (IP). A fixed part of any profits retained through the sale of the antibiotic or the intellectual property will be used to repay the funding support. In case of a substantial contribution of the funding entity, the results of the research (potentially including intellectual property-protected results) could be used to support future research efforts.

Focusing on Small and Medium-Sized Enterprises

Only small and medium-sized enterprises (SMEs) and research institutions which are not able to carry the full cost of clinical development are taken into consideration for funding preferentially.

Interactions with Market Entry Reward

Should a compound that has been developed under a partnership in clinical development be marketed and qualify for the market entry reward (see chapter 5.9), the financial support received during this clinical trial stage will be deducted from the final market entry reward payment.

5.6.3 Targeted Stakeholders

The following stakeholders will have to be successfully engaged to establish partnerships in clinical development for clinical candidates:

- **SMEs and biotech companies:** By focusing the support on small and medium-sized enterprises, additional activity through new players entering clinical development will be fostered.
- **Academic institutions:** By engaging academic institutions into these partnerships for clinical development, essential knowledge and research insights can be leveraged.

5.6.4 Financial Implications

The required investment for the partnerships in clinical Development depends on the amount of studies funded and can be estimated as follows:

- Yearly cost (based on the assumption that one trial in each phase starts per year: approximately €70 million)¹¹⁸

5.7 Global Antibiotics Trial Platform

5.7.1 Objectives

We recommend establishing a global platform for antibiotic trials in order to support the planning and execution of clinical trials. The platform would improve the matching of clinical trials and patients, which is especially challenging in acute antibiotic settings that require quick response times.

The platform can improve recruiting of patients for phase II and phase III trials, thereby improving the quality and speed of clinical trials while potentially reducing costs for companies. The global antibiotics trial platform will address one of the major identified challenges:

- Difficult patient recruitment and high cost in clinical development

5.7.2 Proposed Approach

Setting Up a Platform for Suitable Hospitals

This platform would include relevant hospitals and clinics, which are likely to be able to include potential trial participants as they regularly treat patients being infected by bacteria included in the TPPs (e.g., because they have departments for infectious diseases). These hospitals and clinics would be primarily asked to recruit patients for the clinical trials. Trials of antibiotics that match the criteria of a TPP could be treated preferentially and have privileged access or priority in patient allocation.

Setting Up a Reporting Platform for Patients

The platform contains information about current and planned clinical trials and the patients these trials are looking for. Hospitals (especially those not part of the platform mentioned above) and doctors would be able to access the platform if patients are interested in participating in such trials. It is essential to ensure the data privacy of potential participants.

5.7.3 Targeted Stakeholders

The following stakeholders will have to be successfully engaged to establish a global antibiotic and patient trial registry:

- **Hospitals:** Establishing a stable network of participating hospitals and clinics will be essential for an improved and less resource-intensive clinical development of antibiotics. Within the participating clinics, medical personnel from the relevant areas using antibiotics will have to be engaged.
- **Regulatory agencies:** The relevant regulatory agencies that define and publish guidelines for clinical trials should be consulted in the design of the platform and the

¹¹⁸ Calculation is based on the given number of clinical trials suggested above. Estimations of clinical trials based on AMR Review.



selection of clinics. This ensures that necessary standards are implemented by participants.

- **Surveillance agencies:** The clinical trial platform can improve data collection about antibiotic resistance. Such data is valuable for surveillance efforts by public and non-governmental players.
- **Pharmaceutical companies:** Pharmaceutical companies should be engaged in the development and set-up of the trial platform to ensure usability in the execution of clinical trials.

5.7.4 Financial Implications

Building upon Existing Efforts

For the success of the antibiotics and patient trial registry, it is essential to coordinate with existing databases, such as the COMBACTE CLIN-Net that is currently established in Europe. CLIN-Net aims to support and coordinate clinical trials of antibiotics by developing a network of qualified clinical trial sites. Efforts such as this—currently connecting about 200 hospitals and clinics in Europe—are important steps toward a global trial platform that is able to identify patients according to the relevant standards. The necessary initial and continuous funding for such a trial platform depends to a large degree on its mode of establishment (stand-alone or as part of existing efforts).

5.8 Global Alignment of Regulatory Approval Processes

5.8.1 Objectives

We recommend continuing to align regulatory requirements for antibiotics across the main markets, building on past and current efforts. Creating a unified global approval process for antibiotics between the EMA, FDA, Japan’s Pharmaceuticals and Medical Devices Agency (PDMA) and other relevant approval agencies should be considered as the ultimate goal.

An increased alignment would have the direct positive effects of lower cost requirements and resource intensity for agencies and approval seekers alike. Furthermore, it could decrease time-to-market and thereby make new products available earlier. This lever will address one of the major challenges identified:

- Remaining differences in requirements across regulatory approval agencies in market approval

5.8.2 Proposed Approach

Setting Up an Expert Working Group

A working group bringing together representatives of major regulatory agencies (EMA, FDA, PMDA, etc.) should be established to develop specific recommendations on how to further align regulatory requirements (e.g., regarding the use of superiority trials, required statistical analyses, and accepted endpoints). The working group would develop recommendations to align or unify the current approval processes for urgently needed antibiotics. The working group would build on existing efforts by the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and others.

Guidelines for Aligning Approval Processes

The following guidelines should be considered when aligning regulatory requirements:

- Granting fast-track approval for high priority antibiotics based on the TPP list
- Harmonizing trial requirements regarding the following aspects (not exhaustive):
 - Possibility of pathogen-specific trials
 - Criteria for patient selection
 - Statistical parameters and standards

5.8.3 Targeted Stakeholders

The alignment of approval is a relevant measure for the following players:

- **Regulatory agencies:** National and regional are already engaged in active communication to improve the clinical development and clarify market approval requirement for antibiotics. These agencies should be further engaged to continue this process and focus efforts on the TPPs.
- **Existing international working groups:** Existing efforts developed through working groups should be used as a starting point for the further alignment of regulatory approval for antibiotics.
- **Companies seeking approval for antibiotics:** Seeking the participation of the companies will help to identify remaining inefficiencies and uncertainties perceived by the “users” of the approval process.

