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im Gesundheitswesen

REPORT FOR THE GERMAN GUARD INITIATIVE

Breaking through the Wall

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

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EXECUTIVE SUMMARY

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

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

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

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

- **“Discovery void” in basic research**
Major scientific challenges, especially in understanding ways to fight gram-negative bacteria, in combination with a lack of funding and a brain drain of antibiotics researchers, lead to scarcity of promising innovations.
- **“Valley of death” in preclinical development**
The exit of numerous important players results in difficulties in translating scientific ideas into clinical successes. The reduced activity in this area is not compensated by new players entering the field.
- **High cost and difficult patient recruitment in clinical development**
While the clinical development of antibiotics is less expensive than that of many other therapeutic areas, developmental costs are still substantial (approximately €120 million) and are often prohibitive for small and medium-sized enterprises (SMEs). Additionally, recruiting patients for clinical trials is a challenge given the acute treatment setting and a lack of accessibility of potentially suitable patients for trials.
- **Insufficient alignment of regulatory requirements between leading regulatory agencies**
Remaining differences in regulatory approval requirements lead to additional cost and efforts for companies seeking market approval.
- **Low market attractiveness in commercialization**
Low revenue expectations driven by necessary stewardship efforts and low prices make investments in antibiotics commercially unattractive. The low commercial attractiveness trickles down the value chain, leading to limited activity across all phases of the value chain.

¹ WHO Report on Global Surveillance of Epidemic-Prone Infectious Diseases. World Health Organization. 2015.

² Figure includes drug-resistant HIV and drug-resistant malaria; Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. December 2014.

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

- **Lever 1: Target Product Profiles**
Develop global Target Product Profiles (TPPs) in order to steer research and development into the areas of the highest public health need and in order to have a globally accepted metric for the value of a new antibiotic. The Target Product Profiles will be based on the most urgent bacterial threats.
- **Lever 2: Global Antibiotics Research Fund**
Create a fund that supports basic research at academic institutions and small and medium-sized enterprises (SMEs). The priorities of the fund will be based on a strategic research agenda in-line with the Target Product Profiles. Priorities of the fund could be research into gram-negative bacteria and point-of-care diagnostics.
- **Lever 3: Global Antibiotics Research Prize**
Establish an annual prize rewarding scientific advancements in antibacterial research in order to increase the attractiveness of the research area and awareness for certain research challenges.
- **Lever 4: Antibiotics Research and Development Database**
Implement a database of past and ongoing research projects that allows researchers to identify promising research approaches and avoid duplicating research efforts.
- **Lever 5: Global Antibiotics Expert Network**
Set up a network of global antibiotics experts that supports ongoing research and development projects, especially those supported by the Global Antibiotics Research Fund and the partnerships in clinical development.
- **Lever 6: Partnerships in Clinical Development**
Establish partnerships in clinical development in order to support research institutions and small and medium-sized enterprises in advancing the clinical development of promising antibiotic candidates. Partnerships in clinical development include financial support as well as in-kind support (e.g., access to experts and laboratories).
- **Lever 7: Global Antibiotics Trial Platform**
Connect hospitals and developers through a global platform of antibiotics trials and patients that allows matching suitable patients to ongoing antibiotics clinical trials.
- **Lever 8: Global Alignment of Regulatory Approval Processes**
Continue the alignment of regulatory approval processes for antibiotics, ultimately leading to a unified global regulatory pathway for antibiotics.
- **Lever 9: Market Entry Reward for Innovative Antibiotics**
Introduce a market entry reward for innovative antibiotics that meets the Target Product Profiles. The market entry reward has to be significant (i.e., in the order of €1,000 million) and will provide a reliable and predictable source of income that is delinked from sales volumes, thereby increasing the commercial attractiveness of antibiotics research and development.
- **Lever 10: Reimbursement for Innovative Antibiotics in Hospitals**
Ensure adequate reimbursement levels for innovative antibiotics, especially in a hospital setting.

