BCG

The Boston Consulting Group

Federal Ministry of Health

FOLLOW-UP REPORT FOR THE GERMAN GUARD INITIATIVE

Breaking through the Wall

A Call for Concerted Action on Antibiotics Research and Development

Full Report

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This report was written by The Boston Consulting Group (BCG) for the German Federal Ministry of Health as a follow-up to *Breaking through the Wall—Enhancing Research and Development of Antibiotics in Science and Industry* of October 2015. The 2015 report laid out ten potential levers for more innovation along the antibiotics value chain. The 2017 follow-up provides detail on four key levers as actionable international policy instruments. *Target Product Profiles* are proposed to steer global funding toward the most pressing clinical need. Through a *Global Research Fund*, the international community can foster basic research and preclinical development. With a *Global Development Fund* and a *Global Launch Reward*, targeted incentive mechanisms strengthen clinical development and commercialization of antibiotics respectively. In order to effectuate the launch of new high-need antibiotics, a *Global Union for Antibiotics Research and Development* (**GUARD**) is proposed as a concerted policy initiative.

Title picture (© Fotolia): Enterobacteriaceae, a large family of rod-shaped, Gram-negative bacteria that includes some of the most troubling drug-resistant pathogens (e.g., drug-resistant strains of Salmonella, Escherichia coli, Klebsiella or Shigella)

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List of abbreviations

AMR	Antimicrobial resistance
BARDA	United States Biomedical Advanced Research and Development Authority
BCG	The Boston Consulting Group
BMBF	German Federal Ministry of Education and Research/ Bundesministerium für Bildung und Forschung
BMG	German Federal Ministry of Health/ Bundesministerium für Gesundheit
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CDC	United States Centers for Disease Control and Prevention
CDDEP	The Center for Disease Dynamics, Economics & Policy
COGS	Cost of goods sold
DNDi	Drugs for Neglected Diseases initiative
DRIVE-AB	Driving reinvestment in R&D and responsible antibiotic use
EDCTP	European & Developing Countries Clinical Trials Partnership
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
GAMRIF	Global Antimicrobial Resistance Research Innovation Fund
GARD-P	Global Antibiotic Research and Development Partnership
GDF	Global Development Fund
GLASS	Global Antimicrobial Resistance Surveillance System
GLR	Global Launch Reward
GRF	Global Research Fund
GUARD	Global Union for Antibiotics Research and Development
IMI	Innovative Medicines Initiative
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMICs	Low- and middle-income countries
MMV	Medicines for Malaria Venture
MRSA	Methicillin-resistant Staphylococcus aureus
MSF	Médecins Sans Frontières
ND4BB	New Drugs for Bad Bugs Program
NMEs	New molecular entities
NPV	Net present value
R&D	Research and development
SG&A	Selling, general, and administrative expenses
TA	Therapeutic area
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TTPs	Target Product Profiles
WHA	World Health Assembly
WHO	World Health Organization

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1. EXECUTIVE SUMMARY

The Global Union for Antibiotics Research and Development (**GUARD**) is an initiative that seeks to turn the tide in antibiotics research and development. By addressing the whole value chain with clear targets and coordinated funding, **GUARD** proposes to reinvigorate antibiotics research and development in science and industry, from basic research to commercialization. The initiative builds on significant momentum in recent policy discussions around antimicrobial resistance. **GUARD** represents a novel approach to high-need antibiotics: While balancing various needs as fairly and equitably as possible, it offers a practical guide to what the international community can do, starting in 2017.

Antimicrobial resistance: A severe global public health challenge. Antimicrobial resistance has been a biochemical tug of war between microorganisms for millennia and a public health problem since the discovery of antibiotics in the early 20th century. The development of resistance to antibacterial substances is a natural process. Endowed with an ability to multiply and mutate extremely quickly, bacteria keep developing new mechanisms to protect themselves from antibacterial modes of action in nature and in drugs. Overuse and misuse of antibiotics accelerate the process. Antibiotics must be used sparingly, while constant innovation is needed to keep up with the inexorable development of resistance. What is more, access to life-saving antibiotics (existing and new) in low- and middle-income countries must be improved significantly.

Global consensus: The antibiotics value chain is fundamentally broken. No truly novel antibiotics have been developed in three decades. While the scientific bar is high, commercial prospects of novel antibiotics are limited. The latter is a major reason for the decade-long discovery void. Antibiotics are less commercially attractive than other types of drugs, which has led many large pharmaceutical companies to exit this area. Only five of the twenty largest pharmaceutical players have antibiotic candidates in their pipelines (while most invest heavily in oncology or Alzheimer's disease). This effect ripples down the value chain: big pharma retracts, small and medium-sized companies find fewer investors, basic research is reduced—the pipeline dries up. Fortunately, the need for global action to reinvigorate the value chain is undisputed and global awareness greater than ever.

Long-term goal: Transforming the antibiotics value chain. This report proposes four levers to reinvigorate the antibiotics value chain. The core intention of all levers is to ensure clinical needs are met with novel antibiotics. To this end, the full value chain—from basic research and early drug discovery all the way to commercialization—must be addressed. This is a complex and long-term challenge. Unwanted market disruptions

must be avoided. With a wide range of experts, we examined potential ways to achieve these goals and identified the following four levers as the most urgent and promising:

1) Target Product Profiles help steer funding activities toward clinical need

We propose three types of Target Product Profiles and a scoping for basic research funding.

- *Resistance-breaking Target Product Profiles* describe drugs that tackle resistance patterns across pathogens, e.g., an alternative to β-lactam antibiotics
- *Disease-defeating Target Product Profiles* describe drugs for the treatment of diseases that are caused by resistant pathogens, e.g., hospital-acquired pneumonia
- *Pathogen-matching Target Product Profiles* directly address pathogens that pose a specific challenge, such as pseudomonas or mycobacteria
- *Scope of basic research funding* defines key scientific challenges that should receive more funding (new chemical matter, resistance mechanisms, methodological innovation, alternative approaches, broader microbiology; see section 4.2.3.)

2) Global Research Fund to build infrastructure and fund promising projects

Today, only ~500 scientists are active in antibiotics research globally. An estimated $200 million per year are needed to grow the community of antibiotic researchers by 50% over the next ten years, and to fund a significant number of projects addressing key scientific challenges and drug discovery. Funding decisions are tied to clear criteria: a scoping of important areas for basic research funding, and Target Product Profiles for preclinical projects. The Global Research Fund would triple dedicated global funding for antibiotics-related basic research, and increase preclinical funding by almost 50%. This would benefit primarily academic institutions in their endeavor to expand infrastructure.

3) Global Development Fund to finance all stages of clinical development

Drugs likely to match at least one Target Product Profile are supported through all phases of clinical development by a fund with a $200 million annual budget. Employing forgivable loans as a financing instrument, the fund is sized to be able to push one additional high-need antibiotic to market every year after a ramp-up phase.[1] $200 million per year would add to an estimated $300 million of public funds already available for clinical development.

4) Global Launch Reward to provide an insurance mechanism for companies

A payment of $1 billion per commercialized product that matches at least one Target Product Profile acts as a pull mechanism. High-need antibiotics would become a much less risky commercial proposition than they are today. If the new antibiotic does generate significant operating profit, the reward is returned. Various entry reward models have been discussed before, but a Global Launch Reward as an insurance mechanism may be the most practical model.

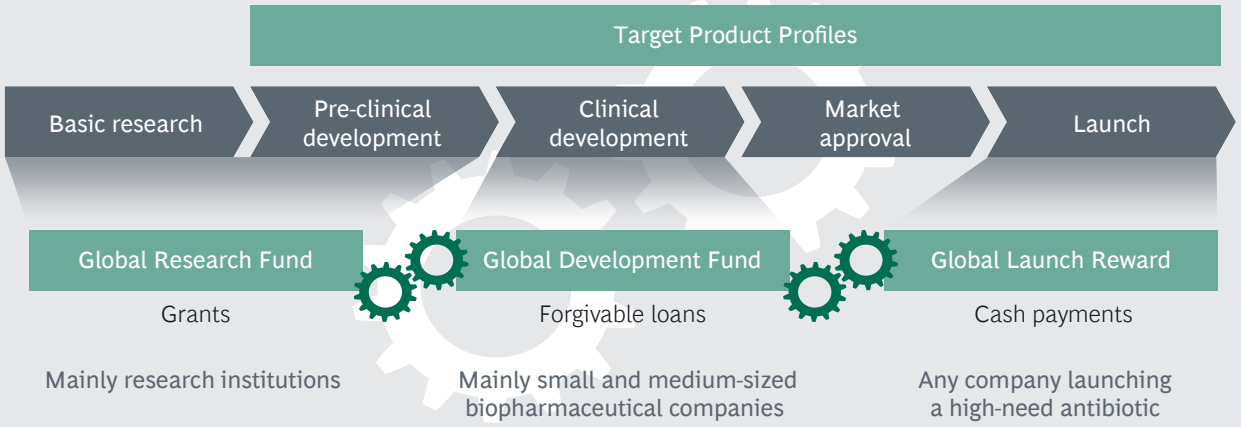
Making it work in practice. In order to foster innovation, we propose the Global Union for Antibiotics Research and Development (**GUARD**) as a global facility managing Target Product Profiles and a range of funding mechanisms. It can be implemented as a whole or in parts—projects could, but do not necessarily have to be carried through the entire value chain by **GUARD**. It is critical that existing initiatives and structures be leveraged

[1] A forgivable loan is a form of loan in which the entire debt or a portion of it is forgiven by the lender when certain predefined conditions are met.

and duplicate structures avoided. Moreover, **GUARD** will not come to fruition overnight; a ramp-up phase of at least five years will be necessary. A group of "country champions" should secure long-term commitment.

The levers described here are designed to produce one new high-need antibiotic per year in a steady state—an ambitious but realistic goal if the international community acts in a concerted effort.

Figure 1 | The GUARD model: A seamless antibiotics value chain



2. OBJECTIVES OF THIS REPORT

BREAKING THROUGH THE WALL—A Call for Action on Antibiotics Research and Development is a report written by The Boston Consulting Group (BCG) for the German Federal Ministry of Health.

In this report, we describe four levers to reinvigorate the antibiotics value chain and propose the establishment of a Global Union for Antibiotics Research and Development (**GUARD**). This report is a follow-up to an initial expert opinion for the German Federal Ministry of Health of October 2015 (*Breaking through the Wall—Enhancing Research and Development of Antibiotics in Science and Industry*).

The 2015 report took a "diagnostic" view: It identified key challenges along the antibiotics value chain and proposed ten levers to stimulate research and development. The 2017 follow-up now focuses on implementation. Here, the four most impactful levers proposed in 2015 are described in more detail. For each lever, we seek to develop a conceptual foundation, estimate the required resources and outline options for implementation.

This report is not a comprehensive review of all relevant aspects of antimicrobial resistance (AMR). It is a deep dive into one critical part of the AMR challenge: antibiotics research and development pipelines. We would like to emphasize that the problem of antimicrobial resistance cannot be solved with new antibiotics alone. The development of new antibiotics without prevention and stewardship, mechanisms in place has been likened to "supplying your alcoholic patients with a finer brandy."[1] Awareness, surveillance, hygiene and prevention, capabilities for stewardship and One Health are also critical components of the World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance. Moreover, it has been argued that a lack of access to existing antibiotics causes more deaths today than AMR does. For existing and new drugs, access is a critical issue.

All findings and recommendations described in this report are based on multiple sources of information. These include:

- Relevant scientific research and publications
- Original analysis of public and proprietary data
- Interviews with various stakeholders from research, academia, industry (small and large biopharmaceutical companies), nonprofit institutions, think tanks, international organizations, and the public sector

This report would not have been possible without extensive expert interviews. We would like to express our deep gratitude to all experts who offered their time, insight, and guidance for this report.

[1] Cited in Outterson, 2014

3. THE CALL FOR ACTION: GLOBAL NEED FOR NOVEL ANTIBIOTICS

ESTIMATES OF THE DEATH toll of antimicrobial resistance vary, but there is solid consensus around the antibiotics value chain being fundamentally broken. In recent decades, few high-need antibiotics have come to market, with virtually no innovation against Gram-negative bacteria. 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 conventional drug discovery strategies. 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, but this was not the case. Moreover, there was a strong emphasis on target identification, while probably too little attention was given to basic research.

Fortunately, global awareness of the need to stimulate research and development (R&D) in antibiotics is at an unprecedented level today. National and international action plans and funding mechanisms are steadily emerging. The number of media headlines about antimicrobial resistance has been increasing by 15% every quarter since 2014. Experts are beginning to see signs of a renaissance of antibiotics research and development.

However, a breakthrough against the most threatening Gram-negative pathogens is still years away, and a great deal more must be done. Higher rates of innovation with a precise focus on global clinical needs require a fundamental transformation of the value chain and cannot be achieved overnight. While 2016 was a strong year in terms of consensus building, 2017 must be the year of practical steps. In our view, the international community must take action in four ways as soon as possible.

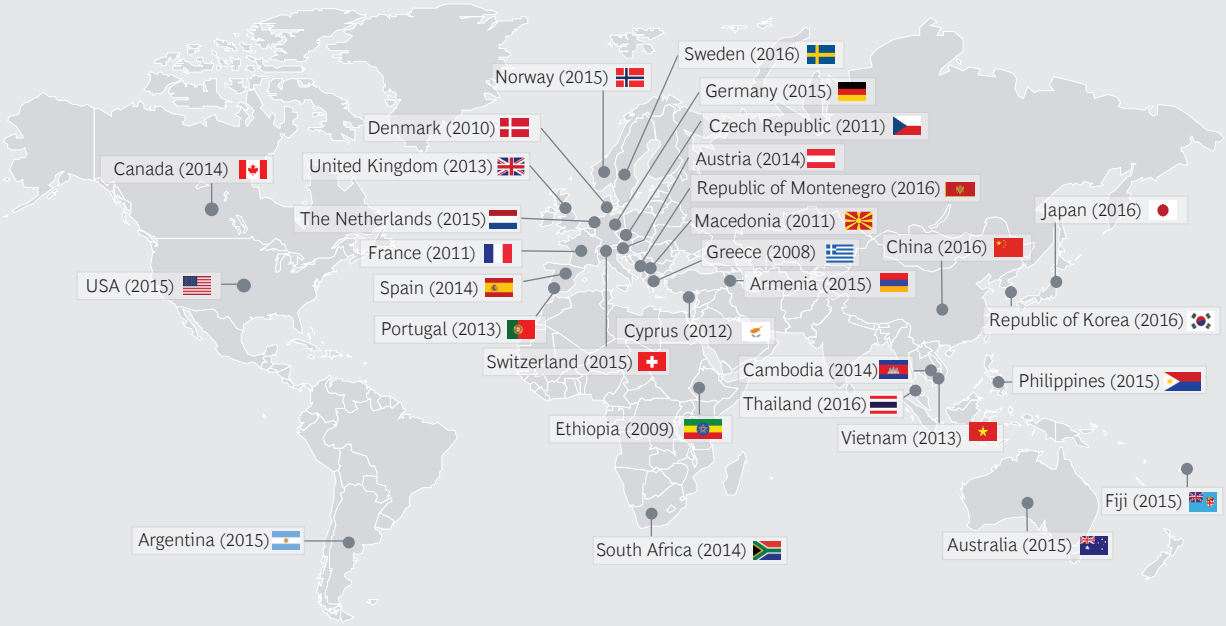
- Create a system of Target Product Profiles to steer research and development efforts to where they are most urgently needed
- Grow the antibiotics researcher community and fund more projects in basic research, early drug discovery, and preclinical development
- Help small and medium-sized biopharmaceutical companies get through clinical development with forgivable loans
- Create a pull incentive to make antibiotics a more attractive commercial proposition

3.1. The need to keep moving: A glance at current activities

There is movement in the field of antimicrobial resistance. We are seeing a growing number of coordination and funding mechanisms, on both national and international levels, but the need is not yet fully met.

The number of national action plans against antimicrobial resistance is increasing year by year (see figure 2):

FIGURE 2 | National action plans on antimicrobial resistance (AMR) across the globe



Source: *Antimicrobial Resistance. Library of National Action Plans.* World Health Organization (WHO), 2017

Additionally, many other countries are developing and reviewing national action plans on AMR, including Brazil, India, and Russia. When the World Health Assembly adopted a Global Action Plan on Antimicrobial Resistance in 2015, only 15% of World Health Organization's member states had a national action plan that aligned with it. By the end of 2017, more than 50% of countries, including most countries with large populations, will have such a plan.

With regard to funding, we also see encouraging developments. We analyzed 13 global and large national funds and estimate that in 2016, half a billion dollars of public funding was allocated to antibiotics research and development. This figure is set to increase in the future with a number of new initiatives on the horizon.

FIGURE 3 | More than $500 million of dedicated antibiotics research and development push funding was available in 2016

[1]Estimate based on 2015 figures
Note: Antibiotics research and development funding estimates based on the analysis of project descriptions and expert interviews. They are not official numbers published by the organizations shown.
Source: BCG analysis; expert interviews

However, there is still a wide gap in antibiotics research and development funding. Although we are seeing signs of improvement, many initiatives at universities and smaller biopharmaceutical companies are still unable to obtain financing, and promising clinical candidates are terminated because of funding issues.

Moreover, the international community could do more to help stakeholders pull together. Each existing fund mentioned above, naturally, has a distinct focus. Most of these facilities were set up to serve a wider set of goals, their key success factors include more than the number of novel antibiotics developed. The direct comparison of three key sources of funding illustrates this point.

- The **Biomedical Advanced Research and Development Authority** (**BARDA**) was established in 2006 to protect the U.S. from key health security threats.[1]
- **InnovFin—European Union Finance for Innovators** is a financing facility of the European Investment Bank and runs a dedicated infectious diseases instrument, decidedly wider in scope than novel antibiotics.
- A **large number of European and national funds** are the principal source for funding for basic research at academic institutions. Here, significant amounts are available, but funding is fragmented and mostly not specific to antibiotics research and development.

Global efforts such as the Global Antibiotic Research and Development Partnership[2] (GARD-P), a joint initiative by the WHO and DNDi, or the Joint Programming Initiative on Antimicrobial Resistance[3] (JPIAMR), a coalition of more than 20 countries, are driving global coordination but are not yet equipped with the necessary scale and scope to address the entire value chain.

GUARD proposes a highly focused funding and coordination facility for antibiotics research and development. The facility should complement existing initiatives and be able to support good ideas at all stages of the value chain—from a hypothesis-driven discovery at a university lab to the commercialization of a new drug.