5.8.4 Financial Implications

A working group should be set up to define further steps. Beyond that, no direct funding is required for this lever.

5.9 Market Entry Reward for Innovative Antibiotics

5.9.1 Objectives

We recommend introducing a market entry reward—a lump-sum payment—paid to companies introducing innovative antibiotics that meet the Target Product Profile (see chapter 5.1). The reward aims to increase the commercial attractiveness of the antibiotics market by providing a reliable and predictable source of income for pharmaceutical companies. The market for antibiotics would be changed through the employment of such a partial delinkage model. The return on investment (RoI) for an antibiotic drug would be able to compete with drugs of other therapeutic areas. The lever addresses the following challenge:

- Low commercial attractiveness in commercialization

5.9.2 Proposed Approach

Incentivizing Innovation with a Market Entry Reward

The market entry reward is a fixed and guaranteed payment that is independent of future sales volume and will be paid to companies introducing an innovative antibiotic that meets the Target Product Profile. Receiving the reward does not entail any transfer of intellectual property, i.e., the company launching the drug can still generate returns from selling the product. However, the company has to pay a share of its profits resulting from the sale of the drug back to the sponsor.

Antibiotic candidates will be evaluated based on their efficacy against the pathogens prioritized in the Target Product Profiles and on their innovativeness (e.g., whether the antibiotic is part of a new class). Their launch date relative to market competitors should be considered as well: A product that is a fast follower in a new class should receive a financial reward as well, though less than the first-to-market-product.

The profit sharing agreements have multiple positive effects:

- First, the profit sharing revenues replenish the fund, which reduces the financial burden on the sponsors of the lever. This way, it is ensured that the fund participates in the potential commercial success of innovative antibiotics while still eliminating the uncertainty that the antibiotic providers face.
- Second, the profit sharing agreements decrease the incentive to sell the antibiotic, thereby reducing current challenges in conservation for this particular product. By this measure, resistance building could be delayed as well.

5.9.3 Targeted Stakeholders

The market entry reward is a relevant measure for the following players:

- **Companies developing and launching antibiotics:** The increased expected profitability of the innovative antibiotics would create interest from large pharmaceutical companies and have a “trickle down” effect, thereby not only supporting companies in the position to produce and sell antibiotic on a large scale, but smaller companies and specialists as well. These companies would benefit as the value of intermediate products (e.g., lead compounds) would increase in anticipation of higher revenues.

5.9.4 Financial Implications

Basic Criteria for Eligibility

New antibiotic products would need to fulfill the following criteria to be eligible:

- Antibiotic suited to the treatment of priority bacteria as defined in the Target Product Profile
- Market approval by EMA, FDA and potentially other major regulatory agencies
- Product is first in a new class or alternatively:
 - Provides substantial added value over current antibiotic in the same class
 - Belongs to an existing class but is launched within one year of the first-in-class antibiotic (capped at a combined 100% of the reward for first-in-class and subsequent products)

Conditions for Receiving the Market Entry Reward

Companies receiving the market entry reward must accept conditions upon receiving the reward. The following aspects must be detailed in such an agreement:

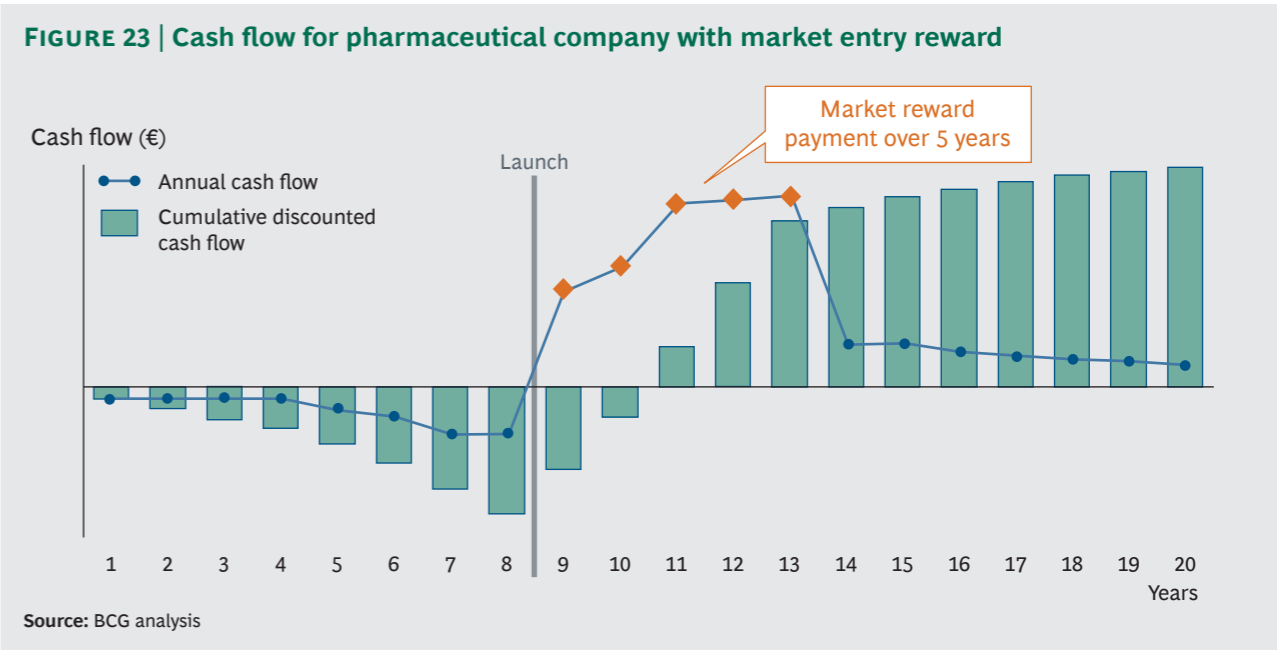
- Global availability of the antibiotic
- Affordability of the antibiotic, especially in developing countries
- If the rewarded product was developed through a development partnership (lever 6), the market entry reward is reduced proportionally
- Profit-sharing agreements in order to share potential commercial upside with the sponsor of the market entry reward