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

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

OBJECTIVES OF THIS REPORT

Growing resistance to antibiotics and a dramatic loss of research and development (R&D) resources and capabilities present a severe public health challenge.

The German Federal Ministry of Health commissioned an advisory consortium consisting of ÖPP Deutschland AG (Partnerships Germany), The Boston Consulting Group, and the Healthcare Management Department of Berlin University of Technology to prepare a report that analyzes the reasons that have led to the decline in antibiotics R&D and proposes sustainable levers to improve the current situation.

This report focuses on a single component of the challenge – the lack of new antibiotics being brought to market. We acknowledge that a successful response to the challenge will also need to address inappropriate use that leads to premature resistance as well as global access to antibiotics. The report supports the German Global Union for Antibiotics Research and Development (GUARD) initiative.

ANTIBIOTIC RESISTANCE: A GLOBAL HUMANITARIAN CHALLENGE

In 1967, it was thought that humanity could “declare the war against pestilence won”³. Today, we know that this was a misconception. Estimates of the current global death toll caused by antimicrobial resistance vary, but figures of up to 700,000 annually⁴ have been put forward. Forecasts estimate that this number will grow substantially over the coming decades⁵. In addition, antibiotic resistance threatens the effectiveness of medical procedures that we have grown accustomed to and may in the worst case propel us into a “medical dark age”. Finally, increased mortality and morbidity are a severe humanitarian challenge and a significant social and economic burden on healthcare systems around the globe.

To provide effective treatment options, it is essential to develop a constant stream of new antibiotics in order to complement necessary stewardship efforts. However, only very few new treatment options have become available in recent years (figure 1) and approvals of new antibiotics have hit an all-time low.

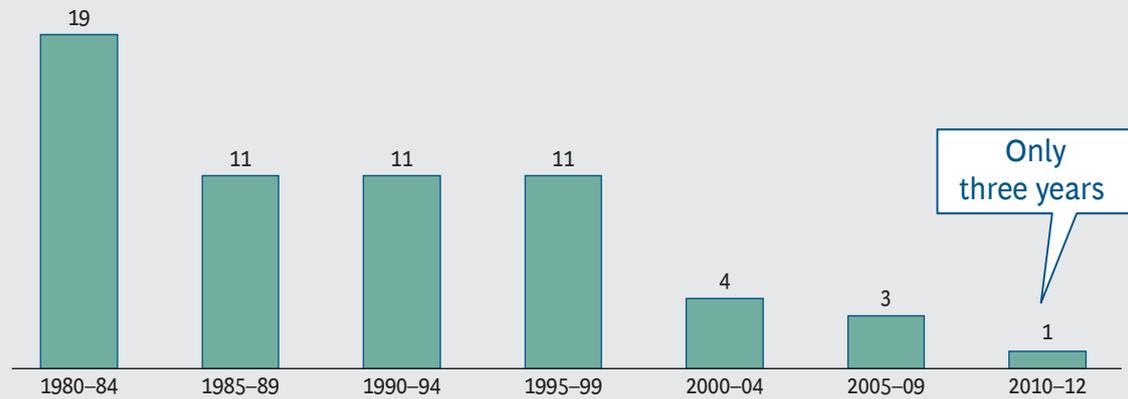
³ *Report on Global Surveillance of Epidemic-prone Infectious Diseases Introduction*. World Health Organization. 2015.

⁴ *Antimicrobial Resistance: Tackling a Crisis for the Future Health and Wealth of Nations*. The Review on Antimicrobial Resistance. December 2014.

⁵ *Securing New Drugs for Future Generations – the Pipeline of Antibiotics*. The Review on Antimicrobial Resistance. May 2015.