[1] BARDA Strategic Plan 2011–2016

[2] The *Global Antibiotic Research and Development Partnership* (GARD-P) was initiated by the *World Health Organization* (WHO) and is hosted by the *Drugs for Neglected Diseases initiative* (DNDi). It was incubated in 2016 and seeks to develop into a global facility that supports the development of new antibiotic treatments and promotes their responsible use, while ensuring equitable access for all in need. By the end of 2017, GARD-P seeks to have established an organizational structure and set out its long-term strategy and roadmap.

[3] The *Joint Programming Initiative on Antimicrobial Resistance* (JPIAMR) is an international initiative to coordinate national funding on antimicrobial resistance. It currently has 22 member states. Its mission is to coordinate national research activities, and to facilitate research collaboration on AMR. The 3rd JPIAMR call launched in 2016 has awarded €28 million to 19 research projects on AMR transmission mechanisms.

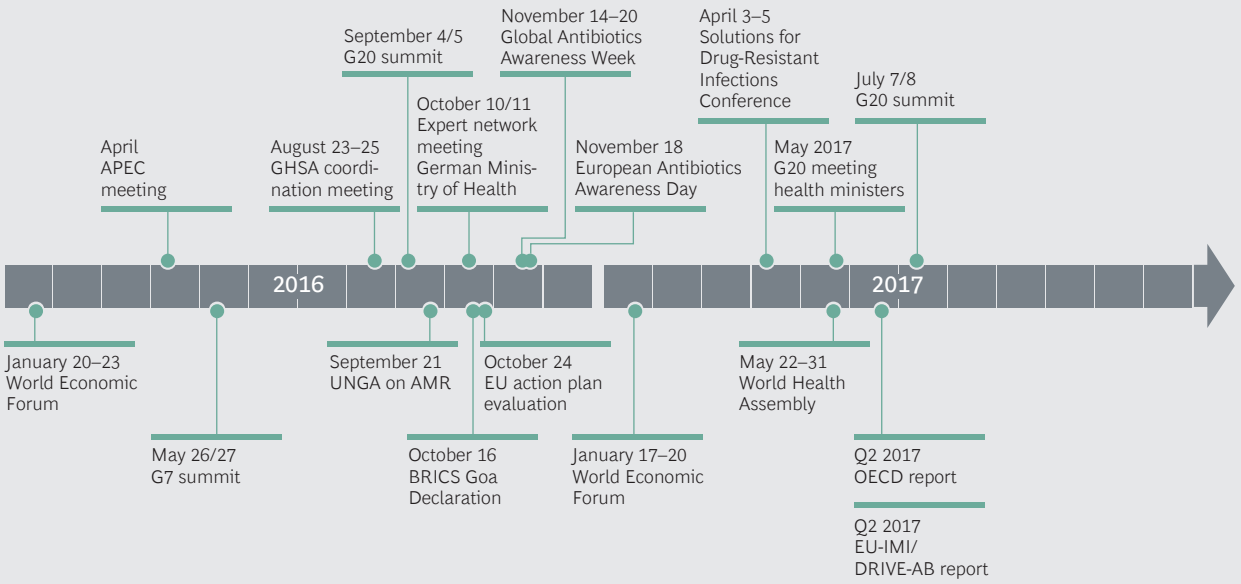
3.2. The year 2017 as a window of opportunity

A number of stakeholders recognize the need for an initiative like **GUARD**.
In fact, several key organizations are already working toward more global funding and coordination:

- The Global Antibiotic Research and Development Partnership (GARD-P), a joint initiative of the WHO and DNDi, is currently in its incubation phase and proposes to grow significantly over the next few years.
- DRIVE-AB is conducting comprehensive research and financial simulations around key economic levers and will propose concrete measures in 2017.
- The United Kingdom is in the process of consolidating and expanding its various AMR-related initiatives.
- The BRICS countries (Brazil, Russia, India, China, and South Africa) have jointly declared the need for concerted action against antimicrobial resistance in 2016 at the 8th BRICS Summit.

The key challenge will be to steer this momentum. The "AMR calendar" shows opportunities for policy discourse in 2017: (see figure 4)

FIGURE 4 | Policy discourse on antimicrobial resistance (AMR) is gaining momentum



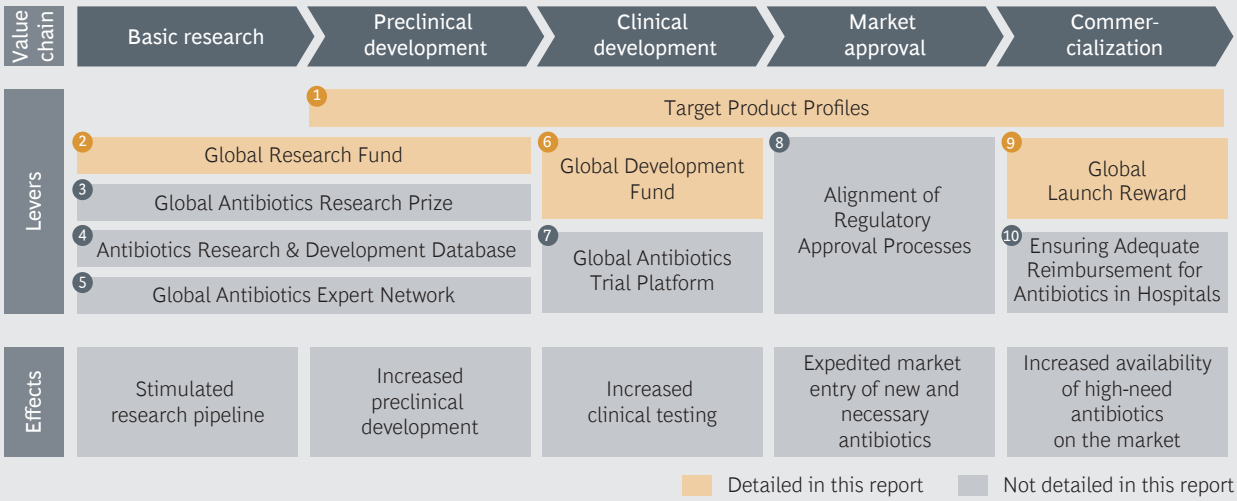
Source: BCG

In sum, we can be cautiously optimistic about the increased momentum around novel high-need antibiotics. The number of national AMR initiatives is growing, significant amounts of funding are being made available and the topic has a firm place on the international agenda. However, current efforts are not enough. We need more funding and more coordination to make this international effort a success. With the strong momentum around AMR today, 2017 could mark a turning point in policy discussions.

3.3. GUARD: Repairing the antibiotics value chain

Our 2015 report identified ten potential levers along the antibiotics value chain.

FIGURE 5 | Report is focused on high-impact levers in antibiotics research and development



Source: BCG; TU Berlin; Partnerschaften Deutschland

In this report, we decided to focus on the four levers we expect to be most impactful if implemented on a global level. In our first report and in extensive expert interviews in 2016 and 2017, we evaluated the advantages and disadvantages of various conceptual approaches to all available levers. In this report, we focus on what we expect to be most impactful, and on those levers that can only be tackled globally. Plenty more can (and probably will) be done by national authorities. The alignment of regulatory approval processes, adequate reimbursement policies (in hospitals and in outpatient settings), clinical trial networks, etc., are still critical pieces of the puzzle. However, the indispensable first step is to fund the most critical parts of the value chain and to set up a Target Product Profile system that helps steer that funding toward clinical need. This is where we hope to make a practical contribution.

Underlying reason for a broken value chain: Antibiotics are commercially unattractive

The development of novel antibiotics is not only a great scientific challenge, but also a relatively risky and therefore unattractive commercial proposition. This can be seen as the heart of the matter: The vast majority of large pharmaceutical companies have given up antibiotics research and development, thereby removing a positive monetary pull effect that used to flow through the entire value chain.

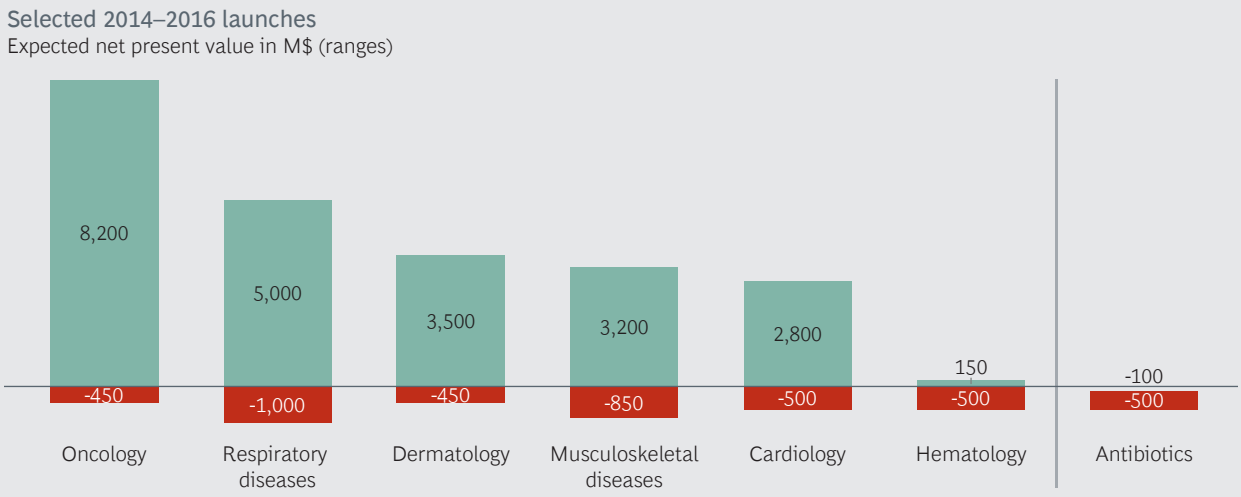
Low expected net present value compared to other types of drugs

A comparison of recent pharmaceutical launches in a range of therapeutic areas shows the wide spread in expected financial profitability (figure 6). In most therapeutic areas, the risk of losing multiple hundreds of millions on a new molecular entity is more than offset by a multi-billion dollar profit potential, which translates into research and development investment. It is not uncommon for a single large biopharmaceutical company to

invest a billion dollars or more per annum in immuno-oncology research and development alone.

Antibiotics are significantly less attractive. For all launches over the last three years, not one antibiotic would have achieved a positive expected net present value (eNPV) at the start of preclinical development—assuming average development costs and durations (see footnotes in figure 6 for details).

FIGURE 6 | Antibiotics with similar financial risk but without the financial upside of other types of drugs (ranges of retroactive expected net present values for actual launches)



Note: Assumptions: Varying development costs per TA ($600M–1,400M). Development costs include costs of failure. Duration of development between 6–8 years (varies across therapeutic areas).
10-year revenue projections for all NMEs, COGS, and SGA based on EvaluatePharma data. Discount rate of 9%.
Source: BCG analysis; EvaluatePharma

We use expected net present value to compare the commercial attractiveness levels of various pharmaceutical research and development propositions. Net present value (NPV) is used in industry to express the worth of the sum of future gains in the present. Expected net present value (eNPV) has an earlier vantage point and includes the negative value of development costs, which offsets future revenues. Expected net present value (eNPV), thus, helps one understand if the revenue potential of a product justifies the upfront investment in its development. Retroactively, we calculated what existing sample drugs (for which we have actual revenue data) would have been worth to their developers at the point in time their development was begun, assuming average development costs per therapeutic area.

Structural reasons for the particular nature of antibiotics as products

There are three structural reasons why investments in antibiotics have low expected net present values and a high risk assessment.

- Prudent use of antibiotics is essential to keep them effective for as long as possible. While critically important from a public health perspective, successful antibiotic stewardship could depress antibiotics revenue potential even more.

- Resistance may develop rapidly after a market launch and diminish the effectiveness of a new antibiotic, depressing revenues in a way that is impossible for a company to control.

- Short courses of treatment, often at low prices, are typical for the treatment of bacterial infections (with exceptions such as tuberculosis), and for the vast majority of indications in developed countries, cheap generics are available, putting strong competitive pressure on novel antibiotics.

Because these reasons are structural, the value chain cannot be expected to mend by itself. It needs market intervention.

3.4. Ambition level: One new high-need antibiotic per year

The number of high-need antibiotics that will be commercialized in the future cannot be predicted with reasonable certainty. Experts are cautiously optimistic, but agree that the commercialization of a new class of antibiotics will take several years from today.

A realistic and ambitious global target is needed to evaluate the effectiveness of global efforts. With current pipelines and average durations and success rates in antibiotics development, we are likely to see several new antibiotics in the next few years, but there are few promising candidates that tackle the most urgent clinical need.

However, additional developments that do not match **GUARD**'s stringent innovation parameters can still be a desirable addition to clinical practice. Fidaxomicin (Dificlir®), for example, is not seen as a game changer, but still makes a valuable difference in the treatment of clostridium difficile infections.[1]

Our mission should be to provide enough funding and nonfinancial support to achieve one additional high-need antibiotic per year, the majority against Gram-negative bacteria, after at least five years of **GUARD** activity.

To achieve this, we see the antibiotics value chain as an interconnected system. While all **GUARD** levers are designed to be modular, the greatest effect is achieved if all pain points along the value chain are tackled simultaneously.

[1] Gräfe, 2013 (online article)

4. TARGET PRODUCT PROFILES: STEERING RESEARCH AND DEVELOPMENT FUNDING

The Target Product Profiles at a glance

A global system of Target Product Profiles and a scope of funding for basic research help direct funding toward the greatest clinical need.

Lever design and instruments

- Prioritization logic for most-needed products (resistance-breaking, disease-defeating and pathogen-matching drugs)
- Standardized description of desired drug properties
- Scope of funding for the most pressing antibiotics-related scientific challenges

Making it work

- Interdisciplinary Scientific Committee to develop global Target Product Profiles
- Predictable and practical update cycle (3-5 years)
- Potentially to be merged with existing Target Product Profile efforts

Target Product Profiles (TPPs) and a clear definition of most-needed basic research efforts are central pillars of the Global Union for Antibiotics Research and Development (**GUARD**) proposal. It is critical to provide clear guidance on what exactly should be supported along the antibiotics value chain.

The guiding principle is that Target Product Profiles must describe high-need products that have a significant positive impact on clinical practice. We propose an adaptable, "living" Target Product Profile system that goes beyond pathogens to address clinical need and to enable funding mechanisms that steer funds to where they are most needed.

4.1. The challenge: Building on priority pathogen lists

Today, Gram-negative bacteria are a particular cause for concern. Awareness of today's most threatening pathogens is necessary, but not sufficient to determine what new drugs are needed. Pathogens, resistance mechanisms, and disease patterns are many, possible combinations are almost infinite. Therefore, we need a clear logic for prioritization.

Priority pathogens as a key input for a Target Product Profile system

The most notorious drug-resistant pathogens are already known, and significant effort is invested in identifying and prioritizing them. Various pathogen lists have been created, each with a particular goal. In 2013, the U.S. Center for Disease Control and Prevention published "Antibiotic Resistance Threats in the United States", a report that provided a first-ever estimate of deaths and infections caused by the top eighteen drug-resistant pathogens in the United States.

Closing an important gap, the World Health Organization (WHO) has recently published a Global Priority Pathogens List for R&D of new antibiotics, narrowing down multi-resistant bacteria to those that most urgently need R&D attention. The list includes carbapenem-resistant microorganisms, extended-spectrum-β-lactamases-producing microorganisms (ESBL) and other forms of resistances.

FIGURE 7 | WHO Global Priority Pathogens List

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

An authoritative list of priority pathogens will be an essential basis for the development of Target Product Profiles.

4.2. Lever design and instruments: Three types of Target Product Profiles

Ultimately, challenges in clinical practice drive drug needs—widespread pathogens, typical resistance patterns, and disease profiles. Few high-need antibiotics will affect one pathogen alone. Therefore, we propose that three different types of Target Product Profiles be developed on the basis of the WHO R&D Priority Pathogens.

4.2.1. From priority pathogens to priority drugs

In hospitals and in outpatient settings, treatment of multiresistant bacteria demands both empiric therapy (mostly with broad-spectrum antibiotics) and targeted therapy (mostly with narrow-spectrum antibiotics). The possible combinations of pathogens, resistance mechanisms, and diseases are many. It is therefore necessary to prioritize clusters of need within the various possible combinations of pathogens, resistance mechanisms, and diseases.

Three types of drugs are needed (some will be effective in more than one category):

- A few (broad-spectrum or narrow-spectrum) *resistance-breaking* drugs, meaning antibiotics that will serve as a new line of defense against multiresistant bacteria across various diseases
- A number of *disease-defeating* drugs (broad-spectrum or narrow-spectrum), meaning antibiotics that can be used as new empirical treatments for particular indications for use (disease profiles)
- A few selected narrow-spectrum *pathogen-matching* drugs against pathogens that pose a specific challenge, such as pseudomonas or mycobacteria

Resistance-breaking Target Product Profiles

Two types of resistance are particularly widespread, troublesome and growing: carbapenemase- and extended-spectrum-beta-lactamase (ESBL)-producing bacteria, frequently enterobacteriaceae, have the ability to deactivate some of the most widely used and potent antibiotics (e.g., penicillins), notably carbapenems. Beta-lactamases are enzymes that damage a chemical structure that many widely used antibiotics have in common. Therefore, one of the most urgent clinical needs is finding ways to break resistance mechanisms such as antibiotic-degrading enzymes of which there are dozens of variants. Other relevant resistance mechanisms are explained in the appendix (chapter 10).

Disease-defeating Target Product Profiles

The European Medicines Agency, like the Federal Drug Administration in the United States, defines five forms of disease caused by bacterial infections that can be particularly hard to treat: Skin and soft tissue infections, community-acquired pneumonia (CAP), hospital-acquired/ventilator-associated pneumonia (VAP), intra-abdominal infection and urinary tract infections. Some of these diseases may become untreatable when caused by resistant organisms. The European Medicines Agency classification is not exhaustive for these purposes, but it serves to illustrate the logic of the Target Product Profile system. In practice, additional diseases profiles, such as neonatal sepsis, must also be addressed by a dedicated Target Product Profile.