Structure of Payments

The reward will be structured in the following way:

- The market entry reward should be in the order of €1,000 million
 - There amount could depend on the efficacy against the Target Product Profiles
 - The reward is paid across the first 5 years after launch to ensure product availability
- Post-approval data on efficacy and safety of the antibiotic should be considered for determining the magnitude of the reward

The order of magnitude of around €1,000 million is required to change the economics antibacterial research and was tested with experts in antibiotics R&D and pharmaceutical corporate strategy. This reward would increase the net present value (NPV) significantly as illustrated in figure 23. The net present value of the development of an antibiotic would change from €-90 million to €300 million, with a market entry reward of this magnitude.



5.10 Reimbursement for Innovative Antibiotics in Hospitals

5.10.1 Objectives

We additionally encourage national policy makers to ensure that new antibiotics which meet the Target Product Profile (see chapter 5.1) are adequately reimbursed within the hospital setting, where these antibiotics will be predominately used to minimize inappropriate usage.

This lever will address one of the major identified challenges:

- Low market attractiveness in commercialization

5.10.2 Proposed Approach

Providing a Market

In order to create a functioning market for innovative and higher-priced antibiotics, we encourage countries to adequately reimburse innovative antibiotics in a hospital setting.

Only new antibiotic products that meet the Target Product Profile and are not adequately covered by existing hospital reimbursement levels would be considered

Conserving the Effectiveness of Antibiotics

To avoid overuse payments should be designed to minimize incentives for inappropriate use.

5.10.3 Targeted Stakeholders

The alignment of approval is a relevant measure for the following actors:

- Companies selling antibiotics

5.10.4 Financial Implications

The additional resources for the countries involved will depend on the number of new, qualifying antibiotics, the epidemiology in the country, and the price level within the country.

5.11 Timing and First Steps

Many stakeholders interviewed for this report stressed the importance of immediate action in order to address the public health challenge presented by antimicrobial resistance (AMR). The levers presented above constitute a multi-year, coordinated global approach. However, many steps can and have to be taken now. The figure below illustrates a potential high-level timing for the implementation of the levers discussed before.

FIGURE 24 | Next steps for implementation of levers

	Immediate Activities	Short-term	Medium-term	Long-term
1 Definition of target product	<ul style="list-style-type: none">• Screen and merge current national efforts• Set up working group	Define list of TPPs	Update continuously based on changing resistance and threat levels	
2 Global antibiotic research fund	<ul style="list-style-type: none">• Line up sponsors for fund	Define strategic research agenda	Define funding conditions (terms, IP ownership, tendering)	Provide funds to research projects
3 Global antibiotic research prize	<ul style="list-style-type: none">• Define entry conditions• Decide on first theme	Announce call for entries, nominate jury	Hold conference and prize annually	
4 Antibiotic research & development database	<ul style="list-style-type: none">• Approach researchers and institutions• Define access rules	Establish digital platform & identify needs and current services	Enable public data access	
5 Global antibiotic expert network	<ul style="list-style-type: none">• Develop list of thought leaders (active and retired)	Conduct first network events	Integrate expert network with other levers (e.g., as advisors in partnerships in clinical development)	
6 Partnerships in clinical development	<ul style="list-style-type: none">• Gather lessons learned from existing partnerships in clinical development healthcare	Detail models (e.g., funding level, profit sharing, IP)	Start first trial	Continue conducting trials
7 Global antibiotic trial platform	<ul style="list-style-type: none">• Identify clinics to be included• Align with ongoing efforts	Invite clinics and connect to platform	Continuous extension and monitoring of network	
8 Global alignment of regulatory approval processes	<ul style="list-style-type: none">• Establish working group	Define areas for further alignment	Propose regulatory adaption	Implement and consider global approval possibilities
9 Market entry reward for innovative antibiotics	<ul style="list-style-type: none">• Develop detailed reward criteria• Determine organizational set-up	Refine reward criteria in participatory process	Publicly announce reward & signal long-term commitment	Reward first product
10 Reimbursement of innovative antibiotics in hospitals	<ul style="list-style-type: none">• Establish national-level working groups	Define adequate compensation levels, avoiding incentivizing over-use	Propose regulatory adaption	Monitor for appropriate implementation

6. THOUGHTS ON IMPLEMENTATION

THE RESEARCH AND ANALYSIS for this report has emphasized the urgency of the implementation of some of the levers. Given the accelerating brain drain in antibiotics research and the irreversibility of some strategic decisions—e.g., dismantling a research unit—delaying implementation might have severe consequences. As explained in previous chapters, the market is currently not providing antibiotics needed to address the global health challenge.

A globally coordinated approach

Given the global nature of pharmaceutical research, development and commercialization, and the global challenge of antimicrobial resistance, we suggest a globally coordinated approach to implementation.

In prior chapters, it has been established that a reinvigoration of the pharmaceutical industry is essential for achieving a sufficient and sustainable supply of antibiotics (see chapter 3). The strategic decision makers of multinational pharmaceutical companies interviewed for this report have emphasized that the attractiveness of a therapeutic area is based on global market potential. Individual national efforts can influence these strategic decisions, especially in bigger markets, such as the USA as efforts like the GAIN act have shown.¹¹⁹ Still, a global, or at least broad international, approach is necessary to change the pharmaceutical industry’s engagement in antibiotics.