FIGURE 1 | Number of antibiotics being approved by the FDA is decreasing

FDA approvals of antibiotics NDAs
(new drug applications)

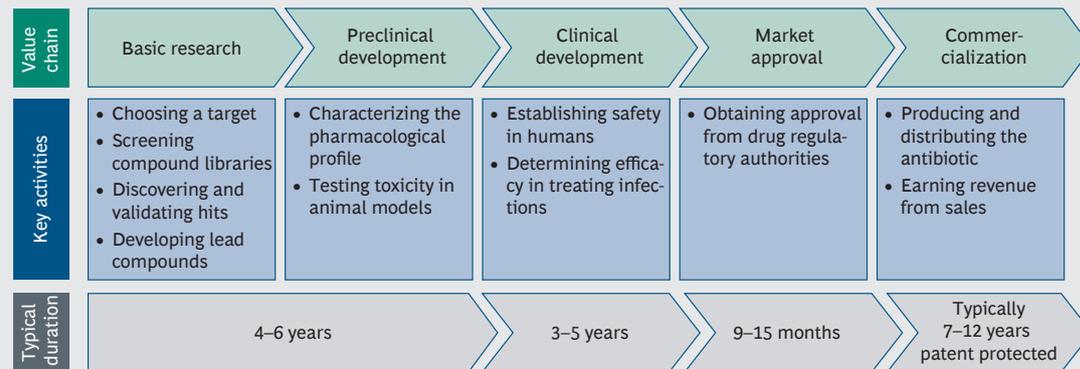


Source: *Antibiotic Resistance Threats in the United States 2013*. Centers for Disease Control and Prevention. 2013.

The main driver behind the decline in new antibiotic approvals is the exit of large parts of the pharmaceutical industry from antibiotics research and development (R&D). From around 20 pharmaceutical companies⁶ featuring large antibiotic R&D programs in the 1990s, only five of the top 50 pharmaceutical companies (ranked by sales) still remain active as of 2014^{7,8}.

While the impact of antibiotic resistance may still appear containable today, failure to address this challenge will lead to a serious and potentially uncontrollable global health threat – especially considering the approximately 10-year development period for a new antibiotic⁹.

FIGURE 2 | Overview of the antibiotics value chain



Source: BCG analysis

⁶ Roche returns to antibiotic research as superbug threat grows. Reuters. <http://www.reuters.com/article/2014/06/02/us-roche-antibiotics-idUSKBN0ED1G820140602> accessed 24 September 2015.

⁷ Tracking the Pipeline of Antibiotics in Development. Pew Trust. <http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2014/03/12/tracking-the-pipeline-of-antibiotics-in-development> accessed 24 September 2015.

⁸ Despite Superbug Crisis, Progress in Antibiotic Development 'Alarmingly Elusive'. IDSA. http://www.idsociety.org/2013_Antibiotic_Development/#sthash.2JhcOfpK.dpuf accessed 23 September 2015.

⁹ OECD Trade Policy Working Paper No. 113. Organization for Economic Co-operation and Development. 2011.

MAIN CHALLENGES IN ANTIBIOTICS RESEARCH AND DEVELOPMENT

The development and marketing of an antibiotic can be segmented into five successive phases along the development and commercialization value chain (figure 2). In each phase major challenges have been identified for public and private research and development. While challenges exist along the entire value chain for public and private players alike, the two major challenges are the low commercial attractiveness of antibiotics and a lack of promising leads in basic research. This combination is unique to antibiotics.

A high commercial attractiveness would at least create high activity and potentially compensate the other challenges, as we are currently seeing in the field of some cancer therapies and orphan diseases. In Alzheimer's disease, for example, the high commercial attractiveness leads to high pharmaceutical activity, despite basic research challenges preventing significant breakthroughs.

1. Challenges in Basic Research and Preclinical Development

Reduced investment in basic research by pharmaceutical companies has generated a “*discovery void*” in the field of antibiotics. This is exemplified by a decreasing number of patents from pharmaceutical companies. The number of patent families filed by the top five patent filers¹⁰ has fallen from over 40 patent families per year in 2001 to 10 in 2014¹¹. Academic institutions have not been able to fully compensate for this decline.