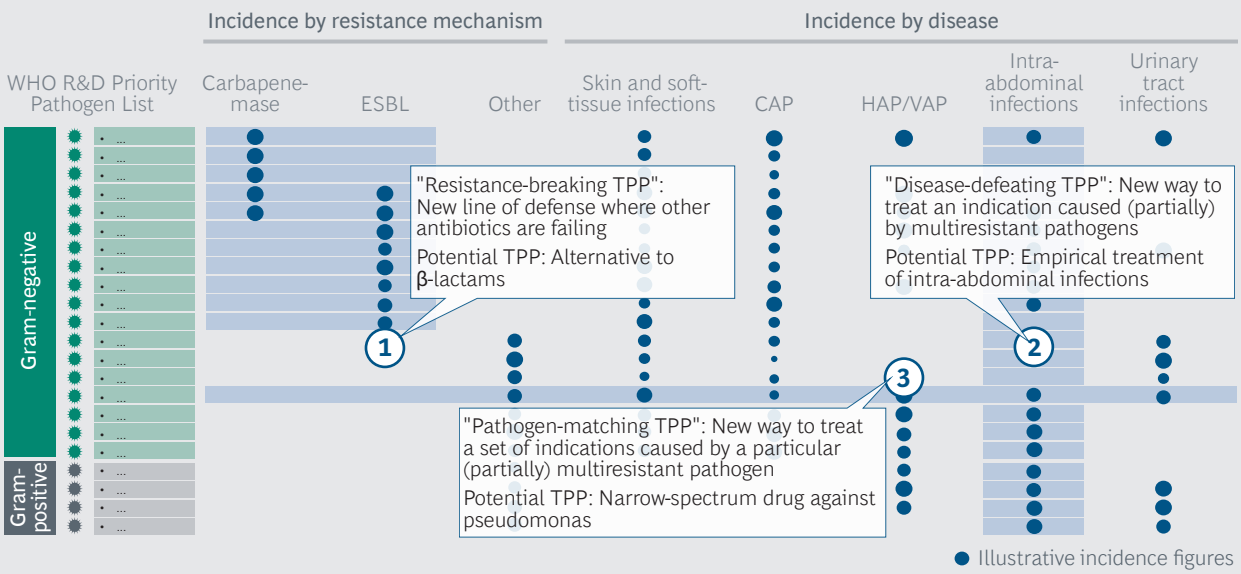
Pathogen-matching Target Product Profiles

Finally, some pathogens are a clinical problem in their own right. Next to Mycobacterium tuberculosis, this category may include Neisseria gonorrhoeae, Clostridium difficile, Helicobacter pylori, and Pseudomonas aeruginosa. Pseudomonas aeruginosa, for example, is found across a spectrum of diseases in immunocompromised patients, frequently associated with bad prognosis and particularly difficult to treat, so it will need a distinct Target Product Profile.

Figure 8 shows the landscape of pathogens, resistance mechanisms and diseases. The blue circles, once filled in with real global incidence (and mortality) data, will indicate where the greatest clinical needs are from a global public health perspective. The blue shading indicates three potential types of clusters of clinical need that might emerge, which are translated into Target Product Profiles in the callout boxes.

Finally, a note on multiresistant tuberculosis: The WHO R&D Priority Pathogen List excludes it because a range of initiatives against it already exists. The disease requires combination drug regimens that must be clinically tested in combination, hence a strong focus on patent pooling in tuberculosis initiatives, and many tuberculosis drug developers are non-profit organizations serving only the needs of low- and middle-income countries. Here, we propose to use the WHO R&D Priority Pathogen List plus tuberculosis for a first pass at Target Product Profiles, as tuberculosis continues to be a major threat. Funding mechanisms for tuberculosis, however, must be designed separately.

FIGURE 8 | Defining three types of development targets based on clinical need



Source: BCG; European Medicines Agency; World Health Organization; expert interviews

4.2.2. Content of Target Product Profiles: Standardized description of high-need antibiotics

A Target Product Profile is a proprietary planning tool used in industry to guide product development and to inform regulatory bodies and investors. The key difference between industry TPPs and coordinative TPPs as proposed here is that coordinative TPPs tend to be wider in scope, but include a few typical parameters that describe the desired drug.

Drug effectiveness:

- Patient population (in-/outpatient, vulnerable groups, and comorbidities)
- Disease cured and targeted cure rate
- Pathogens susceptible
- Degree of innovation needed (e.g., no cross-resistance with specific products, mode of action, chemical class)
- Key comparator substances for non-inferiority/superiority

Drug characteristics:

- Formulation (e.g., pediatric)
- Delivery form (e.g., oral)
- Interactions (e.g., typical combination treatments)
- Contraindications (e.g., pregnancy)
- Storage stability (e.g., cold chain requirements)
- Diagnostic need (e.g., requirements for companion diagnostic)

Depending on the type of Target Product Profile *(resistance-breaking, disease-defeating or pathogen-matching)*, the focus of the Target Product Profile may vary: While a Target Product Profile for a *disease-defeating* drug must be highly specific with regard to what disease profiles it addresses and what delivery form is needed, a Target Product Profile for a pathogen-matching drug must describe the problematic properties of a pathogen in detail.

Moreover, it is standard practice to define an acceptable and ideal level for each parameter to better calibrate success along the path of drug development.

Some coordinative Target Product Profiles, such as those developed by the Drugs for Neglected Diseases Initiative (DNDi) or the Medicines for Malaria Venture, include desired price levels. Our Target Product Profiles do not: Most high-need drugs developed as a result of this initiative will be needed in both low-/middle-income countries and high-income countries, allowing for significant price differentiation in many cases. Because pricing is critical from an access perspective in low- and middle-income countries and, as many would argue, from a stewardship perspective in high-income health systems, we propose to define differentiated pricing and access requirements for new drugs in all funding contracts entered into with **GUARD**.

FIGURE 9 | Target Product Profiles define effectiveness and key characteristics of high-need antibiotics

Development target: _____

		Acceptable	Ideal
Effectiveness	Patient population		
	Diseases/cure rate		
	Pathogens		
	Degree of innovation		
	Key comparators		
Characteristics	Formulation		
	Delivery form		
	Interactions		
	Contraindications		
	Storage stability		
	Diagnostics need		

Source: BCG; expert interviews

4.2.3. A scoping of important areas for basic research funding

While Target Product Profiles can guide funding decisions from preclinical development onward, they are not sufficient to determine what basic research projects should be funded. Just as we urgently need more research efforts that produce the scientific foundation for drug development, we need a defined scope for **GUARD** basic research funding.

We spoke to a wide range of experts about the most important areas of basic research and identified five. The first three are particularly promising and could yield results in the next few years.

New chemical matter. The discovery of new substances or scaffolds with antibiotic properties, natural or synthetic, is key to the development of high-need antibiotics.

Resistance mechanisms. A deeper biochemical understanding of resistance mechanisms, especially Gram-negative drug entry, efflux pumps, and antibiotic-degrading enzymes, is needed to eventually develop modes of action against them.

Methodological innovation. Among other topics, today's methods for accessing novel sources of antibacterial substances (and exploiting known sources of antibiotics), modeling human disease in vitro and in vivo, predicting drug synergies and antagonism, and measuring minimum inhibitory concentrations and resistance are widely seen as having potential for improvement.

Alternative approaches. Promising new approaches such as phages, immunotherapy, infrared light or nanoparticles[1] could produce a step change in antibiotic therapy in the long run.

Broader microbiology. The significance of the host-microbiome, host-pathogen interaction or further insights on biofilm may also yield valuable insights for drug development in the long term.

4.3. Making it work: A global system of Target Product Profiles

The idea of creating Target Product Profiles for antibiotics research and development is not new. The Global Antibiotic Research and Development Partnership (GARD-P), a recently launched venture of the WHO and DNDi, is already in the process of defining Target Product Profiles for the research and development priorities of GARD-P's first business plan 2017–2023. The creation and management of a global Target Product Profile system as proposed here will require significant expansion of the resources working on Target Product Profiles today.

4.3.1. An interdisciplinary committee to develop Target Product Profiles

The single most important factor in defining globally accepted Target Product Profiles is bringing together the right individuals with the necessary expertise to determine which Target Product Profiles are needed and to write those profiles.

This report provides a conceptual framework for a global Target Product Profile system. As a next step, a multistakeholder Scientific Committee will have to choose which Target Product Profiles are to be written in each proposed category and subsequently define the drug profiles in detail.

A successful Target Product Profile committee must include experienced clinical practitioners from various geographical areas (developed countries as well as low- and middle-income countries), active drug developers, and experts in regulatory approval processes.

We estimate that with a full-time effort by a number of specialists, a Target Product Profile system could be fully operational within six months to a year.

4.3.2. Defining a predictable and practical update cycle

The WHO R&D Priority Pathogen List is expected to stay stable for three to five years. Even then, it is likely that only minor additions or subtractions from the list will take place at a time. The Target Product Profile system needs a transparent mechanism to account for changes in global public health challenges related to antibacterial resistance. The system must be flexible enough to reflect progress in drug development and the potential rise of new resistance, while also safeguarding stability for companies that rely on Target Product Profile-based funding.

[1] See Lam et. al., September 2016.

We propose the following updating mechanism:

- Continuous monitoring of the progress of all **GUARD** projects and of the chances of success by an overarching body that manages all **GUARD** levers
- Continuous monitoring of the resistance situation through a global surveillance system, like the Global Antimicrobial Resistance Surveillance System (GLASS) that is currently being built by the World Health Organization
- Target Product Profile review conferences every three years with the option to convene ad hoc conferences in cases of significant changes in either resistance or development pipelines

4.4. Vaccines and diagnostics: Product-specific strategies needed

We strongly encourage the creation of Target Product Profiles for the most-needed vaccines against key pathogens and diagnostic tools in order to enable targeted administration of high-need antibiotics. However, we do not recommend using the same financing mechanisms for vaccines and diagnostics. While these products are not being developed at a satisfactory rate either, the challenges along their value chains are distinctive, requiring remedies different from the funding mechanisms proposed here.

4.4.1. Vaccines and diagnostics are key in the fight against AMR

Vaccines and diagnostics play important roles in the fight against antimicrobial resistance by enabling prevention and stewardship respectively.

Vaccines could be developed against some of the key multiresistant pathogens

Classic vaccines against viral infections (such as the influenza vaccine) can prevent infectious diseases that are often wrongly treated with antibiotics. They also reduce the incidence of bacterial suprainfections. Especially in low- and middle-income countries, they are critical for preventing disease caused by multiresistant pathogens and for preventing the development of resistance by reducing the need for treatment with antibiotics.[1] Vaccines can also be developed against some specific resistant bacteria. Recent successes against methicillin-resistant Staphylococcus aureus (MRSA), for instance, can be attributed in part to Staphylococcus aureus vaccines (MRSA is a Gram-positive pathogen resistant to methicillin).

In principle, new vaccines could be developed against some, but not all, resistant bacteria. A vaccine against Helicobacter pylori is conceivable and is being worked on in Germany.[2]

Better diagnostics are needed for stewardship of existing and new antibiotics

Biomarker tests that help distinguish viral from bacterial infections prevent the improper use of antibiotics for infections they cannot cure. More complex test methods that identify a particular pathogen are often applied in hospital labs for targeted therapies with narrow-spectrum antibiotics.

[1] Médecins sans Frontières statement, September 2016
[2] BMBF Newsletter 78, April 2016

Experts estimate that rigorous testing in outpatient settings with existing lab tests could reduce antibiotic use for respiratory infections by half. With rapid point-of-care diagnostics, results could be even better. In hospital settings, a faster transition from broad-spectrum to narrow-spectrum antibiotics would significantly slow the development of resistance that are encouraged by killing off the entire microbiome with broad-spectrum therapies, but here, expensive diagnostic tests compete with comparatively cheap broad-spectrum antibiotics.

4.4.2. Vaccine and diagnostics value chains not free of challenges, but different from antibiotics

Both vaccines and diagnostic tools could be, and in some cases are, highly profitable products. In contrast to antibiotics, which should be used sparingly, a good vaccine or diagnostic should be used as widely as possible. In fact, in the last ten years, at least 28 vaccines against bacterial pathogens have been brought to market—more than ever before. This is an encouraging trend.

The key to getting industry to develop more vaccines, then, lies not in subsidizing them, but in removing uncertainty around market potential. For vaccines, public commitment to vaccination campaigns creates markets. This is why Advance Market Commitments have proven to be the most widely used pull incentive for vaccines. For diagnostics, the answer is found largely on a national level—diagnostics need to be reimbursable in order to be used more widely and thus become commercially attractive.

5. GLOBAL RESEARCH FUND: INCREASING THE PROBABILITY OF NEW DISCOVERIES

The Global Research Fund (GRF) at a glance

With an annual budget of $200 million, the Global Research Fund seeks to grow the community of antibiotics researchers by 50% and to finance basic research and preclinical development projects.

Lever design and instruments

- Funding for new research units accommodating 250 new researchers
- Project funding (50% for basic research, 50% for preclinical development)
- Initiatives to foster collaboration and translation

Required resources and duration

- $25 million per year for infrastructure funding
- $175 million per year for project funding
- Time frame of ten years to enable long-term buildup of infrastructure

Making it work

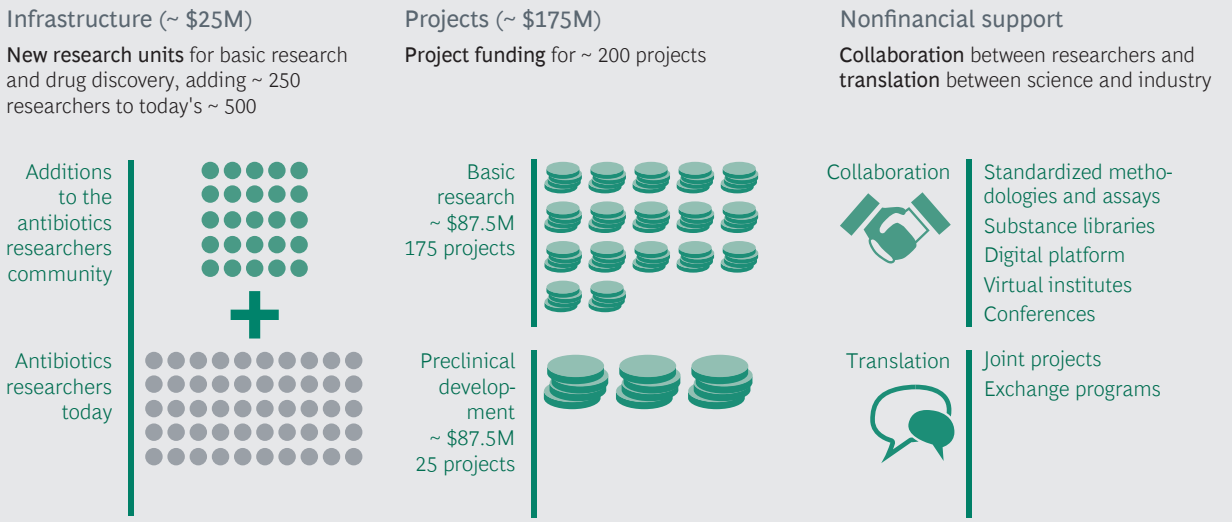
- Clear link to scope of funding for basic research and Target Product Profiles
- Thorough, but compact application process
- Scientific Committee with drug development expertise
- Mid-term and final project evaluations
- Permanent organizational set-up required for program management

BASIC RESEARCH AND PRECLINICAL development, the first two steps in the value chain, play a critical role in the discovery of novel approaches, and in supplying promising compounds for the clinical pipeline. According to small, medium-sized and large pharmaceutical companies as well as other experts, the need for novel approaches is great and urgent, especially against Gram-negative bacteria. In fact, large pharmaceutical companies signaled to us that if a significant discovery were to be made against Gram-negative bacteria, industry would immediately take it up.

Today, however, research institutions focused on antibiotics are few, funding mechanisms inadequate, and translation (the bridge between academia and industry) weaker than in other biomedical fields. In order to create a critical mass in the researcher community, and to support scientifically necessary and clinically promising projects, we propose a Global Research Fund (GRF).

With an annual budget of $200 million, the fund could grow the current antibiotics researcher community by 50%, triple targeted global funding for relevant basic research (funding 175 new projects) and fully finance 25 preclinical development projects (which are likely to meet Target Product Profiles if successful).

FIGURE 10 | The Global Research Fund at a glance



Source: BCG

We would like to stress that this concept should by no means limit scientific freedom or shift funding from national research budgets to the Global Research Fund. Instead, the Global Research Fund aims to add funding to meet pressing clinical need. By basic research, we still mean hypothesis-driven exploration of the five focus topics outlined in section 4.2.3.—projects that do not necessarily result in specific drug candidates, but advance our understanding of key biochemical questions that make drug discovery possible.

5.1. The challenge: A small, fragmented landscape

Besides scientific challenges, there are nonscientific factors dampening the prospects of a major discovery. There are no clear antibiotics-related global goals yet, and consequently no transparency on global progress regarding the exploration of new chemical matter, resistance mechanisms, etc. Moreover, antibiotics research lacks critical mass. Some great ideas do not come to fruition either because they cannot obtain funding or, in cases where a specific lead has been discovered, because translation between academia and industry is not strong enough. This was emphasized by many experts in all relevant fields.

5.1.1. Fragmented, national sources of funding are not meeting needs

Today, antibiotics researchers rely largely on national funding, which is often hidden within larger funding budgets for microbiology or related research areas. As a result, specific funding for antibiotics research cannot be traced, and uncertainty remains as to whether existing funding goes into the research areas that are most needed for

innovation in antibiotics discovery and development. Carving out more dedicated resources for antibiotics from the shadows of broader microbiology and pharmacology is therefore critical. This can be most effectively achieved using collective global funding based on a clear research mission. Ultimately, this research will help replenish clinical development pipelines.

We estimate that of half a billion in existing push[1] funding for antibiotics research and development in 2016, only ~10% was dedicated to basic research.[2] The lion's share of public international antibiotics-related funding goes to clinical development, which is not surprising at first, given that clinical trials are expensive and basic research projects are innately hard to evaluate. As a consequence, however, many important basic research projects struggle to secure funding.

More funding is also needed for preclinical development projects. Combating Antibiotic-Resistant Bacteria (CARB-X), a new Boston-based international preclinical funding initiative, has received a large number of qualified applications in their first call for applications, but will be able to fund only ~5% of projects that expressed interest.[3]

To add further complexity, many important funding mechanisms available to antibiotics researchers are seen as cumbersome and bureaucratic. A number of academics told us that requirements for individual research experience can be so stringent that moving into antibiotics research and development from other, closely related fields is unnecessarily difficult. This seems particularly acute in Europe.