Similarly, an internationally coordinated approach to research in academia is needed. Nationally fragmented funding and research agendas have led to a duplication of research efforts and hampered exchange across research groups.

We recommend starting with an alliance of influential, opinion-leading countries working closely with multilateral organizations (such as the WHO) and other active stakeholders (such as the DNDi). Other countries as well as philanthropic organizations are encouraged to join in this initiative.

6.1 Global Antibiotics—Collaboration Platform

Creation of the global antibiotics collaboration platform

Implementation, coordination, and controlling across initiatives have been a major challenge. We recommend setting up a dedicated, global collaboration platform. Establishing a collaboration platform will help foster the research and development of antibiotics in multiple ways:

- The collaboration platform can support in the implementation of the different levers.
- The collaboration platform would signal a strong long-term commitment to participants from the public, private, and academic world. For companies and research institutions to build or maintain these capabilities, security in planning over a multiyear

time horizon is essential. Its establishment would create momentum and be an important start for effectively implementing some of the suggested levers (see below).

Broad stakeholder involvement within the global antibiotics collaboration platform

Given the complexity of the challenges and the breadth of expertise needed, a key success factor for this collaboration platform is to combine the knowledge of the public and private sector as well as from academia. In other therapeutic areas, e.g., neglected tropical diseases such an approach has been successful. In the case of antibiotics, we suggest setting up an agile and lean collaboration platform employing top-notch personnel from the private and public sector as well as academia. In similar cases, such facilities have been successfully set up as part of public-private partnerships.

Scope and vision of the global antibiotics collaboration platform

The vision of the collaboration platform can be described along three dimensions:

- **Being a thought leader and coordinator:** The platform could raise the profile of antibiotics research and serve as a place for fostering innovative ideas, considering unconventional approaches, and involving players from all sectors. Therefore, in order to identify compounds and develop new research approaches SMEs, biotech firms, pharmaceutical companies, and academia should be actively engaged. The impact of the implemented levers should be continuously monitored and adjustments be taken if necessary.
- **Becoming a knowledge hub for research and development of antibiotics:** The collaboration platform could connect active researchers, improve access to scientific information and become a main advisor for researchers and pharmaceutical developers.
- **Stimulating the market:** The collaboration platform could help to create and implement incentive structures for science and businesses to enhance antibiotic research in industry and science.

Organizational setup of the global antibiotics collaboration platform

There are different options on how to organizationally set up such a collaboration platform. Setting up the collaboration platform as a unit or as part of an existing multilateral organization (e.g., the WHO) has the main advantages of providing access to existing expertise and networks as well as generating increased credibility. Covering the initial investments and running costs for the collaboration platform is a joint responsibility of the states driving this effort. Using existing structures and networks could furthermore enable a quicker implementation of the more urgent levers (e.g., the expert network).

Financing of the global antibiotics collaboration platform

The initial funding for setting up the collaboration platform could be provided by the states leading the charge against antimicrobial resistance. We also recommend that the pharmaceutical industry carry a share of the funding need, e.g., through a contribution based on antibiotics revenue (see chapter 5).

¹¹⁹GAIN: *How a New Law is Stimulating the Development of Antibiotics*. The PEW Charitable Trusts. <http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics>, accessed 23 September 2015.

6.2 Conclusion

Coordinating the market entry reward

Different possible mechanisms for financing this lever are outlined in chapter 5. The Target Product Profiles described in lever 1 form the basis for the final design of the market entry reward.

Successful implementation of the market entry reward requires an open dialog with the pharmaceutical industry that is incentivized by this lever. Multiple pharmaceutical companies have called for a full or partial delinkage model in antibiotics. The primary request is for a multiyear commitment; only then can a significant increase of investments into antibiotics by these firms be expected. Stakeholders from all sectors agree that designing a set of parameters that avoid “gaming” on the one hand, while providing sufficient certainty to the industry is challenging.

Turnaround in antibiotics research and development

The challenges in antibiotics research and development are immense. However, we believe that with a global commitment and by applying the levers discussed in this report, the global community can overcome those challenges—so that our generation and the generations to come can rely on effective protection against bacterial threats.

7. APPENDIX

7.1 Current status of global political context and actions

A gathering political momentum

Collective attention to the issue of antimicrobial resistance (AMR) has been mounting since 1999 when the European Council and an EU-United States summit issued declarations on the growing topic. Since then governments and international bodies have been progressively recognizing the problem of antimicrobial resistance. Thus, the acknowledgment of the scale, urgency and global nature of the challenge is growing.

This trend is being supported by prominent international figures that are increasingly using urgent language when addressing the issue. For example, the President of the United States has said that the effectiveness of antibiotics is a “matter of national security” and that “they are, quite simply, essential to the health of our people and people everywhere”.¹²⁰ The Director-General of the World Health Organization (WHO), Margret Chan, has stated, “antimicrobial resistance is not a future threat looming on the horizon. It is here, right now, and the consequences are devastating”. Britain’s Chief Medical Officer, Dame Sally Davies, has referred to the “*discovery void*” and warned that “antimicrobial resistance poses a catastrophic threat”¹²¹ and German Chancellor Angela Merkel has put the issue high on the agenda of Germany’s current presidency of the G7.

As of today, the vast majority of OECD countries have made public their acknowledgment of the issue.

Emergence of national-level action

Many countries are already moving to address the issue on national levels. Specifically regarding the lack of new antibiotics, some countries have already started incentivizing potential developers, in an attempt to return antibiotics to being an attractive therapeutic area for R&D. The United States is kick-starting the global pipeline using a broad variety of policy tools. The UK and Germany are also notable in the actions already taken to address the issue (for detailed analysis see chapter 7.2).

However, these initiatives have not been able to provide a turnaround on a global level and a truly global response is still a long way off.

