International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development

The Need for a One Health – One Europe – One World Framework

Report for the 2016 Dutch Presidency of the European Union

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Acknowledgments:
We would first like to thank the Dutch Ministry of Health, Welfare, and Sport for the financial support to conduct this research. In particular, we thank Lili Guo and Marja Esveld for their help in the conceptualization, ongoing input, and review of this report. We would further like to acknowledge the multitude of experts that provided invaluable insight into our research, which enhanced the report's findings and conclusions.

Executive Summary

Antimicrobial resistance is currently responsible for over 700,000 deaths annually around the world. AMR mortality is predicted to exponentially rise to above 10 million deaths per year by 2050. The global economic cost of such a rise in mortality and morbidity is estimated to be $100 trillion.

Development of novel antibiotics, alternative therapies, and diagnostics tools is critical to the global fight against AMR. However, the pipeline for antibiotics and related products is limited. Since 2000, only 5 novel classes of antibiotics have been marketed, however none of these target deadly and highly resistant gram-negative bacteria. The total number of submitted antibiotic patents has declined by 34.8% between 2007 and 2012.

A partial picture of the EU/US antibiotic pipeline shows that are at least 19 antibiotic products including alternative therapies in clinical development Phase I, 27 in Phase II, and 6 in Phase III. Despite 52 products in the pipeline, only one is a systemic antibiotic with a novel mechanism of action, and it is limited to a specific bacteria. A development timeline for these drugs is unknown.

A partial picture of US and EU public funding of antibiotic R&D shows that Europe has invested ~€147 million annually between 2007-13 and the US has invested ~$260 million (€240 million) in 2015. Having been stable since 2010, US investment in antibiotic R&D is expected to grow to $413 million (€382 million) in 2016. However, it is unclear how the differences in funding have affected outcomes in the pipeline, which highlights the need for ongoing assessment of public return on investment in antibiotics. Moreover, European and US governments do not appear to have any method of eventually recapturing these large investments should their funding result in marketable antibiotics.

Regarding private investment, global venture capital in antimicrobial R&D has declined by 28% between the two five year periods of 2004-08 and 2009-13. Venture capital investment in Gram-negative antimicrobials has increased by 51% during these two periods, but it still comprises only 12% of total venture capital investment in antimicrobials. The amount of internal capital invested by developers into their own antibiotic projects is unknown.

In response to this growing crisis, there has been a proliferation of initiatives to incentivize the antibiotic development pipeline. In total, there are 61 active R&D initiatives at global, EU, and national levels (UK, France, Germany, Netherlands, Sweden, US, and Canada). Additionally, there are 5 initiatives that are either proposed or in preliminary stages of implementation.

The antibiotic R&D initiative environment is now crowded. There is room for improved coordination between and within initiatives. Many initiatives are founded on various models of partnership that improve the possibilities for stakeholder collaboration, but further complicate coordination efforts. A lack of coherence throughout R&D initiatives risks muddling priorities, duplicating efforts, and missing synergistic opportunities.

Most initiatives improve the economic value of antibiotic R&D, but there is a heavy imbalance towards the use of push incentive tools. Of the active initiatives, 75% use only push mechanisms, 7% use only outcome-based pull mechanisms, 2% use lego-regulatory policies, and 15% only coordinate AMR action and provide no form of R&D incentive. Hybrid push-pull approaches to incentivization are not being used at all. The top three incentives are: direct project funding, research collaborations, and research grants & fellowships. The vast majority of funding flows through push mechanisms of incentivization.

Due to this push/pull imbalance, there is an unequal distribution of initiatives across the antibiotic value chain that favours basic research and early drug discovery phases. In addition, R&D initiatives primarily assist academic institutions and large pharmaceutical companies. SMEs are lacking support and often struggle to reach the clinical phases of development and market approval. Taxation policies that can be tailored to support SMEs developing antibiotics did not appear to be commonly used.

At the end of the antibiotic value chain, commercialization-focused pull incentives that are missing or are underutilized include end prizes/competitions and value-based pricing and reimbursement. Moreover, the EMA and FDA are using regulatory tools to facilitate antibiotic market authorization. But, there remains a lack of harmonization and cooperation between the EMA and FDA, as well as other drug regulatory agencies.

Finally, from a public health perspective, antibiotic stewardship and patient access goals are poorly integrated into the current set of R&D initiatives. Many initiatives have not explicitly linked their incentives to high-priority medical needs in infectious disease.

Given this research report's key findings, we put forth the following 14 recommendations:

1. Align existing and new antibiotic R&D initiatives to function within the broader One Health approach to AMR.

2. Consolidate and coordinate existing and new European AMR initiatives and antibiotic R&D initiatives under a One Europe approach.

3. Establish a global AMR policy coordination & governing body that brings worldwide coherence under a One World approach.

4. Intensify efforts to coordinate and expand European and global antibiotic clinical trial programs under One Europe and One World agendas.

5. Ensure antibiotic incentives are explicitly attached to specific high-priority medical needs in infectious disease.

6. Launch a global AMR observatory that collects AMR and antibiotic pipeline data, shares knowledge, and disseminates best practices in AMR and antibiotic innovation.