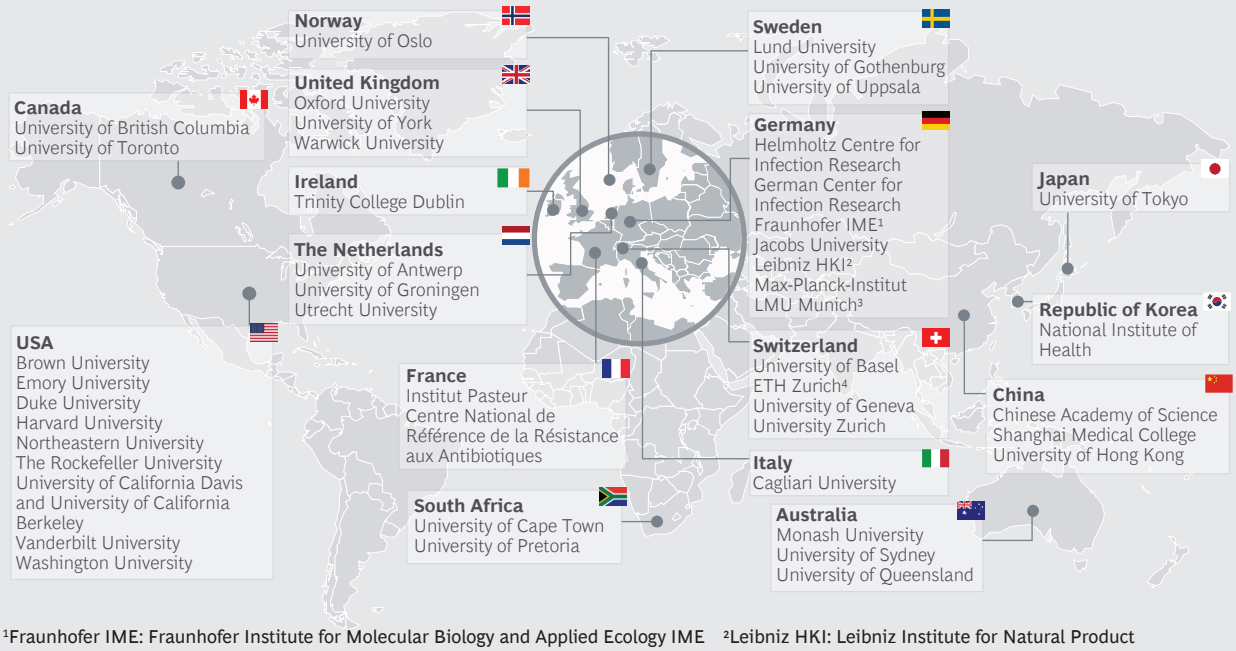
5.1.2. A comparatively small antibiotics research community

Antibiotics researchers are an endangered species. Today, an estimated ~500 specialists (excluding PhD students) are active in antibiotics research. We identified only ~50 institutions that are active in antibiotics research globally (see figure 11). We do not claim that this list is complete, but it illustrates an order of magnitude. In comparison, the German Cancer Research Center alone has over 90 departments and research groups, and employs more than 800 scientists excluding PhD students.[4]

It is not surprising that top talent is attracted to other biomedical fields due to limited career opportunities in antibiotics. An effort is needed to make the antibiotics research ecosystem much more diverse by including scientists from related academic disciplines and by providing young scientists with the possibility of starting a career.

[1] "Push" funding means financial support for a product that is already being developed, whereas "pull" funding incentivizes the developing company to invest its own funds (by promising a monetary reward in case of success).
[2] In comparison, the United States National Institutes of Health alone spends more than five billion dollars on cancer research.
[3] Prof. Kevin Outterson (Executive Director of CARB-X) in discussion with the authors, November 2016.
[4] Deutsches Krebsforschungszentrum, 2016 (online source).

FIGURE 11 | Only ~ 50 academic institutions with dedicated antibiotics research units



[1]Fraunhofer IME: Fraunhofer Institute for Molecular Biology and Applied Ecology IME [2]Leibniz HKI: Leibniz Institute for Natural Product Research and Infection Biology Hans Knöll Institute [3]LMU Munich: Ludwig-Maximilians-Universität München [4]ETH Zurich: Swiss Federal Institute of Technology in Zurich
Note: List not exhaustive
Source: BCG; expert interviews

5.2. Lever design and instruments: More input for the pipeline

The Global Research Fund addresses the early stages of the value chain by building new basic research infrastructure, funding promising basic research and preclinical projects, and providing nonfinancial support to foster collaboration and translation.

5.2.1. Funding antibiotics infrastructure to grow the antibiotics research community by 50%

It is impossible to estimate the number of researchers needed for a scientific breakthrough. However, the probability of a significant discovery would increase significantly if the community of antibiotics researchers were larger. As a first step, we would like to grow the antibiotics research community by 50%. Assuming ~500 active antibiotics scientists today, the Global Research Fund's aim is therefore to add ~250 new researchers. The creation of new, fully-funded infrastructure for antibiotics research could spark a virtuous cycle, whereby antibiotics research receives more public attention and becomes a more attractive career choice for scientists in adjacent fields (microbiology, chemistry, or pharmacology) or aspiring scientists.

The new research infrastructure for these scientists should consist of dedicated units or research groups, either newly established or under the umbrella of existing institutes, with a strong connection to industry drug development experts where possible. These

research units should be distributed across several countries, and proposals should come directly from active researchers.

5.2.2. Project-based grants used to address urgent clinical need

In addition to infrastructure funding, the Global Research Fund will also fund promising projects in basic research and preclinical development. In contrast to existing funds, the Global Research Fund should aim to split its funds evenly between a larger number of less expensive, but riskier basic research projects and a slightly smaller number of more expensive preclinical projects.

In order to foster basic research outcomes that pave the way for innovative drug development, the Global Research Fund has a strict focus on clinical need.

- Basic research: projects addressing important areas of basic research as defined in the **GUARD** scope of funding for basic research (see section 4.2.3.)
- Preclinical development: projects that are likely to result in drug candidates matching at least one Target Product Profile if successful

5.2.3. Fostering collaboration and translation

Additionally, the Global Research Fund could include nonfinancial elements to foster collaboration between researchers, and to bridge the gap between science and industry. Both elements are important. According to a leading European antibiotics researcher, "Networking is not the issue, the community is well connected. The key to progress is real collaboration—shared substance libraries, assays, and global interdisciplinary teams." The gap between science and industry is even wider. "They don't read the same papers, they don't go to the same conferences," another expert told us with regard to academic and industry researchers.

A few potential collaboration tools are listed below.

Collaboration among researchers

- **Standardized methodologies and assays**: Tools to measure e.g., drug penetration and efflux avoidance will be jointly developed and used by **GUARD** research units and project participants.[1]

- **Substance libraries**: Diverse global substance libraries that are updated frequently and shared across institutions have often been called for.[2] A Global Research Fund with a significant budget and a large number of grantees would be ideally positioned to manage this.

- **Digital platform**: A digital platform will provide a structured forum for all **GUARD** participants across the value chain to share insights and challenges.

- **Virtual institutes on specific topics or pathogens**: Different from digital platforms, virtual institutes are infrastructures for collaboration. Work is distributed virtually to whoever has the best skills or resources to conduct an experiment. The Brighton Collaboration Foundation on vaccine safety is a pertinent example.[3]

[1] See also Pew Charitable Trust 2016, p. 10
[2] See also Leopoldina 2013, p. 49
[3] Brighton Collaboration Foundation 2014 (online article)

- **Conferences**: Global Research Fund conferences allow program participants to present their work and findings and to connect with researchers from the perceived "other side" of the academia-industry divide. They could also be part of the project review process.

Translation between science and industry

- **Joint projects**: Joint applications by collaborative groups composed of academic institutions and industry researchers are strongly encouraged. If **GUARD** is implemented as a whole and begins to support clinical development, it could help Global Research Fund grantees find partners for further development.

- **Exchange programs**: Exchange programs between academic institutions and pharmaceutical companies could take the form of a three- to six-month secondment of researchers.

5.3. Required resources and duration: A decade to fill the pipeline

The Global Research Fund will provide funding for both infrastructure and research projects for up to ten years. Overall, the Global Research Fund funding needed is estimated at ~$200 million annually, of which $25 million[1] are needed to add ~250 researchers to the scientific community and ~$175 million to fund basic research and preclinical development projects.

About 200 projects can be supported with this sum. The costs for basic research projects are estimated at ~$0.5 million annually. The Global Research Fund can therefore fund up to 175 basic research projects. Costs for preclinical development projects are estimated at ~$3.5 million annually. Hence, the Global Research Fund can fund up to 25 preclinical development projects.

A time frame of ten years is needed, as the new research infrastructure will take roughly a decade to become fully functional, and basic research projects can take up to ten years to produce results.

5.4. Making it work: Requirements for successful implementation

To make the Global Research Fund successful, a Scientific Committee as well as an effective application and review process is needed to determine the probability of a Target Product Profile match and select the best projects.

5.4.1. Eligibility criteria and required information

GUARD seeks to build new infrastructure and add to existing mechanisms of funding, so a general condition for Global Research Fund grants is that the endeavor supported must be new. Further prerequisites vary depending on the type of funding applied for.

- **Infrastructure proposals**: Both academic researchers and joint academia and industry groups can apply. Applicants should submit a concept outlining the scientific focus of the proposed research unit, a hiring strategy, and an investment plan for

[1] Based on expert cost estimates for PhD, postdoctoral fellowship and senior researcher positions in microbiology

equipment needs. The proposal must demonstrate that new, original infrastructure is planned in order to avoid financing existing infrastructure with **GUARD** funding. Selection criteria can include compatibility of the proposal with the scope for basic research funding described in chapter four, and the feasibility of the investment plan.

- **Basic research projects**: Academics are the main recipients of this fund. Applicants submit a project proposal outlining the research concept and funding needs and are selected based on compatibility with the **GUARD** scope of basic research funding.

- **Preclinical development projects**: Academic researchers, joint academic and industry groups, and small and medium-sized biopharmaceutical companies can apply. Applicants submit a project proposal outlining test design and funding needs. Selection criteria for funding are a probable match with at least one Target Product Profile, proof of in vitro effectiveness, and viable test design.

5.4.2. Establishing a Scientific Committee for application and review

All funding decisions should be made by a committee composed of leading experts in the field of antibiotics research and development. These include scientists with expertise in the core focus areas of **GUARD** and potentially also industry drug developers. This ensures that project proposals can be evaluated both on scientific merit and on their potential for spurring drug discovery. Ideally, committee members should come from various geographical areas.

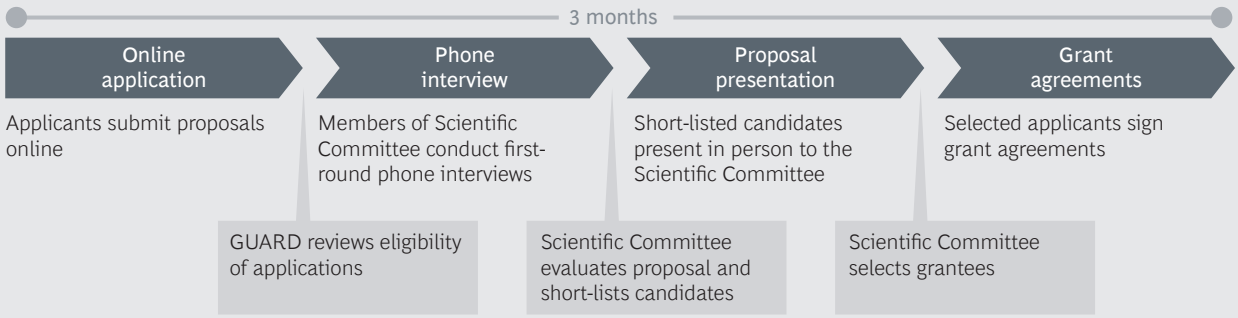
5.4.3. An effective process to select the best projects

The Global Research Fund will select projects in a quarterly application process. Mid-term reviews will ensure that only projects meeting their milestone plans receive further funding.

A thorough but compact application process

Our model involves four application cycles per year as shown in figure 12.

FIGURE 12 | Quarterly Global Research Fund application cycle



Source: BCG

Grant agreements must include rules on project governance and intellectual property rights. Joint applications by more than one organization are expected to present a plan for intellectual property sharing as part of the grant agreement.

Evaluation of success in mid-term and final reviews

Project reviews by Scientific Committees evaluate the promise of findings throughout the funding phase. Projects are reviewed at least every two years, and more often in case of preclinical development projects with a shorter time frame. Based on these reviews, the Scientific Committee makes decisions on which projects will receive further funding. Furthermore, program participants present preliminary findings at **GUARD** conferences. All program participants that receive funding from **GUARD** will have to publish their results.

At the end of the funding phase, the Scientific Committee is also in charge of final project reviews. In the case of preclinical development projects, this also includes an evaluation of need for further support, e.g., the search for a commercial partner or further funding for clinical development.

6. GLOBAL DEVELOPMENT FUND: OVERCOMING INVESTOR UNCERTAINTY

The Global Development Fund (GDF) at a glance

With an annual budget of $200 million, the Global Development Fund supports mainly small and medium-size biopharmaceutical companies in their clinical development efforts towards antibiotics that meet at least one Target Product Profile.

Lever design and instruments

- Partial funding of clinical trials via forgivable loans (in all phases)
- Mechanism to return funding to **GUARD** in case of revenue generation
- Potential standards for responsible use as condition for financial support

Required resources and duration

- $200 million per year for one drug per year at average success rates and cost
- Time frame of ten years to push at least one high-need antibiotic to market

Making it work

- Interdisciplinary investment committee with drug development expertise
- Permanent organizational setup required for program management

The Global Development Fund provides funding in all phases of clinical development of high-need antibiotics. The fund particularly supports small and medium-sized biopharmaceutical companies to engaging and reengaging in the development of antibiotics.

6.1. The challenge: Insufficient funding for clinical development

For multiple reasons, it is challenging to secure funding for the development of antibiotic candidates. This can lead to the termination of clinically promising development projects for reasons of purely financial nature. Worse still, scientifically promising leads may never enter clinical development at all.

6.1.1. Securing funds for clinical trials is a challenge

Especially for small and medium-sized biopharmaceutical companies, it is hard to secure funding for the clinical development of antibiotics, particularly when the company in question is developing only one or two products with a high risk profile. Within large companies, antibiotic candidates compete with much more profitable projects. Generally,

the weak market pull (see chapter 7.1.) for antibiotics due to low and unpredictable revenue reduces activity in this area.

A fragmented funding landscape is especially challenging for smaller biopharmaceutical companies, which often struggle to secure funds. The London School of Economics and Political Science compared venture capital investments in the antibiotics field in 2004–2008 and 2009–2013. Their report finds a 28% decrease between the two periods, from over $1 billion invested over the first 5-year period, to ~$750 million between 2009 and 2013.[1] Venture capital makes up a substantial part of the total investment. With larger pharmaceuticals leaving antibiotics research and development, public intervention is needed to complement private funding and to make antibiotics development more attractive for private money.

6.1.2. The clinical trial pipeline is not delivering what is most needed

The Global Development Fund seeks not only to increase total funding available but also to steer development toward clinical need. The following assessment shows that continued efforts to focus on areas of high global public health urgency are necessary.

Most of today's phase 2 antibiotic candidates will not be effective against the most threatening bacteria. Only one-fourth of current candidates are potentially active against a selection of priority pathogens (see figure 13), and it is unclear to what extent they will have resistance-breaking properties.

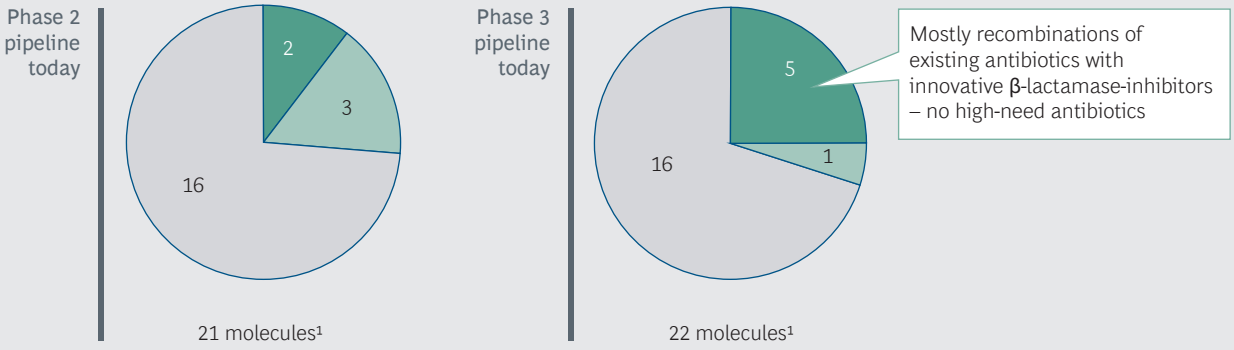
Of the nineteen phase 2 molecules analyzed, only two might be effective against a subset of Gram-negative priority pathogens. In phase 3, the situation is similar. Of the twenty molecules currently in development, only five are potentially effective against Gram-negative priority pathogens. Of those five, three are based on existing modes of action in combination with new beta-lactamase inhibitors. These will not, however, solve the global public health problem associated with carbapenemase and extended-spectrum-beta-lactamase (ESBL) as outlined in section 4.2.1.

Moreover, approximately one-fourth of the substances are not antibiotics but antibodies. Instead of inhibiting cell function in bacterial cells, they trigger the human immune system to fend off infection. The analysis is not intending to equate the two, but seeks to include all potentially relevant current development efforts.

A similar picture emerges when we look at recent launches. Since 2012, there have been only six antibiotic launches that address potential World Health Organization Priority Pathogens—but mostly the Gram-positive ones, and not to a satisfactory extent from a clinical need perspective. For the most critical pathogens, we have not seen a relevant market launch in recent years. An extrapolation of the current pipeline—based on today's average success rates for antibiotic candidates—shows a continuation of this trend (see figure 14).