Initiatives at a regional level

National efforts have been running concurrently with initiatives at a regional level. The first effort to bring the issue to a higher-level was the creation in 2009 of the Transatlan-

¹²⁰ Obama announces plan to fight antibiotic-resistant superbugs. CBS News. <http://www.cbsnews.com/news/obama-announces-plan-to-fight-antibiotic-resistant-superbugs/> Accessed 23 September 2015.

¹²¹ Press release: Antimicrobial resistance poses ‘catastrophic threat’, says Chief Medical Officer. GOV.UK. <https://www.gov.uk/government/news/antimicrobial-resistance-poses-catastrophic-threat-says-chief-medical-officer-2>. Accessed 23 September 2015.

tic Task Force on Antimicrobial Resistance (TATFAR)¹²². TATFAR is a collaboration between the US (Department of Health and Human Services (HHS)) and EU (represented by the European Commission (EC)). They identified 17 recommendations covering 3 key areas, where exchange is facilitated.

Regionally, the EU has been driving transnational push incentives, many of which have pulled in expertise from beyond the EU. Based on the EC’s 2011 Action Plan Against the Rising Threats of AMR¹²³ two main actions—related to R&D—have been the focus:

- To promote, in a staged approach, unprecedented collaborative R&D efforts to bring new antibiotics to patients
- To reinforce and coordinate research efforts

Notable examples of this report are highlighted in chapter 4.1 and include increased funding for basic research projects through its FP7 and FP8 (Horizon 2020) framework agreements. Creation of a Joint Programming Initiative on AMR (JPIAMR) and an EU-wide public private partnership (PPP), the IMI comprising around seven antibiotic-relevant projects lead by the € 600 million New Drugs for Bad Bugs (ND4BB) program.

Considerations of a global problem

Regional level commitments are increasingly gathering momentum and taking on a more unified global voice—through the use of trans-national forums such as the G7, G20 and World Economic Forum (WEF). Global bodies, such as the United Nations (UN) agencies, lead by the World Health Organization (WHO), have become active in assuming a global coordination role.

Beginnings of a global dialogue

With regards to global institutions, the World Health Assembly (WHA) has called on the United Nations to convene a high-level meeting of political leaders in 2016. This follows the 2015 World Health Assembly Resolution (WHA 67.25), that called on member states to have a national action plan that aligns with the tripartite Global Action Plan (GAP) in place by 2017 (see figure 25). The GAP resulted from an extensively consultative and collaborative process.

¹²² TATFAR Progress Report 201:4 Recommendations for future collaboration between the US and EU. European Commission and US Department of Health. 2014.

¹²³ Antimicrobial Resistance. European Commission. 2015.

FIGURE 25 | Overview of the recent global processes and outcomes on AMR



Source: TU Berlin



7.2 Country Profiles

The following chapter provides an overview of initiatives focused on the promotion of research and development in antibiotics in G7-countries.

The descriptions below are based on a desktop research and should not be considered as exhaustive and definitive. The given examples seek to illustrate the range of initiatives currently in place in G7-countries. Furthermore, national strategies and action plans are mentioned (if available).

Canada

Canada’s initiatives focus on the surveillance of antibiotic use and resistance. Investments are being made to educate the public, bring together researchers, and foster antibiotics development. A national action plan has been published on this effort. The majority of initiatives are led by the government.

National strategies and action plans

Antimicrobial Resistance and Use in Canada: A Federal Framework for Action¹²⁴
This framework points out a coordinated, collaborative federal approach to responding to the threat of antimicrobial resistance and forms a foundation for interdisciplinary action on a local, national and global scale.

Federal Action Plan on Antimicrobial Resistance and Use in Canada - March 2015¹²⁵
The Action Plan builds on the strategic areas of focus and priority action items outlined in the Framework for Action (mentioned above) by identifying specific steps that will be undertaken.

Examples for national initiatives enhancing research and development in antibiotics

Novel Alternatives to Antibiotics (NAA) Funding Opportunity^{126, 127}
The Novel Alternatives to Antibiotics is a governmental fund that focuses on supporting research into alternative methods of treating bacterial infections, for example, with the use of phages (discussed in chapter 3.1). A total exceeding of CAD 13 million in investments has been made in such research.

Canadian Foundation for Infectious Diseases¹²⁸
This is a charitable foundation that raises funds for innovative research and is active in educating both the public and health-care professionals on topics related to antibiotic resistance. It also aims to attract new talent and retain experts in the field of antibiotics. This work is done in part with other Canadian organizations involved in infectious disease and antibiotic development.

Canadian Society of Microbiologists¹²⁹
The Canadian Society of Microbiologists aims to foster advancement and collaboration in the field of microbiology, with antibiotic research being one of their areas of focus. It holds annual conferences and grants awards to distinguished researchers in the field.

¹²⁴Antimicrobial Resistance and Use in Canada: A Federal Framework for Action. Government of Canada. October 2014.
¹²⁵Federal Action Plan on Antimicrobial Resistance and Use in Canada: Building on the Federal Framework for Action. Public Health Agency of Canada. March 2015.
¹²⁶Government of Canada supports world-class research on antimicrobial resistance. Government of Canada. April 2015.
¹²⁷About CIHR’s Antimicrobial Resistance Initiatives. Canadian Institutes of Health Research. April 2015.
¹²⁸What we do. Canadian Foundation for Infectious Diseases. 2015.
¹²⁹About CSM. Canadian Society of Microbiologists. 2013.



France

France’s initiatives focus on good patient care, surveillance aspects and the promotion of research. A national antibiotic plan has been published on this effort. Research in antibiotics is centralized and conducted at large national research institutions with a focus on basic research.

National strategies and action plans

National Antibiotic Plan (Plan national d’alerte sur les antibiotiques) 2011–2016¹³⁰
The plan is a continuation of effective and recognized actions existing in the two previous action plans. The main goals are to stress the need for good patient care, to better understand the threats of antibiotics and to strengthen surveillance on consumption and resistance as well as the promotion of research.