As a result of reduced research activity, there is a brain drain of researchers. Most active researchers are approaching retirement and there is a risk that critical expertise may be lost permanently. Multiple experts interviewed for this report estimate the number of specialized antibiotics researchers to have shrunk to only between 250 and 500 individuals worldwide.

The loss of expertise is exacerbated by the fact that antibiotics research is currently facing some serious scientific challenges. Especially gram-negative bacteria are a difficult target as their extra membrane prevents many antibiotics from entering the cell and killing it.

Even promising research approaches often disappear in what experts refer to as the “valley of death”. Due to a lack of investment for clinical development programs and a lack of exchange between academic research institutions and pharmaceutical and biotech companies that are able to drive clinical development, many ideas never make it into the clinical phase.

2. Challenges in Clinical Development

Compared to other drugs, antibiotics have relatively high success rates in clinical development. This is due to animal models being relatively reliable in antibiotics research, allowing antibiotics to “fail early” in development, thus reducing the costs of failure. Additionally, antibiotics trials are usually short in duration, which further reduces clinical development costs. Still, the clinical development of a single antibiotic candidate is an expensive endeavor that has been estimated to cost € ~ 120 million on average for each marketed antibiotic (not including the cost of failure)¹². Total development costs from basic research to commercialization – including the cost of failure for unsuccessful attempts and the cost of marketing – is estimated at €700–1,100 million.¹³

¹⁰Top five in order: Pfizer, GlaxoSmithKline, AstraZeneca, Kain Knight Group, Merck & Co.

¹¹BCG analysis based on Thomson Innovation database.

¹²Securing New Drugs for Future Generations – the Pipeline of Antibiotics. The Review on Antimicrobial Resistance; May 2015.

¹³Securing New Drugs for Future Generations: The Pipeline of Antibiotics. The Review on Antimicrobial Resistance. May 2015; The fallacies of hope: will we discover new antibiotics to combat pathogenic bacteria in time?. Vicente, Hodgson, Massidda. July 2006. Report to the President on Combating Antibiotic Resistance. Executive Office of the President of the United States. September 2014; Policies and Incentives for Promoting Innovation in Antibiotic Research. Mossialos, Morel, Edwards et al. 2010.

In addition to the financing challenge, clinical development of antibiotics is complicated by difficulties of recruiting patients into clinical trials. Given the acute treatment setting, the time window to identify patients and initiate treatment is very narrow and point-of-care diagnostic tools are lacking.

3. Challenges in Market Approval

A common challenge faced by drug developers across all therapeutic areas is that approval processes between regulatory authorities are not aligned in all regards.¹⁴

For antibiotics, additional costs and delay of market entries resulting from remaining differences in the approval process have been recognized, and transnational efforts have been initiated to improve the alignment of approval processes (e.g., TATFAR, the Transatlantic Taskforce on Antimicrobial Resistance).

However, differences across global regulatory requirements exist, e.g., in selection criteria for clinical trials, the definition of clinical endpoints and the specification of statistical parameters.