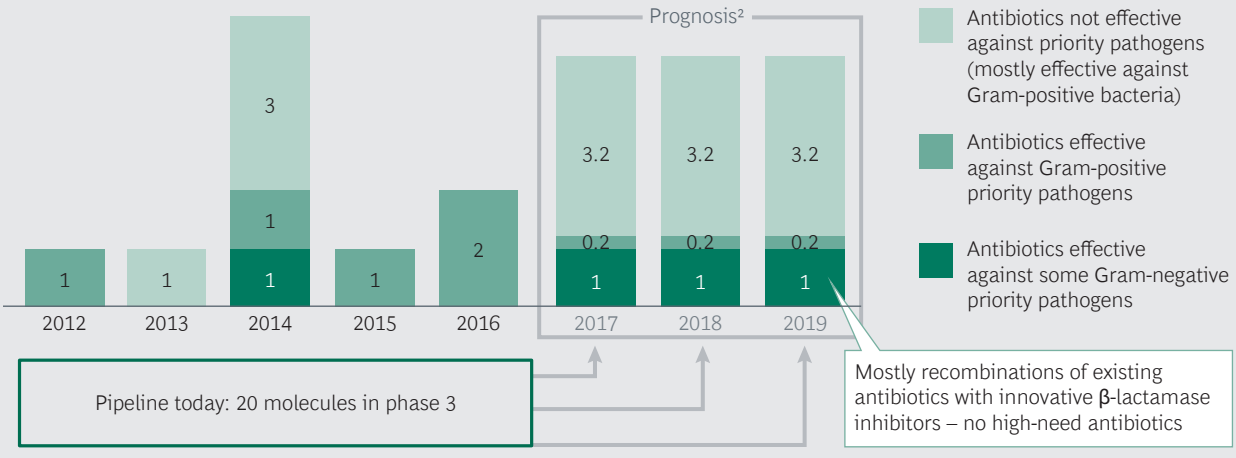
[1] Renwick et al., 2016

FIGURE 13 | Current pipeline will not solve the Gram-negative problem



¹In the pipeline in 2016 in Europe based on data provided by the Verband Forschender Arzneimittelhersteller (vfa)
²For the purpose of this analysis priority pathogens include: Carbapenem-resistant microorganisms (Acinetobacter baumannii, Enterobacter spp., Escherichia coli, Klebsiella pneumonia, Pseudomonas spp.), Extended-Spectrum-β-lactamases (ESBL)-producing microorganisms (Enterobacter spp., Escherichia coli, Klebsiella pneumonia), Methicillin-resistant Staphylococcus aureus/MRSA [Gram-positive], Vancomycin-resistant Staphylococcus aureus [Gram-positive] Vancomycin-resistant Enterococcus [Gram-positive]
Source: BCG analysis; expert interviews; Sanofi-Fraunhofer-Zentrum für Naturstoffforschung

FIGURE 14 | No breakthrough against Gram-negative pathogens among recent launches and current candidates



¹2012: Ceftarolin, 2013: Fidaxomicin, 2014: Bedaquilin, Delamanid, Para-Aminosalicylic Acid, Telavancin, and Ceftobiprol 2015; Tedizolid; 2016: Oritavancin and Dalbavancin
Assumptions: Market entry of 12 new drugs over three years of 22 candidates currently in phase 3. Assumed success rate for phase 3: ~ 76%; assumed success rate for market approval ~ 80%.
Source: BCG analysis; Verband Forschender Arnzeimittelhersteller (vfa); expert interviews; *Neue Antibiotika: Den Vorsprung gegenüber resistenten Bakterien wahren.* vfa (2016); *Modelling the antibiotic development process.* AMR Review (2015)

6.2. Lever design and instruments: Funding additional clinical trials

The Global Development Fund will primarily help biopharmaceutical companies, but is open to any organization active in the clinical development of antibiotics. Financial support is awarded as a forgivable loan and structured as a revenue-sharing agreement.

6.2.1. Forgivable loans as key instrument

Forgivable loans are the most adequate financial instrument to reduce the risk for companies conducting clinical trials while ensuring a return for **GUARD** in case of clinical success. The loan is only paid back if the compound is launched or the candidate sold. There are multiple reasons to use forgivable loans:

- **Clinical development is almost always for profit**. The majority of clinical trials, especially in later stages, are conducted by profit-oriented companies. An assessment of the current antibiotics pipeline shows that all phase 2 and 3 candidates are at least partially owned by private companies (43 candidate molecules in total).

- **Forgivable loans have proven successful**. The model has proven attractive in funding medium and large-scale research projects in the past years, and it is widely used for commercially risky investment propositions with high social value. In Europe, the film industry and students in higher education, for example, are supported with forgivable loans to great effect. InnovFin, a financing facility of the European Investment Bank with a dedicated fund for infectious diseases, employs a similar structure.[1] The AMR Centre in the United Kingdom plans to use a similar mechanism (revenue sharing) for clinical trial support.[2]

- **Emphasis on early-stage development**. A forgivable loan would be most attractive in early-stage development, where the candidates are still far away from market launch and where failure rates are high. Funding early-stage development, most loans would be forgiven, as only 1 in ~9 candidates survive phase 1. Using forgivable loans would therefore come close to a grant scheme for small, early-stage developers.

6.2.2. Partial funding approach to attract additional private capital

GUARD seeks to stimulate additional activity in the antibiotics development value chain, not to replace existing funding. Companies accepting funding from **GUARD** are required to either invest their own capital or secure additional funding sources. Phase 1 and 2 are funded with up to 75% of the required funding of the trial. Phase 3 is covered with up to 50% of the required funding.

Especially later-stage trials are conducted with a clear for-profit motivation. Since later-stage molecules have a higher chance of entering the market and generating revenues, **GUARD** support for 50% of required funding will be sufficient and in-line with market standards. Phase 3 trials are also more cost-intensive. A 50% upper funding limit for the Global Development Fund therefore reduces the financial exposure of **GUARD**, while still maintaining a substantial level of financial support.

[1] European Investment Bank, 2015b (online source)
[2] AMR Centre website (accessed December 2016)

Requiring a significant financial investment from the company will increase the quality of applications and keep up private investment in the field of clinical development of antibiotics.

6.2.3. Structuring the loan as debt or revenue sharing

The great majority of clinical studies are conducted by private companies (as mentioned above). Such private companies routinely build risk positions to accept debt similar to the forgivable loans proposed here.

To ensure that not only companies but also universities and other research institutions can accept financial support, the following two slight variations of the forgivable loan should be considered:

- Instead of claiming back debt, **GUARD** could receive a share of revenues. Such a revenue-sharing agreement would effectively work like a forgivable loan: Upon sale or generation of revenue, **GUARD** would receive returns.

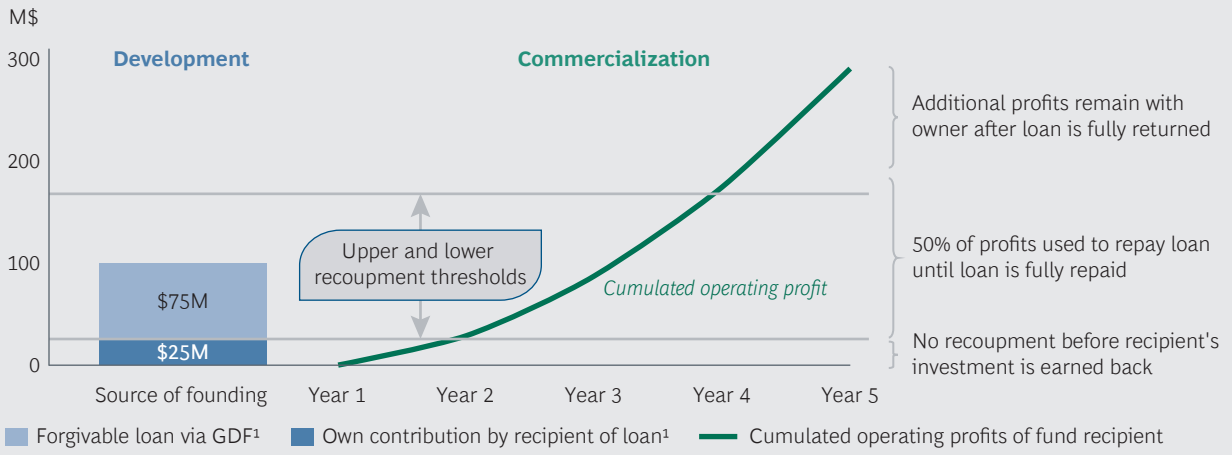
- Alternatively, universities and research institutions may be encouraged to spin off a new company, that can accept debt with the goal of further developing the candidate into phase 2 and onward, something that is seen regularly in drug development.

6.2.4. Repayment may occur upon launch or transfer of ownership

Debt repayment to **GUARD** can begin at two different points. Generally, companies successfully developing and launching a compound share operating profits with **GUARD** until the loan is repaid in full (see figure 15). Operating profits are defined here as revenues minus cost of goods sold (COGS) and selling, general and administration expenses (SG&A).The duration of the repayment period depends on the revenue. Additional operating profits are not shared with **GUARD** beyond the amount of the financial support.

In many cases, a change of ownership will occur during clinical development. Experts estimate that drug candidates change ownership 2.5 times on average between preclinical development and market launch. In the case of a compound or its holding company being sold, the loan must be repaid to **GUARD**. In the case of a revenue-sharing agreement with a research institution, either the agreement may be transferred to the new owner or a buyout negotiated.

FIGURE 15 | GDF repayment scheme with recoupment thresholds based on cumulated operating profits



[1]Illustrative costs of $100 million, close to average costs of development for antibiotics in phase 3 as estimated by the AMR Review (2015). Range of share of external funding and own contribution based on benchmarks such as Horizon 2020, InnovFin Infectious Diseases and funds from the German Federal Ministry of Education and Research.
Source: BCG analysis; European Investment Bank 2016; AMR Review 2015; expert interviews

6.2.5. Conditions for receiving a Global Development Fund loan

The activities of the Global Development Fund are an opportunity for **GUARD** to support efforts toward good antibiotic stewardship and access for populations in need. **GUARD** should seek agreements with the organizations receiving development support. The degree to which such agreements are feasible, however, varies across clinical stages. A small biopharmaceutical company in an early stage of development will not be able to make global access commitments. Here, the loan recipient can only issue a statement of intent together with **GUARD**. In later phases, where **GUARD** financial support is significantly larger and product characteristics clearer, binding stewardship and access agreements should be negotiated on a case-by-case basis where possible.

Such an agreement should, for example, include targets for the following aspects:

- **Availability** (e.g., list of markets, duration of availability, distribution partnerships)
- **Pricing** (e.g., affordable pricing in key regions with high need)
- **Marketing** (e.g., acceptable company activity, specifications of use)
- **Use specification** (e.g., dosage, application)
- **Further development** (e.g., pediatric formulation)

6.3. Required resources and duration: Steady state in four years

The Global Development Fund is scaled to provide sufficient funding to launch one new antibiotic per year in a steady state. Based on typical clinical trial success rates, durations and costs for antibiotics, the number of phase 1, 2 and 3 trials supported are estimated to amount to one launch per year. Global Development Fund activity is of course primarily driven by the availability of high-quality candidates. Because of the challenges in basic research (see section 5.1), the number of candidates will most likely be low in the first years of operation. Funding activity is therefore not expected to reach the full scale of ~$200 million per year for the first few years.

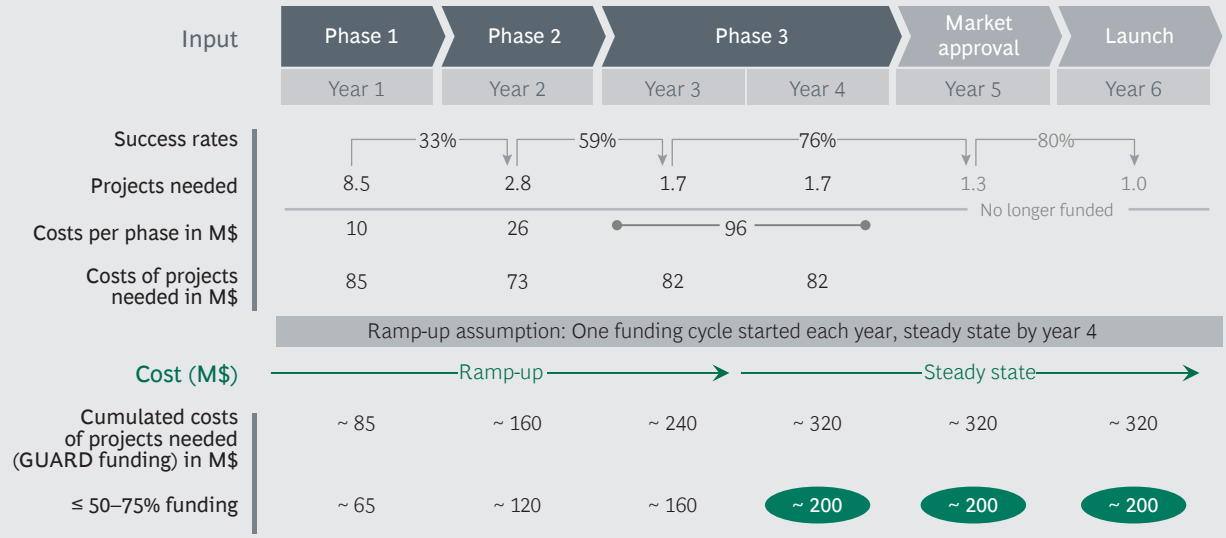
6.3.1. Creating sufficient financial support to stimulate the entire pipeline

Based on typical estimates of cost, duration, and length per phase (see figure 16), we estimate a total funding need of $200 million per year in a steady state (probably achieved in year four):

- 8-9 phase 1 entries per year with costs of ~$10 million for each candidate (up to 75% funded by the Global Development Fund)
- ~3 phase 2 entries per year with costs of ~$26 million for each candidate (up to 75% funded by the Global Development Fund)
- ~2 phase 3 entries per year with costs of ~$96 million for each candidate (up to 50% funded by the Global Development Fund)

However, this does not mean that an antibiotic candidate would necessarily be funded by **GUARD** from beginning to end. It should explicitly be possible to borrow from the Clinical Development Fund for one phase only. Clinical Development Funding also would not imply automatic eligibility for a Market Launch Reward. For the latter, actual Target Product Profile match must be proven, whereas for development funding, the bar is the expected Target Product Profile match.

FIGURE 16 | GDF sizing: Up to 75% of funding for one additional launch every year will cost the fund ~ $200 million in steady state



Source: BCG analysis; Modeling the antibiotics development process. AMR Review (2015).

7. GLOBAL LAUNCH REWARD: AN INSURANCE MECHANISM FOR INDUSTRY

The Global Launch Reward (GLR) at a glance

The Global Launch Reward is a $1 billion payment that seeks to improve the commercial attractiveness of high-need antibiotics (each meeting at least one Target Product Profile), embedded in an insurance-like mechanism.

Lever design and instruments

- $1 billion cash payment to companies launching high-need antibiotics (in installments)
- "Insurance": If operating profits are realized, Global Launch Reward is returned as percentage
- Binding contract upon entry into phase 2 provides planning stability and prevents a race to the finish line in the development process
- Payments conditional on access, quality, and good stewardship conditions

Required resources and duration

- Drugs in phase 2 or later at GUARD launch excluded to avoid windfall profits
- Available for at least 10 years to align with development planning horizons

Making it work

- Scientific Committee to assess candidates
- Permanent organizational setup required for program management

The Global Launch Reward (GLR) will increase the financial attractiveness and reduce the financial risk of launching innovative antibiotics. Increasing the financial attractiveness of antibiotics is intended to create a pull effect throughout the entire value chain, stimulating basic research as well as clinical development in the field. The Global Launch Reward is designed to ensure sustainable use of the resulting antibiotic products. We considered potential market-distorting effects and suggested safety mechanisms.

7.1. Lever design and instruments: Cash payments as insurance

The Global Launch Reward is intended to increase the commercial attractiveness of antibiotics significantly and attract a range of companies to invest in the area. Risks and responsibilities must be carefully considered and shared with public and private stakeholders in order to ensure success. A market intervention of the required magnitude will necessarily have market-distorting effects; the following design decisions are intended to minimize those effects.

7.1.1. A reward needs to be at least $1 billion to raise the net present value to a sufficient level

The pharmaceutical industry has exhibited a clear trend toward a highly focused portfolio strategy. Companies continuously seek to reduce the number of therapeutic areas in which they are active. This approach is rewarded and thus reinforced by the capital markets. Therapeutic areas are in direct competition for funding. This has led to an exit of pharmaceutical firms from antibiotics.

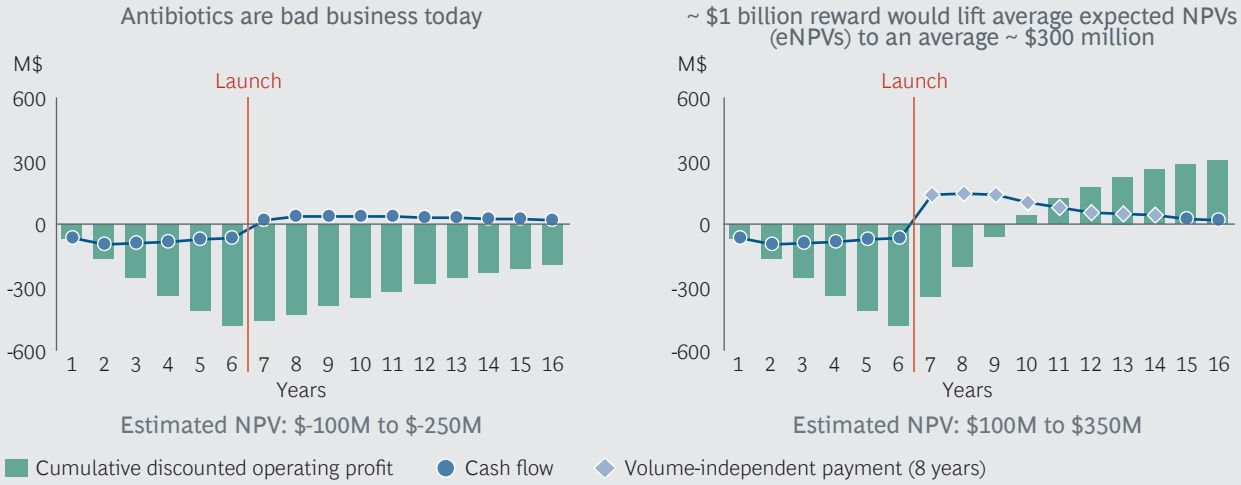
Making antibiotics a generally attractive investment opportunity will require significant capital. A significantly positive net present value (defined as the difference between the present value of future cash flows earned from a defined investment) at the beginning of development should be sufficient to attract small and mid-sized companies to invest in the area and to keep those large pharmaceutical companies in the business of antibiotics. This is important because only large pharmaceutical companies have the necessary regulatory, production, and distribution capabilities to roll out a drug globally. However, small and medium-sized biopharmaceutical companies should be supported to take development as far as they can, because they can play a critical role in developing high-need drugs. The small and medium-sized biopharmaceutical companies interviewed for this report have estimated an expected net present value of $200–300 million to be highly attractive.

To achieve an expected net present value of ~$300 million a Global Launch Reward of $1 billion per launched antibiotic is required. This estimate is comparatively low relative to other estimates, which range from $1 billion to $4 billion. Despite being on the low end of the spectrum, we expect the Global Launch Reward to be effective because its recipients do not forfeit the opportunity to generate profits with the developed drug. Instead, an operating profit-sharing mechanism is proposed (see section 7.1.3).

Profit potential may be slightly reduced via price and availability obligations, but the recipient would maintain the right to market the antibiotic in the major markets (with some minor restrictions (see 7.1.6). By preserving the profit opportunities offered by high-need antibiotics, the Global Launch Reward increases the net present value without being the only source of the recipient's profits.

The Global Launch Reward lifts the expected net present value from a negative value to $~300 million (assuming average peak sales seen for antibiotics over the last years and average development costs—see details in figure 17).