Examples for national initiatives enhancing research and development in antibiotics

French National Institute of Health and Medical Research (Institut national de la santé et de la recherche médicale, Inserm) Transfert¹³¹
The National Institute of Health and Medical Research (Transfert) is a legally incorporated subsidiary of the French National Institute of Health and Medical Research¹³². Their efforts concentrate on adding value and minimizing risk for innovative projects at the pre-industrial stage, as well as bridging discovery and clinical development. The institution helps researchers to establish the proof of concept of their innovations and is involved in registering patents and searching for industrial partners.

The National Alliance for Life Sciences and Healthcare (Avenir) Program (Action Thématique et Incitative sur Programme (ATIP)¹³³
The ATIP-Avenir Program is a funding program designed for young researchers and is jointly operated by French National Center for Scientific Research¹³⁴ and the French National Institute of Health and Medical Research. It enables young scientists to build and lead a team within an established National Institute of Health and Medical Research or National Center for Scientific Research laboratory in France in order to conduct research in the fields of life and health sciences. This includes research in the prevention and treatment of infection by pathogens (e.g. antibiotics) in the field of immunity, infection and microbiology.

Partnership agreement between French National Alliance for Life Sciences and Health and Sanofi-Aventis¹³⁵
Sanofi-Aventis has joined a corporate sponsorship agreement for the Action Thématique et Incitative sur Programme (ATIP) - Avenir Program on the basis of an annual allowance to the program’s participants, plus a promise to considerably invest in public-private research partnerships.

¹³⁰Plan national d’alerte sur les antibiotiques 2011-2016. Ministère du Travail, de l’Emploi et de la Santé, novembre 2011.
¹³¹Missions. Inserm Transfert. 2015.
¹³²The National Institute of Health and Medical Research is a biomedical and public health research institution responsible for the strategic, scientific and operational coordination of biomedical research.
¹³³ATIP-Avenir program. French National Alliance for Life Sciences and Health. 2015.
¹³⁴The National Center for Scientific Research is a public organization under the responsibility of the French Ministry of Education and Research.
¹³⁵Announcement. French National Alliance for Life Sciences and Health. 2010.



Germany

Multiple German initiatives in antibiotics are intended to promote basic research. Funding is often provided to public research institutions, but funds are also available to promising projects in antibiotics research from other players. An antimicrobial resistance strategy was recently published. The majority of initiatives are led by the government.

National strategies and action plans

German Antimicrobial Resistance Strategy 2020 (Deutsche Antibiotika-Resistenzstrategie, DART 2020)¹³⁶

The strategy was developed by the Federal Ministry of Health (BMG), the Federal Ministry of Food, Agriculture and Consumer Protection (BMEL) and the Federal Ministry of Education and Research (BMBF) in cooperation with numerous associations and organizations. The goal of the strategy is to reduce and avoid the spread of antibiotic resistance and nosocomial infections. The aim is to strengthen the One Health approach, expand monitoring systems, intensify preventive measures, establish or strengthen regional, national and international cooperation and to support research and development.

Examples for national initiatives enhancing research and development in antibiotics

German Center for Infection Research (Deutsches Zentrum für Infektionsforschung, DZIF)

The German Center for Infection Research is an alliance of universities, university hospitals and federal research institutions with expertise in the area of infectious diseases. The Center is dedicated to meet the most important infectiological challenges with an integrative approach. The main objective is to accelerate the transmission of research results into practice. Two out of nine Thematic Translational Units (TTU) of the German Center for Infection Research devote their research to antibiotic resistance. The current research emphasis is on hospital germs and antibiotic resistant bacteria as well as novel anti-infectives.

Infect Control 2020¹³⁷

Infect control 2020 is part of the “Twenty20 – Partnership for Innovation” initiative of the Federal Ministry of Education and Research situated at the Hans-Knoell-Institute¹³⁸. It facilitates cooperation between scientists and the industry in collaboration with patient associations and the general public. The aim is to develop new strategies for early recognition, containment and combating of infectious diseases. Therefore, 30 partners from research institutions, clinics and the industry from various sectors work together, in order to develop new concepts for infectious control. A main emphasis of projects is the development of information and communication strategies for the systemic and long-term repression of multi-resistant pathogens. Another priority of the initiative is the development of new forms of interdisciplinary cooperation and promotion as well as qualification of young researchers.

¹³⁶DART 2020. *Fighting antibiotic resistance for the good of both humans and animals*. Die Bundesregierung, May 2015.

¹³⁷Vision. Leibniz Institute for Natural Product Research and Infection Biology- Hans-Knoell-Institute. 2013.

¹³⁸The Hans-Knoell-Institute (HKI) is a publically funded research institute, which carries out research into natural products and develops new diagnostics and intervention strategies.

Center for Natural Product Research (Zentrum für Naturstoffforschung)¹³⁹

The Center for Natural Product Research is a private public partnership model of Sanofi and the Fraunhofer Institute for Molecular Biology and Applied Ecology¹⁴⁰. The goal is to promote research in new therapies for infectious diseases and the search for new substances for antibiotics.

¹³⁹Press release. Fraunhofer Institute for Molecular Biology and Applied Ecology. 2014.

¹⁴⁰The Fraunhofer Institute for Molecular Biology and Applied Ecology (IME) is a publically funded research institute conducting research in the field of applied life sciences from the molecular level to entire ecosystems.

Italy

The focus of the Italian initiatives is primarily on a better understanding of the spread of antibiotic resistance through means of surveillance and monitoring programs. Other efforts in combating antibiotic resistance are directed at the responsible and appropriate use of antibiotics. The majority of initiatives are led by public institutions.