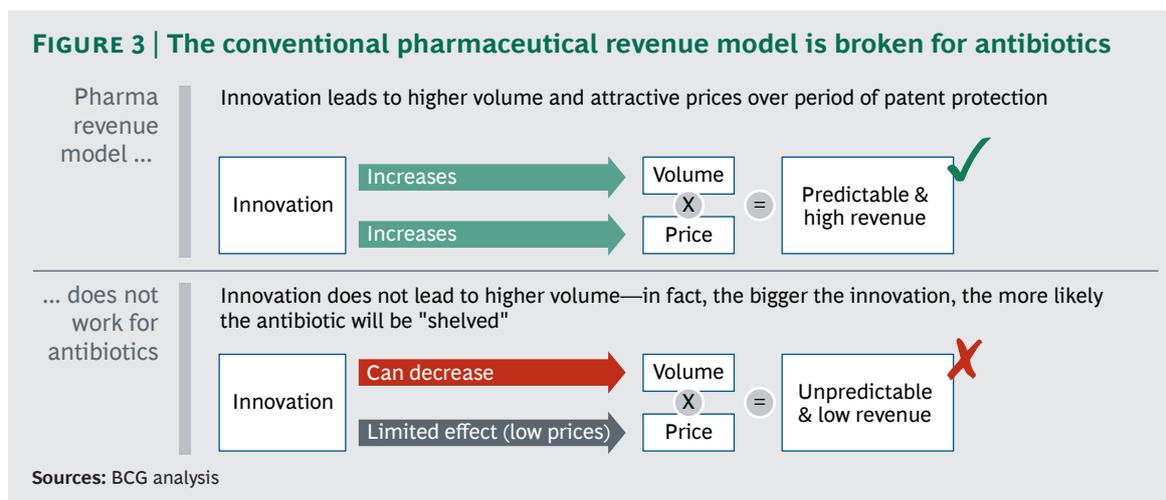
A globally unified approval process could potentially reduce those differences and is called for by interviewed experts and the literature, though significant legal challenges exist.¹⁵

4. Challenges in Commercialization

A key challenge and one of the main drivers of the exit of pharmaceutical companies is the low commercial attractiveness of the antibiotics market.

Most experts estimate the net present value (NPV) of developing and marketing a new antibiotic to be negative or at most only marginally positive. The traditional pharmaceutical business model, in which innovation drives volume and prices, does not hold for antibiotics (see figure 3).

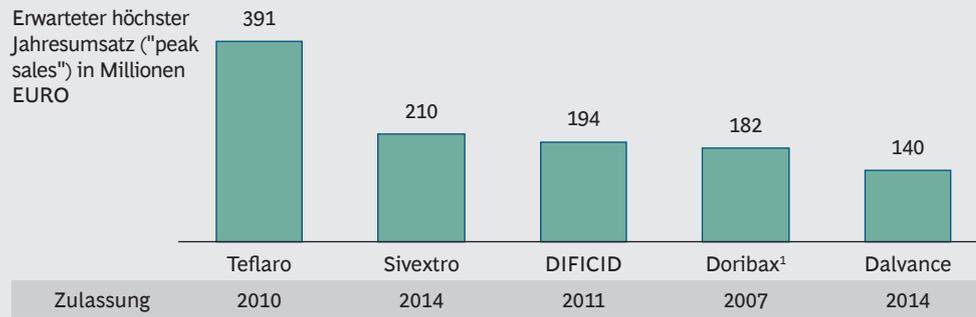
In the antibiotics market, volumes are rightfully limited by stewardship efforts. This is especially true for innovative antibiotics, which are likely to be prescribed only as a treatment of last resort. So, unlike therapeutic areas such as cancer, orphan diseases or Alzheimer’s disease, the sold volume of antibiotics and number of patients is low even for innovative products. Additionally, prices in the market are often low due to generic competition. As a result, revenue and profit expectations for antibiotics are low.



¹⁴Comprehensive study on regulatory requirements for development and filing of generic drugs globally. Handoo, Arora, Khera, et al. September 2012.

¹⁵A comprehensive study on regulatory requirements for development and filing of generic drugs globally. Handoo, Arora, Khera et al. September 2012; International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary. Forum on Drug Discovery, Development, and Translation; Institute of Medicine. October 2013.

FIGURE 4 | Recent antibiotics peak sales forecasts showing low revenue potential



¹Actual sales numbers from 2013

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

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

"We need new policies to tackle antimicrobial resistance." London School of Economics and Political Science. "The fallacies of hope: will we discover new antibiotics to combat pathogenic bacteria in time?" Federation of European Microbiological Societies, Microbiology Review, 2006.