FIGURE 17 | ~ $1B reward would lift average expected NPVs to ~ $300M



Note: Assumptions: $600 million development costs, 9% discount rate, $300 million peak sales, 40% operating profit
Source: BCG analysis; EvaluatePharma

7.1.2. Balancing financial impact and risk through the payout schedule

We propose a stacked payout over multiple years for the Global Launch Reward for multiple reasons:

Giving **GUARD** flexibility for conditionality of payments

A significant part of the relevant information about an antibiotic's effectiveness and safety is collected in the first years after its launch. Many of the experts we interviewed assert that regulatory hurdles for new antibiotics will be lowered significantly in the coming years, possibly down to as low as ~300 patients for clinical safety assessments. This is much lower than the usual ~3,000 patients that are needed for a robust picture on safety. Both the United States Food and Drug Administration and European Medicines Agency are clearly moving in this direction. In the United States, the 21st Century Cures Act, approved in December 2016, creates a limited pathway for the development of antibiotics targeting multidrug-resistant infections.[1] The European Medicines Agency, too, offers an expedited approval pathway for antibiotics addressing urgent needs.[2] To ensure that the Global Launch Reward is only awarded to antibiotics addressing urgent health needs, post-authorization studies need to be considered and subsequent payouts need to be conditional upon agreed standards.

Collecting this information typically takes multiple years. The Global Launch Reward is therefore structured to be paid out over the first eight years on the market. To increase the expected net present value and reduce uncertainty for recipients, the Global Launch Reward is not paid out in equal increments but is front-loaded. Of the total value of $1 billion, $600 million will be paid out in the first three years. The remaining $400 million will be paid out over years four to eight of commercialization.

[1] The Center for Disease Dynamics, Economics and Policy (CDDEP), 2016
[2] European Medicines Agency (EMA), 2013

Should an antibiotic be removed from the market due to efficacy or safety concerns or fail to meet the standards defined in the relevant Target Product Profile, **GUARD** would not be bound to the agreement and future payments would not be made.

Lowering the volatility of a potential payout

The Global Launch Reward has the potential to require significant capital from **GUARD**. Payouts of Global Launch Reward will most likely not occur regularly (in contrast to the more predictable investments via the Global Research Fund). Therefore, multiple payouts could fall into the same year. A stacked payout would decrease the volatility of the payments for **GUARD** and is recommended.

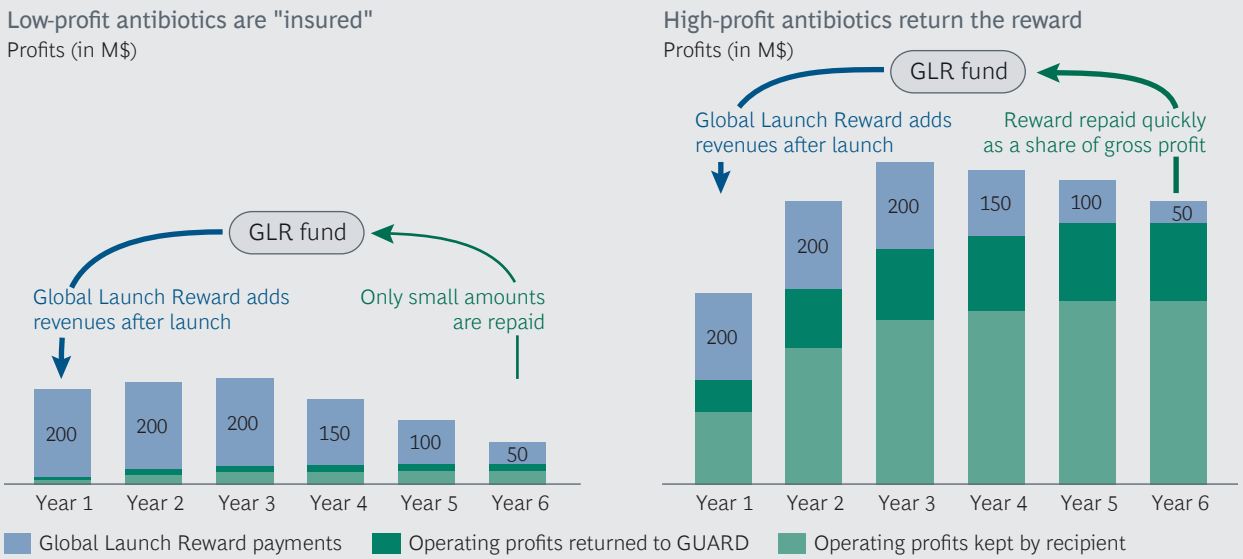
7.1.3. Difference from previous proposals: The insurance model

One of the most important elements by means of which the Global Launch Reward differs from other proposed solutions is its built-in repayment mechanism. As described, recipients of the Global Launch Reward do not forgo the profit potential of marketing the antibiotic in question which lowers the required capital for **GUARD** significantly (this is a key difference from other, higher estimates of pull incentives). This allows **GUARD** to achieve similar effects to other proposed models with a leaner approach.

In the model suggested here, recipients are required to return 30% of their profits to **GUARD** (up to the original amount of the Global Launch Reward). For antibiotics with medium to low profit expectations, this will be a fraction of the payout amount received. An antibiotic with peak sales of $200 million will, for example, return an estimated $25 million per year during the peak sale years (30% of ~$80 million gross profit at an assumed average margin of 40%).

Companies launching an antibiotic that is commercially more successful would be less reliant upon payments through the Global Launch Reward and repay the amount more quickly (see figure 18).

FIGURE 18 | The insurance mechanism: Antibiotics with high operating profits return the Global Launch Reward



Source: BCG analysis

From the public's perspective, this repayment mechanism protects **GUARD** from supporting companies that do not require the Global Launch Reward. It thereby ensures that public funding is invested primarily in antibiotics that would otherwise not be launched.

From the perspective of private companies, the Global Launch Reward remains attractive. The proposed model lifts minimum expected operating profits dramatically while not limiting future returns. To be clear, most high-need antibiotics will have to be used sparingly and will not be top-selling products in terms of volume. However, there will be a market for them—there will always be a need for antibiotics of last resort—and high prices in developed markets are acceptable (and in some cases even desirable).

7.1.4. Designing a functional repayment mechanism

To ensure that the repayment mechanism works as intended, a few factors need to be considered in its design.

- **Setting upper limits for the repayment period**: Some high-need antibiotics may return only a fraction of the financial support they received over the lifetime of the product. Repayment obligations should be forgiven once the product's patent expires. Prices are highly likely to drop once generic competitors enter the market, making a post-patent profitability spike exceedingly unlikely.

- **Securing predictable return of funds for GUARD**: Because companies may not calculate or publicize operating profit on a product-by-product basis, **GUARD** should seek to receive a minimum of 15% of the product revenues through the payment mechanism.

- **Limiting the repayment mechanism to the size of the Global Launch Reward**: Companies should not be required to pay back more than they have received.

7.1.5. Minimizing market-distorting effects and securing second entrants

The Global Launch Reward is a significant financial intervention into the antibiotics market, partially delinking sales volume from profit. Its implementation is intended to shift the research and development focus toward the areas of highest need, as defined in the Target Product Profiles. A market intervention of such proportion is likely to create market distortions. The main concerns of the experts interviewed for this study are on the one hand the uncertainty of shifting Target Product Profiles and, on the other hand, the "race to the finish line."

Uncertainty of shifting Target Product Profiles

Companies considering investment in cost-intensive clinical trials have stressed the importance of target predictability. As development of new molecular entities can take a decade, the stability of the Target Product Profiles over a long period is essential. As described in chapter 4, the Target Product Profile list may require changes and updates every three to five years. Global Launch Reward contracts should, therefore, be signed by both parties (**GUARD** and the potential recipient) at the beginning of phase 2 in clinical development, promising a $1 billion reward if at least one Target Product Profile valid at the time of signing is met. In this way, the recipient is protected from changes to the Target Product Profiles.

The race to the finish line

Global Launch Reward contracts can also effectively avoid the so-called race to the finish line. Companies have expressed the concern that if only the first-to-market can receive a reward for a particular Target Product Profile, the motivation to be the first to cross the finish line may either compromise the quality of the development process, or lead to fewer companies working on similar leads. If a Global Launch Reward contract signatory, however, is conceded an eight-year window for launching the new molecular entity, it will not be forced into a race to the finish line dynamic.

GUARD could sign multiple agreements on the same Target Product Profiles for several reasons. First, given high failure rates in antibiotics development, it is highly advisable to have several strings to the bow in areas of high clinical need. Second, even if multiple new antibiotics match the same Target Product Profile, there may be a significant public health benefit to having both antibiotics available. The social value depends on the similarity of the modes of action of the two antibiotics in question. The Global Launch Reward should be differentiated based on two scenarios of public health value.

- **The second antibiotic has a different mode of action**, a lesser risk of cross-resistances with existing drugs and can therefore be used as an additional line of defense. This drug should be eligible for a full Global Launch Reward.

- **The second antibiotic has the same mode of action** and/or significant cross-resistances with existing drugs, lowering its public health value. **GUARD** should not actively discourage parallel development of similar drugs, but must account for their lower public health value than in the first scenario. Here, the second entrant should receive only 75% of the Global Launch Reward. Should a third company apply for a Global Launch Reward with a similar antibiotic targeting the same Target Product Profile, it would receive 50%, and a fourth entrant would receive 25%. Beyond that, companies would not be rewarded for a launch. In order to prevent a race to the finish line, the order is determined by date of signed agreement, not market entry.

7.1.6. Ensuring proper use of new high-need antibiotics

It is paramount that the high-value antibiotics developed and awarded under **GUARD** be used prudently. With the acceptance of the Global Launch Reward, the recipients join **GUARD** in this effort for sustainable use. The following aspects should be agreed upon between **GUARD** and the recipient.

- **Global availability**. With the acceptance of the Global Launch Reward, the recipient agrees to pursue the launch of the antibiotics globally. The recipient of the Global Launch Reward is furthermore required to keep the antibiotic available in the agreed-upon markets for the duration of Global Launch Reward payments.

- **Affordable pricing in low- and middle-income countries**. The larger part of an antibiotic's expected profits will come from developed countries. The Global Launch Reward preserves these profit opportunities for the recipients. In commercially attractive markets, the recipients maintain the right to set prices following national guidelines without additional intervention by **GUARD**. In low- and middle-income countries, however, pricing policies should reflect local standards of affordability and stewardship, which includes limiting marketing efforts.

As described above (see 7.2.2.), should the recipients not honor the agreements, **GUARD** should be able to reduce or terminate payments of the Global Launch Reward.

Additionally, **GUARD** could advocate for improved price differentiation and stewardship concerning the broader antibiotics and vaccines portfolio of the recipients of a Global Launch Reward. Specific agreements on other antibiotics already marketed by the recipient could be a condition of a Global Launch Reward in some cases.

An alternative way for **GUARD** to foster access and sustainable use is to act as a distributor: **GUARD** could secure exclusive rights to license the drug in low- and middle-income countries. Markets with high profit potential would remain with the developer of the antibiotics. Both GARD-P and the TB Alliance work with variations of this model. However, distribution requires an extremely mature organizational base and expertise. As an alternative, **GUARD** contracts could require the approval of the same compound in the form of two different drugs at differentiated price levels. In this way, all markets remain with the company, while reimports from low-price markets to high-price markets, which would undermine price differentiation agreements, can be prevented.

7.2. Required resources and duration: A long-term commitment

GUARD seeks to have a long-term positive impact on antibiotics research and development infrastructure, and such investment in the biopharmaceutical industry takes years. If a Global Launch Reward is to really change the game and make antibiotics more commercially attractive long-term, it needs to be a long-term commitment. **GUARD** should allow companies to build infrastructure and start antibiotic drug development processes with the certainty that they can still enter into a Global Launch Reward contract once the development reaches phase 2. Given average durations of clinical development, we suggest that Global Launch Reward contracts be available for at least ten years.

7.3. Making it work: Rigorous contractual obligations

To ensure proper functioning of the Global Launch Reward, multiple intermittent and permanent tasks need to be assigned to a managerial organization.

7.3.1. Launch Reward Committee to take contract decisions

A Launch Reward Committee is required to ensure that only high-need antibiotics are awarded a Global Launch Reward. There are multiple points in the lifetime of an potential antibiotic in which committee work is required.

- **Phase 2 signing of agreement**. The Launch Reward Committee needs to assess applications of phase 2 candidates. Candidates meeting the Target Product Profile requirements would be eligible to be the subject of a contractual agreement should the Launch Reward Committee decide in their favor.

- **Development of sustainable standards of use**. Before a Global Launch Reward is paid out, both **GUARD** and the recipient must come to a common understanding of how sustainably the new antibiotic can best be used. This might vary significantly on

a case-by-case basis. Here too, the Launch Reward Committee must be consulted in the design of the use agreement.

- **Evaluation of postapproval studies**. As argued (see section 7.1.2), information from post-approval studies is essential to assessing the effectiveness and safety of an antibiotic. The Launch Reward Committee needs to assess these studies and consider reducing or terminating future payments if necessary.

7.3.2. Organizational requirements for a successful Global Launch Reward

In addition to the tasks of the Launch Reward Committee during the different stages of the pharmaceutical life cycle, there are a range of administrative and managerial tasks to be considered when implementing the Global Launch Reward.

- **Managing financial flows** (incl. payments to recipients as well as incoming funds from the repayment mechanism)

- **Convening Launch Reward Committees** (incl. coordination with high-level **GUARD** decision-making regarding strategic priorities)

- **Stewardship management** (negotiating, monitoring and enforcing the agreements between **GUARD** and the recipient (availability, price, marketing policies, etc.)

8. MAKING IT WORK: ORGANIZATION, IMPLEMENTATION, AND CONTROLLING

MANAGING ALL **GUARD** LEVERS will require a strong organizational setup, steady financing and a realistic implementation plan. Fundamentally, the proposed levers can be launched as a whole or separately, allocating them to existing organizations with similar goals.

8.1. Modular approach: Options for organizing the proposed levers

For all **GUARD** levers, permanent organizational elements are required to ensure effective implementation. In addition to managerial capacities, each lever requires a distinct expert committee that reviews proposals and takes funding decisions.

There are two basic ways in which **GUARD** could be organized. The first is entrusting the four levers to one dedicated existing organization to manage **GUARD** in a coherent, synergistic way. As this would require significant upfront investment in organizational capacity, another potentially faster, but less concerted option is to allocate **GUARD** levers to various existing organizations. In either option, we recommend leveraging existing organizations, especially their well-established expert committees.

Option 1: One organization to govern **GUARD** as a whole

If **GUARD** were to be managed by one organization, the following entities would have to be established for coherent program management:

- **Strategic Board**: The board sets the strategic direction for all levers and determines fundraising targets. It ideally consists of health policymakers from a wide range of countries, representatives of the World Health Organization, and leading experts in the field of antibiotics research and development.

- **Permanent Management Office**: This body is responsible for the day-to-day operational management of various aspects of **GUARD**.
  - Application and review processes, convention of expert committees
  - Controlling (e.g., monitoring antibiotic pipelines and progress against Target Product Profiles)
  - Conferences and exchange programs
  - **GUARD** publications
  - Target Product Profile review process and update cycle
  - Delivery of contracts, payments, and repayments for each lever

The management office should also oversee stewardship efforts by the recipients of the Global Launch Reward in all relevant markets. This body needs an estimated five to ten full-time staff members with expertise in finance and program management.

- **Scientific Committee**: The Scientific Committee is convened by the Permanent Management Office and has two principal tasks. First, it determines the need for changes to the Target Product Profile system and manages the review process scientifically. Second, it steers the Global Research Fund project portfolio by selecting and reviewing project and infrastructure proposals in accordance with the scope for basic research funding and Target Product Profiles. Furthermore, it advises the **GUARD** Strategic Board on research goals and fundraising targets. The Scientific Committee must be a multistakeholder group with extensive scientific, clinical, policy and—importantly—drug development expertise. It should consist of ~15-20 global experts.

- **Investment Committee**: This committee is also convened by the Permanent Management Office. Its principal task is to select and review Global Development Fund projects in accordance with Target Product Profiles and to advise the **GUARD** Strategic Board on development goals and fundraising targets. This committee consists of ~15-20 renowned global drug developers and investment experts.

- **Launch Reward Committee**: This committee evaluates requests for a Global Launch Reward contract based on scientific and economic criteria. It should consist of individuals with expert drug development and regulatory know-how.

Option 2: Modular, independent management of all levers

The structure described above is not indispensable to putting **GUARD** into action. All levers could be managed separately by independent organizations already engaged in similar work. There is a range of suitable organizations with a proven track record in antibiotics and adjacent fields. For instance, the work on antibiotics Target Product Profiles led by the Global Antibiotic Research and Development Partnership (GARD-P) could be expanded to manage a system as proposed in this report. Various funding mechanisms have effective application processes and selection committees in place.

However, we believe that one organization in charge of all four levers would be the most desirable setup for several reasons.

- **Efficiency**: There is a number of interdependencies between the levers, which require coordination (e.g., the relay of pipeline information between Target Product Profile system management and institutions or companies with promising candidates), which is easier to do within one organization than between organizations.

- **Effectiveness**: The more funding can be administered within one system of targets, the more effectively the funds can be put to use toward urgent clinical needs.

- **Expertise**: A pooling of knowledge and experience on all stages of the value chain would help close the translational gap and create more critical mass in antibiotics research and development. An integrated **GUARD** facility would be ideally positioned to achieve this, acting as a strong voice for one of the key ways to tackle antimicrobial resistance.

8.2. The case for investment: Benefits of GUARD will far exceed cost

Payments associated with the Global Research Fund and the Global Development Fund will amount to ~$150 million in the year and ~$400 million in steady state after four years. Target Product Profiles, which are prerequisites for funding applications and grants, will have to be developed fully before clinical development can be funded. Basic research infrastructure and project applications could be received earlier. One Global Launch Reward would add another ~$200 million per annum after at least four years of ramp-up. In contrast to the expenses associated with other levers, however, it is not possible to predict exactly how many Global Launch Rewards will be paid out.

The funding need for **GUARD** is therefore substantial, but it is relatively small in comparison with the direct and indirect costs associated with antibiotic resistance and current research funding in other medical fields. Moreover, effective antibiotics are a humanitarian cause: Multiresistant infections not only incur economic cost, but also cause personal tragedies to thousands, if not millions of individuals.

Antimicrobial resistance is an increasing financial burden for global health systems

Antimicrobial resistance is a burden on health-care systems globally and poses a particular threat to vulnerable communities. The full cost of the problem cannot be estimated with certainty due to a lack of valid data, but sample figures show the magnitude of the issue, and we can safely say that the economic cost of the lack of effective antibiotics dwarfs the investment needed to reinvigorate the development pipeline.