Examples for national initiatives enhancing research and development in antibiotics

Antibiotic Resistance Project¹⁴¹

The antibiotic resistance project is mandated by the National Institute of Health¹⁴² with the purpose of collecting data on antibiotic resistance through a network of sentinel laboratories. The surveillance data is submitted to the European Antimicrobial resistance interactive database.

National Guidelines System (Sistema Nazionale per le Linee Guida, SNLG)¹⁴³

The National Guidelines System is the result of an agreement between the Health Ministry’s General Directorate of Health Programming and the National Institute of Health. The purpose of the National Guidelines System program is to produce evidence-based recommendations for clinical practice on relevant clinical issues such as perioperative antibiotic prophylaxis in adults. This includes the promotion of evaluation processes in drug prescription and the creation of diagnostic and therapeutic paths. The main objectives of the National Guidelines System program regarding antibiotics are improving health care appropriateness and promoting a more responsible and appropriate use of antibiotics by means of improving healthcare professional’s education and training.

The Medicines Utilisation Monitoring Centre (Osservatorio sull’impiego dei medicinali, OsMed)¹⁴⁴

The centre is part of Italian Medicines Agency. It performs and coordinates activities concentrating on monitoring of antibiotic consumption and selling.

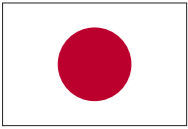
¹⁴¹Antibiotico-resistenza. Istituto Superiore di Sanità. 2012.

¹⁴²The National Institute of Health performs controls for public health. The Institute conducts scientific research in a wide variety of fields. As part of the Institute, the National Epidemiology, Surveillance and Health Promotion Centre develops and applies epidemiological and bio-statistical methods to monitor the spread of antibiotic resistance.

¹⁴³National Guidelines System (SNLG). National Guidelines System (SNLG) & Italian National Institute of Health (ISS). 2006.

¹⁴⁴The Medicines Utilisation Monitoring Centre (OsMed). Italian Medicines Agency. 2015.





Japan

Historically, Japanese pharmaceutical companies have been at the forefront of global antibiotics development. In recent years. Consequently, pharmaceutical companies shifted their focus to other areas of research. Still, a number of academic instutions are active in antibiotics research.

Examples of national initiatives enhancing R&D in antibiotics

National Institute of Infectious Diseases (NIID)¹⁴⁵

The National Institute of Infectious Diseases is a research institute that is connected to the Ministry of Health, Labour and Welfare. It is involved in basic and applied research into infectious diseases, quality control of antibiotics and other drugs, monitoring of spread of diseases, and publication of information regarding infectious diseases.

Global Health Innovative Technology (GHIT) Fund¹⁴⁶

This is a public-private partnership between the government of Japan, Japanese pharmaceutical companies, and the Bill & Melinda Gates Foundation¹⁴⁷. Its goal is to screen compound libraries of the participating pharmaceutical companies to find new compounds that can be developed into drugs against infectious diseases. The focus is on tuberculosis, malaria, and other neglected diseases. While Japanese stakeholders are engaged in this project, the target population is mainly outside of Japan.

Emerging / Re-emerging Infectious Diseases Project of Japan¹⁴⁸

As part of Japan Agency for Medical Research and Development¹⁴⁹, this project aims to promote research into infectious diseases both in Japan and overseas by providing research grants. In particular, it focuses on supporting the development of novel and effective drugs and diagnostics agents. It also works to improve infection control measures.

Drug discovery support network¹⁵⁰

Also part of Agency for Medical Research and Development, the goal of the network is to facilitate a smoother and more rapid transition of antibiotics candidates from basic research to preclinical research, clinical development, and commercialization. Supported projects include a research project on antibiotics at the University of Tokyo.

¹⁴⁵ *Outline-Organization*. National Institute of Infectious Diseases. 2015.

¹⁴⁶ *Japan screening massive drug compound libraries for new treatments*. CenterWatch. June 2013.

¹⁴⁷ *The Bill & Melinda Gates Foundation* is a nonprofit-organization, that works with partner organizations worldwide to tackle critical problems in four program areas (Global Development Division, Global Health Division, United States Division and Global Policy & Advocacy Division).

¹⁴⁸ *Emerging / Re-emerging Infectious Diseases Project of Japan*. Japan Agency for Medical Research and Development. 2015.

¹⁴⁹ *The Japan Agency for Medical Research and Development (AMED)* is involved in the research and development of medicines, and provides funding, e.g., for basic research and clinical trials. The goal is to achieve a streamlined process of drug development and promote an environment conducive to medical research and development. It has, for example, provided a research grant for analytical methods to assess the quality of antibiotics.

¹⁵⁰ *Siryou4*. Drug Discovery Support Network. October 2014.



United Kingdom

The United Kingdom has launched a number of initiatives addressing the development of new antibiotics. Initiatives at all stages of the development cycle have been implemented and efforts for better coordination and information sharing on funding activities have been made. The United Kingdom has also published their Five Year Antimicrobial Resistance Strategy. Additionally, several projects are privately initiated.

National strategies and action plans

UK Five Year Antimicrobial Resistance (AMR) Strategy 2013 to 2018¹⁵¹

The goal of the Strategy is to slow the development and spread of AMR. This is to be achieved by improving the knowledge and understanding of AMR, conserving the effectiveness of existing treatments and stimulating the development of new antibiotics, diagnostics and novel therapies.

Examples for national initiatives enhancing research and development in antibiotics

Antimicrobial Resistance Funders Forum (AMRFF)¹⁵²

The Antimicrobial Resistance Funders' Forum has been established to provide a forum for the sharing of information on activities relating to antibiotic resistance by key private and public member organizations, such as the Wellcome Trust¹⁵³ and the Medical Research Council¹⁵⁴. The Forum provides a framework for a more coordinated approach to tackling antibiotic resistance. The Funders Forum coordinates and supports the initiation of funding and delivery programs and adds value to existing programs through synergy of activities and gap awareness.