The low commercial attractiveness of antibiotics is compounded by an industry trend towards focusing portfolios on few (profitable) therapeutic areas. In particular, this has led to large pharmaceutical companies exiting the area of antibiotics and being rewarded by the capital markets for focusing their activity on financially more attractive fields such as oncology.

RECOMMENDED LEVERS TO FOSTER RESEARCH AND DEVELOPMENT IN ANTIBIOTICS

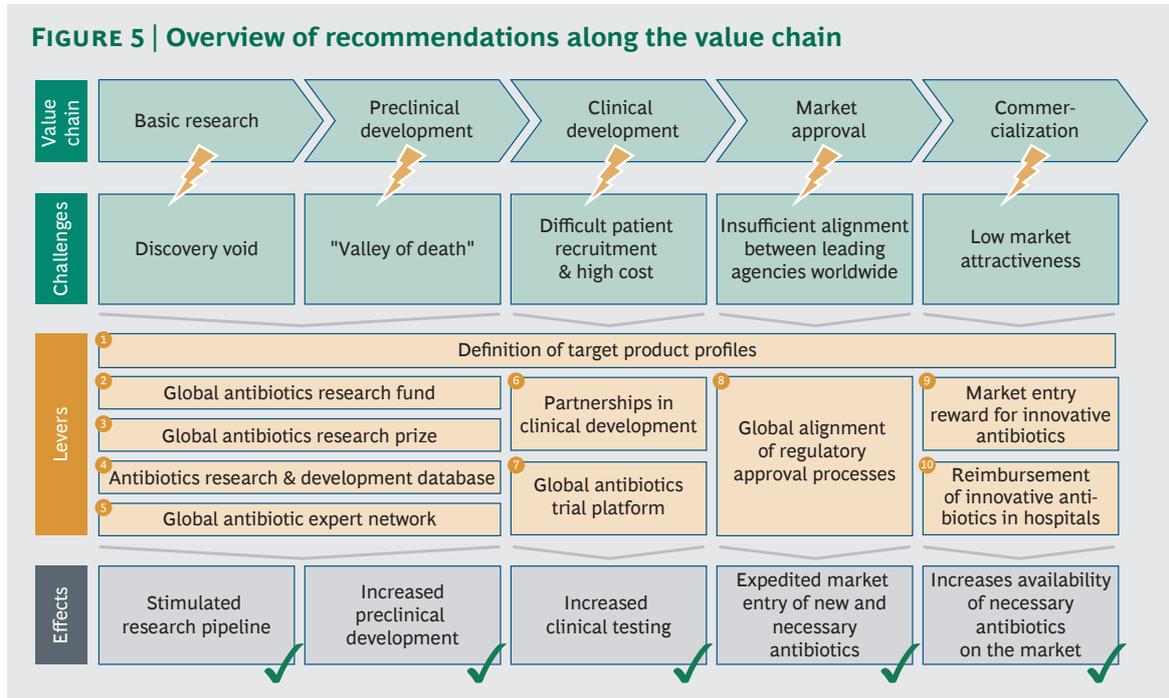
This report recommends implementing a set of 10 levers that address the multiple challenges along the value chain. While the levers are designed to work together as a package, they do not all have to be implemented at the same time.

Financing recommended levers and contribution of the pharmaceutical industry

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

- **Contribution based on antibiotics sales:** The worldwide antibiotics market is estimated at around €40 billion. A sales-based contribution of up to 5% of sales could provide significant resources to fund activities in antibiotics research and development. This way, companies benefiting from the sale of antibiotics would contribute to the development of new and innovative antibiotics. Such a contribution could be limited to animal health antibiotics and would also have the additional effect of deterring irresponsible

FIGURE 5 | Overview of recommendations along the value chain



use. Alternatively, such a contribution could be limited to companies that are not active in the research and development of new antibiotics.