In India, an estimated 58,000 neonatal sepsis deaths are caused by drug-resistant infections annually.[1] In the United States alone, "antibiotic resistance is responsible for more than 2 million infections and 23,000 deaths each year (…), at a direct cost of $20 billion and additional productivity losses of $35 billion."[2] In November 2016, Reuters investigated a showcase of the "terrible human and financial price" of an "epidemic raging through the U.S. health care system": sepsis after a successful transplant cost one life, two donated organs and $5.7 million in healthcare costs.[3] Another example is MRSA: An infection is estimated to cause additional costs of €5,000–10,000 per patient for hospital treatment alone.[4] In Germany, an estimated 11,000 patients are infected with MRSA every year,[5] producing a burden of up to €100 million for German hospitals alone.

While many of the costs of on AMR are disputed,[6] and the numbers cited above mainly reflect the problem in developed economies, the global cost of antimicrobial resistance is easily more than several billion dollars every year. Proper stewardship and prevention can go a long way toward cutting that cost. But the damage done by decades of imprudent use remains: We still urgently need new antibiotics, and investment in research and development would still be worth it from a purely economic point of view.

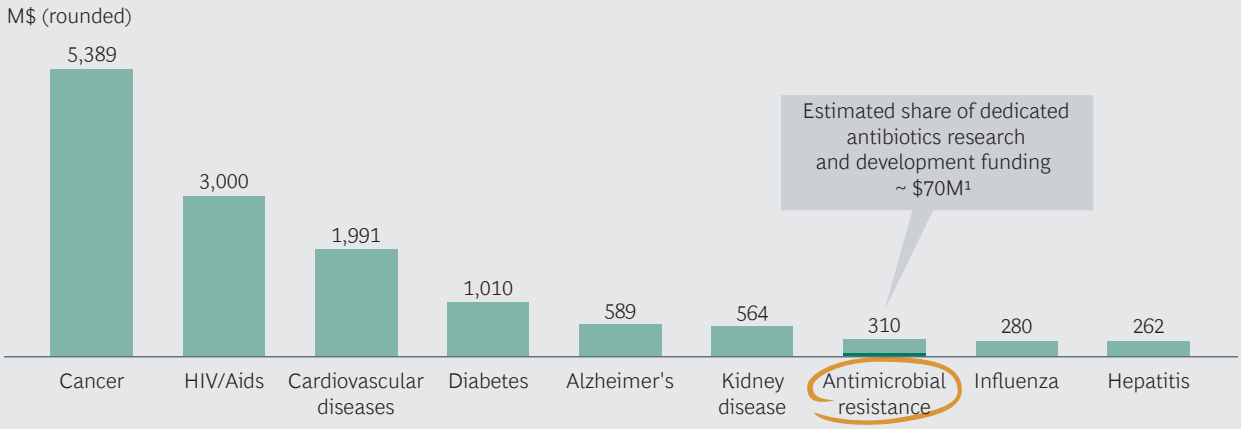
[1] Laxminarayan et al., 2013
[2] Centers for Disease Control and Prevention (CDC), 2013
[3] Abutaleb et al., November 2016
[4] Korczak and Schöffmann, 2010
[5] Gastmeier, April 2015
[6] McNeill, Reuters, September 2016

Antimicrobial resistance research funding is relatively small

Not only is the financing need for **GUARD** small compared with the costs of antibiotic resistance, but research funding for antibiotics is still low in comparison with other medical fields. The distribution of United States National Institutes of Health (NIH) funding illustrates this. In 2015, funding for cancer research was almost twenty times higher than funding for antimicrobial resistance (see figure 19). This may not be surprising, as cancer is one of the leading causes of death in the United States and Europe. However, even though the AMR death toll today is nowhere near cancer or heart disease, it has the innate potential to explode in the case of a multiresistant epidemic, and it is the only public health concern that threatens to disrupt the foundations of modern medicine. Providing the financial means to implement **GUARD** could relieve global health care systems of the increasingly high (and potentially exponential) costs of antimicrobial resistance.

FIGURE 19 | Public funding for antimicrobial resistance small compared to other medical fields

United States National Institutes of Health funding in financial year 2015



¹Estimated share of dedicated antibiotics research and development funding in 2015 based on project list of total AMR funding.
Source: National Institutes of Health Research Portfolio Online Reporting Tools (RePORT)

Potential sources of funding

In our view, **GUARD** should be publically funded to a substantial extent, in order to avoid conflicts of interest and ensure a strict focus on global public health needs rather than commercial priorities. However, as described above, academia and industry will need to take responsibility and show commitment.

Also, funding from philanthropic foundations should be welcomed. Direct funding from the pharmaceutical industry should, if at all, only be accepted under the condition that it is not directly allocated to projects, but to **GUARD** as a whole. This is to avoid situations in which organizations other than **GUARD** and the researcher/developer have a claim to a scientific or clinical outcome.

In contrast to the Global Research Fund and the Global Development Fund, the Global Launch Reward is somewhat uncharted territory, both in terms of quality and magnitude. Commitments to potential expenditures of $1 billion per high-need antibiotic can only

be shouldered by a large public coalition of funders, not by individual states, let alone private actors. Clear contractual agreements on fair global access and pricing of high-need antibiotics are paramount for the success of such a coalition.

8.3. A swift scale-up: High-level implementation roadmap

GUARD levers will have to follow distinct ramp-up and funding paths over the initial ten years of program activity (see figure 20). We suggest an initial ten-year period because it might take a decade to reinvigorate the value chain in such a way that the rate of innovation returns to a stable and sufficient level. Given the nature of clinical development timelines, we recommend continuous monitoring and strategic reviews of **GUARD**'s effectiveness every two years to allow for required improvements. After ten years, a final review should decide whether or not **GUARD** should be continued.

Implementation of this roadmap and realization of the **GUARD** mission require concerted action, which could be facilitated by a coalition of international country champions.

Timeline for implementation of the **GUARD** levers

All four levers will follow individual implementation schedules.

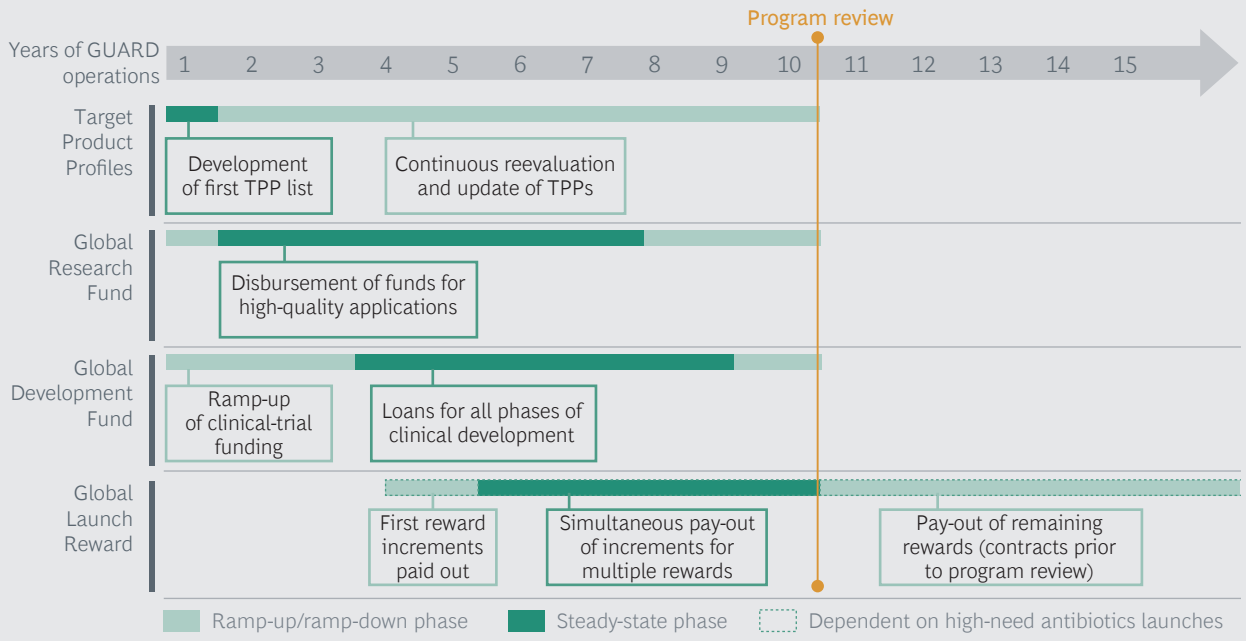
- Work on **Target Product Profiles** should begin as soon as possible and leverage existing work (e.g., GARD-P). We expect around six months to one year of dedicated work by a Scientific Committee to be able to produce an initial set of Target Product Profiles. The finalization of the first set of Target Product Profiles could mark the start of **GUARD** as a global facility.

- The **Global Research Fund** should start accepting applications immediately at the inception of **GUARD** and run for ten years, at least until 250 permanent new researcher positions have been created.

- The **Global Development Fund** should start accepting applications once Target Product Profiles have been defined. We recommend that the initial focus be on phase 1 and 2 projects. The fund could then grow into later phases, potentially supporting candidates throughout the entire development process.

- The **Global Launch Reward** is the least predictable lever in terms of timing. It will probably not be paid out for at least five years after the start of **GUARD**.
  After that, if efforts earlier in the value chain are successful, multiple rewards might be paid out simultaneously.

FIGURE 20 | The GUARD model over time



Source: BCG

A coalition of country champions needed for implementation

The implementation of the roadmap described above will be possible only with effective international cooperation. Most research on antibiotics is conducted in developed countries, but the problem of antimicrobial resistance is a global one and of importance for virtually every health system. To properly address this problem, a coalition of pioneers or country champions is needed. Promising initiatives have already been started, especially by countries that have developed and initiated national action plans on antimicrobial resistance in accordance with the WHO Global Action Plan on Antimicrobial Resistance.

We encourage these countries to continue their leading role in the fight against anti-microbial resistance.

The international community will now have to decide how to organize its fight against antibiotic resistance—starting with a debate about which of the levers described in this report to implement.

8.4. Controlling: Monitoring progress and ensuring transparency

Generally, **GUARD**'s success should be measured against the long-term goal of one additional high-need antibiotic launch per year. However, it will take years to achieve such a high level of pipeline productivity. Thus, it is essential to define performance indicators for intermediate progress.

8.4.1. Continuous controlling of performance indicators for each lever

For all levers, it is important to assess both activity (e.g., the number of grants, loans paid out) and performance of projects funded (e.g., number of new PhD positions created, number of high-need antibiotics launched). For each lever, specific performance indicators should be considered.

Controlling Target Product Profiles

Target Product Profiles (and to a lesser extent the scope for basic research funding) will have to be reviewed regularly. Clinical needs change when new resistance patterns develop or when new high-need antibiotics enter the market. By implication, Target Product Profiles must be adapted when such changes occur.

Once a first set of Target Product Profiles is published, **GUARD** must begin to monitor not only the activity of its own programs, but the entire global antibiotics pipeline in order to be able to manage a review process for Target Product Profiles. Generally, the more mature the project, the better the publically available data. In order to maintain a thorough understanding of the antibiotics pipeline in all phases, **GUARD** must be well connected in the antibiotics research and development community.

As for changing clinical needs, **GUARD** should seek close cooperation with relevant global bodies, such as the Global Antimicrobial Resistance Surveillance System (GLASS) that is currently being built by the World Health Organization.

Moreover, **GUARD** should seek to continuously improve the standard of Target Product Profiles by reviewing their practicality and scientific usefulness in the eyes of clinical development professionals.

Controlling the Global Research Fund

In the early stages of the Global Research Fund, the following activities should be monitored closely to assess its acceptance as a valuable funding source by the research community:

- Number of applications for infrastructure and project grants
- Number of projects funded
- Share of allocated annual budget disbursed

Once the first **GUARD** infrastructure and research projects have begun, additional *performance* indicators should be monitored, including:

- Total size of the research community (i.e., number of active specialists in the field)
- Number of PhD, postdoctoral, and senior researcher positions created
- Number of publications on key challenges in antibiotics
- Number of successful **GUARD** preclinical candidates

Controlling the Global Development Fund

In the first few years, controlling efforts for the Global Development Fund will naturally be focused mainly on activity parameters, since output will require multiple years to materialize. These activity parameters could include the following:

- Number of high-quality applications
- Number of projects funded
- Share of allocated annual budget disbursed

- Private sector funding leveraged (see chapter 6.2.2.)
- Financial returns

A note on financial returns: **GUARD** should, of course, monitor the recoupment of funds from the Global Development Fund or the Global Launch Reward, as they can help lower the financial burden of **GUARD** on public budgets. However, such paybacks are not an indication of program success. **GUARD** should not seek to maximize returns.

As soon as clinical trials are completed, controlling efforts should also focus on the following *performance* parameters:

- **Market launches**: The success of **GUARD** will ultimately be measured by the number of high-need antibiotics.

- **Success rates**: **GUARD** should monitor and evaluate the success rates of the development phases it funds. The current success rates for antibiotics in development can serve as a benchmark.

- **Duration of trials**: **GUARD** should also measure the required durations for each trial phase and compare them to benchmarks. However, shorter trials are not to be equated with success. The duration of a clinical trial depends on a variety of factors, such as scientific challenges and financial stability/resource commitments. **GUARD** can only have a positive influence on the latter.

The Global Launch Reward

The $1 billion launch reward will, of course, require precise accounting in addition to continuous performance monitoring. Nevertheless, a number of performance indicators must be accounted for regularly.

- **Global access to high-need antibiotics that receive the Global Launch Reward**: The payout of the Global Launch Reward is conditional upon access in agreed-upon markets. **GUARD** should monitor whether these conditions are met after launch.

- **Pricing commitments**: **GUARD** should monitor the price differentiation commitments agreed upon with the recipient of the reward, ideally in cooperation with the Global Antimicrobial Resistance Surveillance System initiated by the World Health Organization. Payments to reward recipients may be adjusted based on stewardship compliance.

- **Number of reward contracts and candidate status**: **GUARD** should track the likely coverage of Target Product Profiles with new reward commitments and compounds in development. If a bias toward a particular Target Product Profile emerges, priorities may need to be readjusted.

Moreover, **GUARD** should cooperate closely with reward recipients to make sure that operating profits are accurately reported and shared.

8.4.2. Strategic reviews every two years create transparency

In addition to regular monitoring efforts, biennial strategic reviews should evaluate overall progress and impact of the initiative and, if necessary, help adjust strategic priorities. This review includes a thorough evaluation of the **GUARD** project portfolio, and also an evaluation of the broader antibiotic pipeline. Launches of high-need antibiotics may also occur outside **GUARD**, but still lead to a shift in research and development priorities.

The results of these strategic reviews should be published. The more transparent the initiative, the stronger the stimulus for debate about progress made and next steps in the entire antibiotics research and development community. At full capacity, **GUARD** could serve as a catalyst in the antibiotics research and development community, driving research and development efforts toward global clinical and public health needs.

9. CONCLUSION AND WAY FORWARD: A CONTRIBUTION TO POLICY DEBATE IN 2017

The international debate on antimicrobial resistance has gained significant momentum over the last few years. There is consensus among a variety of stakeholders that broad, concerted international action is necessary to make sure that the most urgently needed new antibiotic treatments are developed. The German initiative for a Global Union for Antibiotics Research and Development (**GUARD**) can serve as a starting point for policy discourse in 2017. In essence, **GUARD** proposes a way to use the current momentum by defining clear goals and additional funding mechanisms to turn the tide in antibiotics research and development.

GUARD: Stimulating the whole value chain from basic research to commercialization

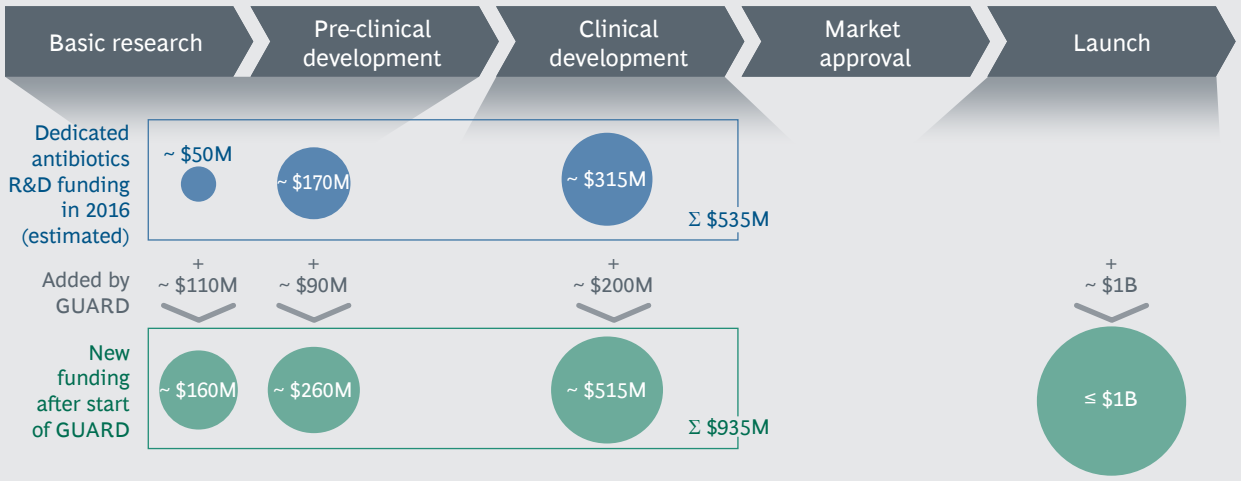
In this report, we propose a comprehensive global program to reinvigorate the whole antibiotics value chain. **GUARD** aims to double targeted international funding for all stages of discovery and development. Four specific levers are proposed.

- **Target Product Profiles and scope for basic research funding**: A systematic approach to defining the most urgently needed antibiotics and the most pressing scientific problems in order to direct funding to where clinical need is greatest
- **A Global Research Fund**: Significant investment in antibiotics research infrastructure and grants for the most important projects in basic research and preclinical development ($200 million per annum for ten years)
- **A Global Development Fund**: Forgivable loans to help drug developers fund all phases of clinical development ($200 million per annum for ten years)
- **A Global Launch Reward**: A $1 billion pull mechanism with an insurance function to make high-need antibiotics a more attractive commercial proposition

The ideas described in this report can be implemented as a whole, with one organization managing **GUARD** at every step of the value chain, or as independent initiatives managed by separate organizations, in each case leveraging suitable existing structures.

2017 will be a year of important international policy discussions about pressing issues in global health, including antibiotics research and development. A value chain transformation of the scale proposed here will not be implemented overnight, but we hope that on the basis of this report, stakeholders can begin a focused discussion on where and how to start. We believe that the formation of a group of "country champions" is the most promising way forward.

FIGURE 21 | Effect of GUARD: Global Research Fund and Global Development Fund will double dedicated annual antibiotics R&D push funding



Source: BCG analysis

Further national efforts are needed to achieve results

A number of national action plans on antimicrobial resistance have already been proposed and implemented in the last few years. Norway may soon start to test national delinkage models for new and existing antibiotics; a similar model is being discussed in the United Kingdom. These national efforts should be continued and intensified. The antibiotics research and development issue cannot be solved without dedicated action on the national level.