Innovate UK/ Medical research council Biomedical Catalyst scheme¹⁵⁵

The Biomedical Catalyst scheme is a funding program jointly operated by Innovate UK¹⁵⁶ and the Medical research council, supporting pre-clinical life science. Under this scheme, funding is awarded to projects exploring new approaches to antibiotic resistance. Grants are available to UK academics and small and medium enterprises (SMEs) seeking to move their research more quickly from discovery to commercialization. They are jointly financed by public and private funds. Three categories of grants are available at different stages of product development: Feasibility Award/ Confidence in Concept, Early Stage Award and Late Stage Award.

National Endowment for Science Technology and the Arts (NESTA) Longitude Prize Antibiotics 2014- 2019¹⁵⁷

Longitude Prize 2014 is an offered award by the National Endowment for Science Technology and the Arts¹⁵⁸. It is supported by public and private funds awarded for antibiotics. The prize is given to the candidate who contributes to the prevention of the rise of antibiotic resistance. It rewards a £10m fund to a competitor who can develop a point-of-care diagnostic test that is cost-effective, accurate and easy-to-use to test for bacterial infections. The Longitude Prize is given to the competitor who has fully met all requirements.

¹⁵¹ *UK Five Year Antimicrobial Resistance (AMR) Strategy 2013 to 2018*. Department of Health, Department for Environment Food & Rural Affairs, September 2013.

¹⁵² *Antimicrobial Resistance Funders' Forum*. Medical Research Council. 2015.

¹⁵³ *The Wellcome Trust* is a biomedical research charitable foundation and an ardent supporter of research addressing antibiotic resistance.

¹⁵⁴ *The Medical research council* is a publicly funded government agency responsible for coordinating and funding medical research within the UK.

¹⁵⁵ *Biomedical Catalyst*. Medical Research Council. 2015.

¹⁵⁶ *Innovate UK* is a non-departmental public body which funds, supports and connects innovative British businesses.

¹⁵⁷ *Longitude Prize – The Challenges*. NESTA. 2015.

¹⁵⁸ *National Endowment for Science Technology and the Arts* is dedicated to supporting ideas that can help improve lives, with activities ranging from early stage investment to in-depth research and practical programs.



United States of America

Multiple initiatives in the United States promote the understanding of antibiotic resistance and surveillance of the phenomenon. Furthermore, efforts have been made to promote the attractiveness of the market and improve approval regulations for antibiotics. Both a Biomedical Advanced Research and Development Authority Strategic Plan and a National Action Plan for Combating Antibiotic-Resistant Bacteria have been published. A majority of initiatives are led by the government.

National strategies and action plans

Biomedical Advanced Research and Development Authority (BARDA) Strategic Plan 2011–2016¹⁵⁹

The goal is to develop and provide medical countermeasures for Chemical, Biological, Radiological, and Nuclear threats, pandemic influenza, and emerging infectious diseases. The implementation measures to achieve these strategic goals include support of product advanced development, stockpile acquisition, manufacturing surge capacity infrastructure building, and product innovation.

National Action Plan for Combating Antibiotic-Resistant Bacteria¹⁶⁰

The Action Plan provides a roadmap for the next five years to guide the Nation in rising to this challenge. The plan outlines steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria.

Examples of national initiatives enhancing R&D in antibiotics

Division of Microbiology and Infectious Diseases (DMID)¹⁶¹

The Division of Microbiology and Infectious Diseases is part of the National Institute of Allergy and Infectious Diseases and funds research into most human infectious agents apart from HIV. Funding is provided in the areas of basic research, preclinical development, and the clinical evaluation of safety and efficacy of antibiotics. It also provides resources for researchers and investigators to aid the development pathway.

Antibacterial Resistance Leadership Group (ARLG)^{162, 163}

The Antibacterial Resistance Leadership Group was launched by the National Institute of Allergy and Infectious Diseases¹⁶⁴ in 2013 and has developed a clinical research agenda that identifies the most important issues of antibiotic resistance. It aims to advance research on antibiotics by evaluating and improving clinical trial design and implementation. Moreover, it is involved in infection control programs and diagnostics testing.

¹⁵⁹ BARDA Strategic Plan 2011–2016. Biomedical Advanced Research and Development Authority. October 2011.

¹⁶⁰ National Action Plan for Combating Antibiotic-Resistant Bacteria. The White House. March 2015.

¹⁶¹ Research Areas Division of Microbiology and Infectious Diseases. National Institute of Allergy and Infectious Diseases. April 2015.

¹⁶² About the ARLG. Antibacterial Resistance Leadership Group. 2015.

¹⁶³ Leadership Group for a Clinical Research Network on Antibacterial Resistance. National Institute of Allergy and Infectious Diseases. March 2015.

¹⁶⁴ The National Institute of Allergy and Infectious Diseases is part of the National Institutes of Health, which provide funding for medical research.

Generating Antibiotic Incentives Now Act (GAIN Act)^{165, 166}

The Generating Antibiotic Incentives Now Act was initiated in 2012 to make the antibiotic market more attractive to developers. It allows fast-track designation and priority review of antibiotics and grants five additional years of market exclusivity to qualifying antibiotics. In order to define which antibiotics qualify as “Qualified Infectious Disease Products” under the GAIN Act and receive these benefits, a list of pathogens of public health concern was composed. Guidance documents on how to conduct pathogen-specific clinical trials have been published. Finally, the act directs the Government Accountability Office to conduct a study regarding the incentives required to foster the research, development, and marketing of Qualified Infectious Disease Products (QIDP).

¹⁶⁵ GAIN: How a New Law is Stimulating the Development of Antibiotics. The Pew Charitable Trusts. November 2013.

¹⁶⁶ Repairing the Antibiotic Pipeline: Can the GAIN Act Do It?. Forsyth. 2013.