- Profit-sharing mechanism:** In cases where funding is provided for profit-oriented activities (for example late-stage clinical development) profit-sharing agreements should be used to at least partially recoup the investments made. These profit-sharing agreements would be based on the sales revenue generated from the antibiotics in question. Usually, the sponsor would receive a fixed percentage of profits (or revenues) over the entire lifecycle of the product.
- Alternative funding sources:** A range of alternative sources of funding could be considered. One such source is the sale of transferable priority review vouchers (PRVs) that are already awarded in the area of neglected tropical diseases.¹⁶ PRVs have achieved prices of €220–320 million when sold on the open market. Regulatory approval agencies such as the European Medicines Agency (EMA) or US Food and Drug Administration (FDA) could alternate in selling such vouchers. This could create significant funds without placing a financial burden on governments or international organizations. Nevertheless, it should be noted that indirect societal costs (namely higher health care expenditure) can be incurred by this instrument, as it potentially distorts other pharmaceutical markets.

1. Definition of Target Product Profiles (TPP)

In order to steer R&D into the areas of highest public health need, we recommend the development of Target Product Profiles (TPP) for the most urgently needed antibiotics.

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

¹⁶United Therapeutics Sells Priority-Review Voucher to AbbVie for \$350 Million. Wall Street Journal. <http://www.wsj.com/articles/united-therapeutics-sells-priority-review-voucher-to-abbvie-for-350-million-1439981104> accessed 24 September 2015

2. Global Antibiotics Research Fund

The establishment of a research fund would substantially increase activity in basic research and pre-clinical development. While there are already several initiatives on national or supra-national level, we recommend bundling these efforts in a global fund.

Following a strategic research agenda informed by the Target Product Profiles (lever 1), the research fund will support research projects of academic institutions and small and medium-sized enterprises with a focus on the biggest challenges in antibacterial research.

From today's perspective, these challenges could be:

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

Funding should generally be available for research institutions and for small and medium-sized enterprises. Interested parties can apply for funding on a project basis. Project funding can run over multiple years, depending on the nature of the project and project progress will be tracked and evaluated on a regular basis.

Should projects result in profits for the funded institutions (e.g., through the sale of intellectual property), profit-sharing agreements can be used to restock the fund.

3. Global Antibiotics Research Prize

In order to increase public attention and awareness for the current challenges in antibiotics and positively incentivize R&D efforts, we recommend establishing a research prize and an annual antibiotics conference. The prize and conference would be focused on core challenges in current antibiotics research. Gram-negative bacteria pose such an exceptional challenge and could serve as a theme for the first prize and conference.

4. Antibiotics Research & Development Database

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

The database will help to improve the allocation of research efforts and funds through more informed decision-making by the involved stakeholders. It will furthermore facilitate the exchange of ideas between researchers working on similar problems.

5. Global Antibiotics Expert Network

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

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

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

6. Partnerships in Clinical Development

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

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

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

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

7. Global Antibiotic Trial Platform

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

The platform will include relevant hospitals and clinics, which are likely to be able to include potential trial participants as they regularly treat patients being infected by bacteria included in the Target Product Profiles (e.g. because they have departments for infectious diseases). These hospitals and clinics would be primarily asked to recruit patients for the clinical trials.

8. Global Alignment of Regulatory Approval Process

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

A working group bringing together regulatory representatives of major international and national bodies of approval should be established to develop specific recommendation on how to further align regulatory requirements (e.g., regarding the use of superiority trials, required statistical analyses, accepted endpoints etc.).

The working group would develop recommendations to align or unify the current approval processes for urgently needed antibiotics. The working group would build on existing efforts by The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and others.

9. Market Entry Reward for Innovative Antibiotics

We recommend introducing a market entry reward—a lump-sum payment—paid to companies introducing innovative antibiotics that meet the Target Product Profile. The reward would increase the commercial attractiveness of antibiotics and partially delink profit expectation from sales volumes.