Existing global initiatives as a basis for continued action

Several bilateral and multilateral initiatives are already taking steps to stimulate the antibiotics value chain. The Global Antibiotic Research and Development Partnership (GARD-P), launched by the World Health Organization (WHO) and the Drugs for Neglected Diseases initiative (DNDi) is working toward four development partnership projects by the end of 2017.[1] We encourage the continuation of these efforts. **GUARD** aims to complement and strengthen these initiatives by providing a global framework of Target Product Profiles, coordinating mechanisms, and additional, targeted funding.

In conclusion, we are cautiously optimistic that a significant transformation of the antibiotics value chain and the discovery of innovative high-need antibiotics can be achieved over the course of a decade. However, surveillance, prevention, One Health approaches and stewardship are as important in the fight against antimicrobial resistance, and fair access to existing antibiotics must not be neglected as a public health concern in the quest for novel antibiotics. Each aspect is a necessary but not a sufficient condition for success. What matters most in 2017 is for a broad coalition of actors to agree on tangible next steps.

[1] DNDi website (accessed December 2016)

10. APPENDIX: SCIENTIFIC BACKGROUND ON RESISTANCE MECHANISMS AND MODES OF ACTION

Billions of years before antimicrobials were discovered as drugs, bacteria and fungi were already producing antimicrobials. These include antibacterial, antifungal, antiviral and antiparasitic substances. Antimicrobial resistance can be likened to a permanent tug-of-war between microorganisms. Since the beginning of broad antibiotic use of in the 1940s, many pathogens causing disease in the human body have, therefore, developed mechanisms to resist antibiotics (antibacterial substances in the form of drugs).

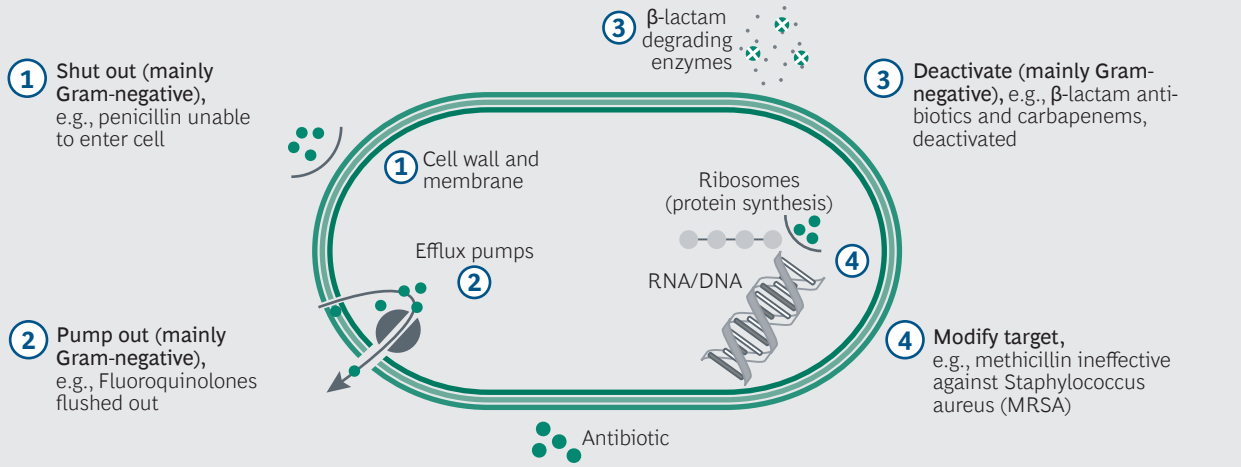
Gram-negative bacteria, a newer species from an evolutionary perspective, are generally faster and more effective at defending themselves due to their more sophisticated cell structure, which includes an additional outer cell membrane. Their name comes from a special technique to differentiate bacteria developed by Christian Gram in 1884. Gram-positive bacteria retain a violet color that does not attach to the additional cell membrane of Gram-negative bacteria.

Four types of resistance mechanisms

All bacteria are endowed by nature with the ability to generate and fixate mutations and to exchange genetic information across populations. Over millennia, four distinct mechanisms of resistance have developed. Gram-negative bacteria are particularly effective at employing the first three, but all resistance mechanism can occur in both types of bacteria (unfortunately, also in various combinations at the same time).

Bacteria can shut out entry of any antibiotic by making cell walls impermeable. Alternatively, they can pump out any substance damaging to the cell through a mechanism called efflux. Many pathogens, moreover, have the ability to deactivate antibiotics with enzymes before they can enter the cell. A fourth and final mechanism is to modify binding sites within the cell through mutation in such a way that the antibiotic cannot initiate its intended mode of action.

FIGURE 22 | Resistance mechanisms: Four modes of bacterial self-defense



Examples of antibiotics classes affected by mechanism of resistance

Source: BCG; expert interviews

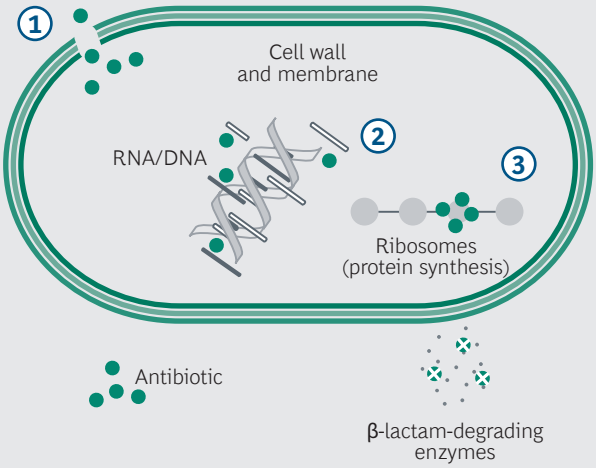
The drugs: How antibiotics work

Antibiotics kill or stall the growth of bacterial cells by interfering with either one or more of the following mechanisms: cell wall and membrane integrity as well as bacterial synthesis of DNA/RNA and protein. Bactericidal drugs effectively kill bacteria, e.g., through lysis, while bacteriostatic drugs merely stall their growth. Both mechanisms are drug concentration dependent and principally equipped with clinical efficacy.

Generally speaking, most antibiotics still work. For example, E. coli or salmonella infections (both Gram-negative) are successfully treated with antibiotics every day. It would be incorrect to state that antibiotics are generally less effective against Gram-negative bacteria. Rather, Gram-negative strains have put up a more effective defense against previously highly effective antibiotics.

In the literature around antimicrobial resistance, the keywords "β-lactam antibiotics", "carbapenem", and "colistin" are mentioned frequently in the context of Gram-negative resistance. Together, they illustrate the logic of resistance development. All of these antibiotics perforate the cell envelope (wall or membrane) of many Gram-negative and Gram-positive bacteria (through various modes of action). The first widely used β-lactam antibiotic, penicillin, was highly effective until resistance to it proliferated. Cephalosporins and carbapenems were developed later and faced little resistance for a long time. Today, in an increasing number of cases, cephalosporins and carbapenems are failing. Forcibly, an old, antibiotic with side-effects, colistin, has to be resorted to, the current antibiotic of last resort for multidrug resistant Gram-negative infections. Fortunately, resistance to colistin is still rare, but it does exist and spread.

FIGURE 23 | Principles of action: Three ways to kill/stall bacteria



1 Perforate cell envelope (almost half of all antibiotics used)
- β-lactam antibiotics (e.g., carbapenems, penicillins, cephalosporins, monobactams)
- Glycopeptides (Gram-positive only, e.g., Vancomycin)
- Polymyxins (Gram-negative only, e.g., Colistin)

AB-degrading enzyme inhibitors often used in combination

2 Inhibit RNA/DNA processes
- Quinolones ("-oxacins")
- Nitroimidazoles (e.g., metronidazole)

Greatest Gram-negative resistance concerns

3 Inhibit protein synthesis
- Tetracyclines (both Gram-negative and Gram-positive)
- Macrolides (mostly Gram-positive, e.g., Clarithromycin)

Source: BCG; expert interviews

Innovation in antibiotics research and development

Various classes of antibiotics have been improved over time. For instance, there are several generations of cephalosporins, each with different general and resistance-breaking properties, but the rate of incremental innovation has slowed. While some existing classes may still be further improved, the key challenge today is to find a new, unexhausted mode of action, and thus new classes of antibiotics that are effective against Gram-negative bacteria. There has been no such step-change against Gram-negative pathogens in decades.

Key institutions and initiatives

The following paragraphs are based on the official websites of key AMR-related institutions and initiatives.

Antimicrobial Resistance Centre

The Antimicrobial Resistance Centre is a research center at the London School of Hygiene & Tropical Medicine (LSHTM) in the United Kingdom. It was launched in December 2016. The LSHTM includes a wide range of disciplines, from microbiology and clinical medicine to social studies and economics. The school's Antimicrobial Resistance Centre will foster connections among these different scientific approaches in order to facilitate high-quality research on AMR. Furthermore, it aims to facilitate AMR-related international collaboration as well as to provide educational materials on AMR.

http://amr.lshtm.ac.uk/

AMR Centre

The AMR Centre is a public-private partnership for research and development. Its mission is to support the development of new antibiotics and diagnostics through a fully integrated development capability based at Alderley Park, a life sciences center in the United Kingdom. It was established in 2016 and is part of the CARB-X consortium.

http://amrcentre.com/

BARDA

Biomedical Advanced Research and Development Authority (BARDA) is part of the U.S. Department of Health and Human Services. Its mission is to support the development and procurement of drugs, vaccines, and other products that are priorities for national health security. BARDA's Broad Spectrum Antimicrobials (BSA) Program uses public-private partnerships to incentivize research and development of novel antimicrobial drug candidates, e.g., with GlaxoSmithKline (GSK), AstraZeneca, The Medicines Company, and Hoffmann-La Roche. The BSA Program's total budget was ~$192 million in the 2016 financial year, of which ~$30 million went to CARB-X in 2016.

https://www.medicalcountermeasures.gov/barda.aspx

CARB-X

The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) was launched in 2016 to fund preclinical development projects. CARB-X is a consortium composed of the National Institute of Allergy and Infectious Diseases (NIAID) and BARDA, the Wellcome Trust (a charitable organization based in the United Kingdom), the California Life Sciences Institute, the Massachusetts Biotechnology Council, and the AMR Centre. Boston University is the home of CARB-X. It will coordinate funding of ~$350 million over five years. In the first year, the CARB-X portfolio will primarily focus on therapeutics to treat infections caused by Gram-negative bacteria.

http://www.carb-x.org/

DND*i*

The Drugs for Neglected Diseases *initiative* (DNDi) is a nonprofit drug research and development organization. It was founded in 2003 and supports the development of new drugs, new formulations of existing drugs, diagnostics and vaccines to combat neglected diseases. By 2023, DNDi aims to deliver 16 to 18 new treatments with an estimated total budget of €650 million, and it has already raised ~€400 million (~61%) of that amount. DNDi receives funding from governments, institutions such as the Bill and Melinda Gates Foundation and Médecins Sans Frontières (MSF), private foundations, and private individual donors.

http://www.dndi.org/

DRIVE-AB

Driving reinvestment in research and development and responsible antibiotic use (DRIVE-AB) is a project managed by public and private partners from 12 countries. It was launched in 2014 and is part of the New Drugs for Bad Bugs program (see below) funded by the Innovative Medicines Initiative (see below). DRIVE-AB aims to produce an evidence-based, consensus definition of "responsible antibiotic use," with standardized quality and quantity indicators. Furthermore, it develops economic models to incentivize the discovery and development of new antibiotics. It has a total budget of ~€11 million for 2014–2017.

http://drive-ab.eu/

EDCTP

The European & Developing Countries Clinical Trials Partnership (EDCTP) is a public-public partnership among countries in Europe, countries in sub-Saharan Africa, and the European Commission. It was created in 2003. EDCTP aims to accelerate the development of new or improved drugs, vaccines, microbicides, and diagnostics to fight HIV/AIDS, tuberculosis, and malaria, as well as other poverty-related infectious diseases. EDCTP focuses on phase II and III clinical trials. EDCTP is cofunded by the European Union via Horizon 2020. For the period 2014–2024 the European Union will contribute up to €683 million, provided the funding is matched by contributions from the European participating states.

http://www.edctp.org/

FIND

The Foundation for Innovative New Diagnostics (FIND) is a global nonprofit organization and a product development partnership (PDP) focused on diagnostics. Its mission is to accelerate the development, evaluation, and delivery of high-quality, affordable diagnostic tests for poverty-related diseases in low- and middle-income countries. According to its 2014 Annual Report, FIND had grant revenue of ~$31 million in 2014. FIND receives funding from governments, international organizations, foundations, and private donors.

http://www.finddx.org/

GAMRIF

The Global Antimicrobial Resistance Research Innovation Fund (GAMRIF) is a fund initiated by the United Kingdom and China. It is likely to be launched in 2017. GAMRIF seeks to invest in high-quality research and development to stimulate innovation against antimicrobial resistance and to encourage further investment by other governments and the private sector. It will invest ~£50 million over five years.

https://www.gov.uk/government/news/uk-and-china-start-global-fund-to-tackle-drug-resistant-infections

GARD-P

The Global Antibiotic Research and Development Partnership (GARD-P) is a joint initiative of the World Health Organization (WHO) and the Drugs for Neglected Diseases initiative (DNDi). It was launched in 2016 and seeks to develop into a global facility supporting the development of new antibiotic treatments and promoting their responsible use while ensuring equitable access for all in need. By the end of 2017, GARD-P seeks to have established an organizational structure and set out its long-term strategy and roadmap. It aims to have four projects that address urgent global health needs ready for implementation by the end of 2017. GARD-P has secured seed funding commitments from Germany, the Netherlands, South Africa, the United Kingdom, and Médecins Sans Frontières, totaling over €2 million of the projected €3 million required for the incubation phase.

http://www.dndi.org/diseases-projects/gardp/

The Global Fund

The Global Fund Against AIDS, Tuberculosis and Malaria is a partnership organization among governments, civil society, and the private sector. It was founded in 2002 to help governments around the world finance initiatives against HIV/AIDS, tuberculosis, and malaria. In 2016, the Global Fund Fifth Replenishment Conference took place and secured pledges of financing for the 2017–2019 period. Of the total $12.9 billion raised at the conference, $12 billion was pledged by donor governments.

http://www.theglobalfund.org/en/

GLASS

The Global Antimicrobial Resistance Surveillance System (GLASS) is an initiative of the World Health Organization (WHO). It was started in 2015. GLASS aims to facilitate and encourage a standardized approach to AMR surveillance globally. Currently GLASS collects and reports data on AMR rates aggregated at the national level. The system will make it possible to obtain comparable and validated AMR data. GLASS will also collect data on the implementation status of national surveillance systems.

http://www.who.int/drugresistance/surveillance/glass-enrolment/en/

GUARD

The Global Union for Antibiotics Research and Development (GUARD) is an initiative introduced by the German Federal Ministry of Health. It has not yet been launched, but potential program elements are described in this report. Its mission is to spur innovation in antibiotics research and development along the entire antibiotics value chain.

IMI

The Innovative Medicines Initiative (IMI) is a public-private partnership between the European Union and the European Pharmaceutical Industry Association (EFPIA). It was launched in 2008. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. For the period of 2014–2024, it has a budget of €3.3 billion. Half of the budget comes from the European Union's Horizon 2020 program. One of the programs IMI supports is the New Drugs for Bad Bugs program (ND4BB).

https://www.imi.europa.eu/

InnovFin Infectious Diseases

InnovFin Infectious Diseases is a financing instrument within the European Investment Bank's and European Commission's broader "InnovFin—EU Finance for Innovators" program. InnovFin Infectious Diseases was launched in 2015. It provides funding for the development of vaccines, drugs, and medical and diagnostic devices to combat infectious diseases. Its focus is on projects that have completed the preclinical stage. According to a paper published by David M. Brogan and Elias Mossialos in 2016, initial estimates of InnovFin Infectious Diseases' budget "suggest that up to €300 million may be spread across a total of 9–12 projects."

http://www.eib.org/attachments/documents/innovfin_infectious_diseases_flysheet_en.pdf

JPIAMR

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) is an international initiative to coordinate national funding on antimicrobial resistance. It currently has 22 member states. Its mission is to coordinate national research activities and to facilitate collaboration on AMR research. The third JPIAMR call, launched in 2016, has awarded~€28 million to 19 research projects on AMR transmission mechanisms.

http://www.jpiamr.eu/

MMV

The Medicines for Malaria Venture (MMV) is a product development partnership (PDP) for antimalarial drugs. It was founded in 1999. MMV supports the discovery, development and delivery of new, effective, and affordable antimalarial drugs. MMV receives funding from government agencies, private foundations, international organizations, corporations, corporate foundations, and private individuals. According to its annual report for 2015, MMV had income of ~$87 million in 2015.

http://www.mmv.org/

ND4BB

The New Drugs for Bad Bugs Program (ND4BB) is a partnership among industry, science, and biotech organizations to combat antibiotic resistance in Europe. It is funded by the Innovative Medicines Initiative (IMI). ND4BB has seven subprograms, focusing on scientific, regulatory, and business challenges to antibiotic development. These programs are TRANSLOCATION (identifying new ways of getting potential antibiotics into bacteria), ENABLE (a drug-discovery platform for antibiotics), COMBACTE (facilitating

pan-European clinical collaboration), COMBACTE-CARE (focusing on carbapenem-resistant enterobacteriaceae infections), COMBACT-MAGNET (focusing on preventing and treating life-threatening infections caused by Gram-negative bacteria), iABC (focusing on inhaled antibacterials in bronchiectasis and cystic fibrosis), and DRIVE-AB (developing new economic models for antibiotic development). The programs have a combined budget of ~€700 million for the period 2013-2021 (the length of the different programs varies).

http://www.imi.europa.eu/content/nd4bb

TB Alliance

The TB Alliance is a not-for-profit organization and a product development partnership (PDP) dedicated to the discovery and development of tuberculosis drugs. It was founded in 2000. Its mission is the development of improved, faster-acting, and affordable tuberculosis drug regimens that are available to all. The TB Alliance manages a large pipeline of new TB drugs and has advanced multiple products to market. The TB Alliance receives funding from national development cooperation agencies and from individual donations.

https://www.tballiance.org/

The Brighton Collaboration Foundation

The Brighton Collaboration Foundation is an international nonprofit organization. It was founded in 1999. It is a global research network and aims to improve vaccine research by providing standardized, validated, and objective methods for monitoring vaccine safety profiles and benefit-to-risk ratios.

https://www.brightoncollaboration.org/public.html

Acknowledgements (experts interviewed for this report)

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