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

Antibiotic candidates will be evaluated based on their efficacy against the pathogens prioritized in the Target Product Profiles and on their innovativeness (e.g., whether the antibiotic is part of a new class). Their launch date relative to market competitors should be considered as well: A product that is a fast follower in a new class should receive a financial reward as well, though less than the first-to-market-product. We estimate that in order to significantly alter the commercial evaluation of the antibiotics market, the market entry reward should be in the order of up to €1,000 million for an innovative antibiotic meeting the Target Product Profile.

Companies receiving a market entry reward must accept conditions upon receiving the reward:

- global availability of the antibiotic,
- affordability of the antibiotic, especially in developing countries,
- sufficient production capacity in case of emergencies, and
- enable antibiotic stewardship.

10. Reimbursement for Innovative Antibiotics in Hospitals

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

TIMING AND FIRST STEPS

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

FIGURE 6 | Next steps for implementation of levers

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

THOUGHTS ON IMPLEMENTATION

A globally-coordinated approach

Given the global nature of research, development and commercialization and the global challenge antibiotic resistance poses, we suggest a globally coordinated approach to implementation. Nationally fragmented funding and research agendas have led to a duplication of research efforts and hampered exchange across research groups. It is essential to create a global research agenda and coordinate global funding in antibiotics.

In order to move toward a globally coordinated approach, we recommend starting with an alliance of influential, opinion-leading countries working closely with multilateral organizations (such as the World Health Organization) and other active stakeholders such as the Drugs for Neglected Diseases (DNDi). Other countries as well as philanthropic organizations are encouraged to join in this initiative.

Creation of the global antibiotics collaboration platform

Implementation, coordination, and controlling across initiatives have been a major challenge. In order to further detail and implement the key levers described before, we recommend setting up a dedicated, global collaboration platform.

The establishment of a dedicated organizational structure could provide a strong signaling effect to the stakeholders involved. GAVI the Vaccine Alliance is a successful example.¹⁷ Another example of a dedicated organization is the DNDi, taking on the challenge of neglected diseases with success in multiple areas.¹⁸

A collaboration platform would signal a strong long-term commitment to participants from the public, private, and academic world. For companies and research institutions to build or maintain these capabilities, security in planning over a multiyear time horizon is essential.

Broad stakeholder involvement within the global antibiotics collaboration platform

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

Scope and vision of the global antibiotics collaboration platform

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

- **Being a thought leader and coordinator:** Given the fundamental importance of antibiotics for public health, the collaboration platform should serve as a thought leader and driver in the global debate on antibiotics, including stewardship. Therefore, in order to identify compounds and develop new research approaches SMEs, biotech firms, pharmaceutical companies, and academia should be actively engaged.
- **Becoming a knowledge hub for research and development of antibiotics:** By coordinating and amplifying innovative approaches in antibiotics research and development, the collaboration platform will help advance the understanding of antibiotic resistance. The collaboration platform will connect active researchers, improve access to scientific information and become a main advisor for researchers and

¹⁷ *Market-shaping success story: three vaccine price reductions.* GAVI the Vaccine Alliance. <http://gaviprogressreport.org/2013/market-shaping-success-story/> accessed 24 September 2015

¹⁸ *Drug discovery and development for neglected diseases: the DNDi model.* Ioset and Chatelain. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084299/> accessed 24 September 2015

pharmaceutical developers. In order to promote research, the collaboration platform might also leverage intellectual property rights that it obtained from co-development efforts in which it carried a substantial part of the funding.

- **Stimulating the market:** The collaboration platform could also help create and implement incentives for science and businesses to enhance antibiotic research in industry and science. The incentives will span across the entire value chain and thus cater to the needs of different players in the market.

Organizational setup of the global antibiotics collaboration platform

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

Coordinating the market entry reward

The market entry reward (lever 9) constitutes a substantial financial commitment. It is essential to avoid any conflict of interest in designing and coordinating this reward. We recommend tasking a credible and neutral global institution with further detailing the market entry reward and its financing mechanisms.

Turnaround in antibiotics research and development

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