7. Establish European and global commitment to antibiotic pull incentives.

8. Explore the role for European joint procurement of high-value antibiotics to ensure their conservation.

9. Consider the feasibility of European tax policies that encourage antibiotic R&D.

10. Incorporate methods of clawing back public investment in antibiotic R&D into incentive packages.

11. Improve antibiotic harmonization across global drug regulatory agencies and encourage joint antibiotic authorization between the EMA and FDA.

12. Address key market weaknesses by enabling SME participation and facilitating preclinical development.

13. Explore the incentive preferences of different industry players.

14. Investigate the value of different partnership models in antibiotic R&D and learn from the experiences of the US Biomedical Advanced Research and Development Authority.

Table of Contents

List of Abbreviations 7

List of Figures and Tables 10

1. Objectives 12

2. Background 12
- **2.1 Combating the rise of antimicrobial resistance** 12
- **2.2 The lagging antibiotic development pipeline** 14
- **2.3 Barriers within the antibiotic development value chain** 17
  - 2.3.1 Barriers to basic research 18
  - 2.3.2 Barriers to preclinical development 19
  - 2.3.3 Barriers to clinical development 19
  - 2.3.4 Barriers to market approval 20
  - 2.3.5 Barriers to commercialization 20
- **2.4 Incentives to spark innovation in the antibiotics market** 20
- **2.5 Funding landscape for the development of antibiotics** 22

3. Research Methodology 24
- **3.1 Literature review** 25
- **3.2 Expert input** 25
- **3.3 Country case studies** 25
- **3.4 Framework for initiative analysis and discussion** 26

4. Results 27
- **4.1 Key International initiatives that foster R&D of antibiotics** 28
  - 4.1.1 Joint Programming Initiative on Antimicrobial Resistance 28
  - 4.1.2 Transatlantic Task Force on Antimicrobial Resistance 29
  - 4.1.3 European & Developing Countries Clinical Trials Partnership 29
  - 4.1.4 World Health Organization's Global Action Plan on Antimicrobial Resistance 31
  - 4.1.5 G7 Global Union for Antibiotics Research & Development Initiative 32
- **4.2 Key European initiatives that foster R&D of antibiotics** 32
  - 4.2.1 Directorate-General for Research and Innovation, European Commission 32
  - 4.2.2 New Drugs for Bad Bugs, Innovative Medicines Initiative 33
  - 4.2.3 InnovFinn Infectious Disease Finance Facility 35
  - 4.2.4 European Medicines Agency 36
- **4.3 Key national initiatives that foster R&D of antibiotics** 37
  - 4.3.1 United States of America 37
  - 4.3.2 Canada 41
  - 4.3.3 United Kingdom 42
  - 4.3.4 France 44
  - 4.3.5 Germany 46
  - 4.3.6 Netherlands 47
  - 4.3.7 Sweden 48

5. Discussion 48
- **5.1 How do the current initiatives measure across the evaluation criteria?** 49
- **5.2 What is the current balance between push and pull incentives?** 50
  - 5.2.2 Incentives currently being used 50

5.2.2 Incentives that are missing 51
5.3 What are our knowledge gaps in the global antibiotics market? 53
5.3.1 Global antibiotic R&D investment 53
5.3.2 The global antibiotic pipeline..... 54
5.4 What is the current level of coordination between and within initiatives? 56
5.4.1 Inter-initiative coordination 56
5.4.2 Intra-initiative coordination 56
5.5 What is the distribution of initiative support across the value chain? 57
5.5.1 Basic research 59
5.5.2 Preclinical and clinical trials 59
5.5.3 Market approval 60
5.5.4 Commercialization 60
5.6 How are SMEs supported through existing initiatives? 60
5.7 Are public health needs reflected in the current set of initiatives? 61
5.7.1 Stewardship and patient access 61
5.7.2 Medical needs..... 62

6. Conclusions & Recommendations..... 62

References..... 67

Appendix 1: Antibiotics currently in development or recently approved in the US Market……74

Appendix 2: BEAM Alliance products in clinical development……...79

Appendix 3: Overview of antibiotic R&D initiatives……81

Appendix 4: Criteria-based analysis of antibiotic R&D initiatives……..90

List of Abbreviations

Abbreviation	Name
ABSSSI	acute bacterial skin and skin structure infection
ACE	Antibiotic Conservation Effectiveness
AHIF	Antibiotic Health Impact Fund
AIFM	Antibiotic Innovation Funding Mechanism
AMR	Antimicrobial resistance
AMRFF	Antimicrobial Resistance Funders Forum
ANR	French National Research Agency
ANTUK	Antibiotic Research UK
ARLG	Antibacterial Resistance Leadership Group
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Industry Organisation
BMBF	German Federal Ministry for Education and Research
BSA	Broad Spectrum Antimicrobials
BSAC	British Society of Antimicrobial Chemotherapy
CABP	community acquired bacterial pneumonia
CDC	US Centers for Disease Control and Prevention
cIAI	complicated intraabdominal infection
CIHR	Canadian Institute of Health Research
CIHR-III	Canadian Institute of Health Research - Institute of Infection and Immunity
COMBACTE	Combating Bacterial Resistance in Europe
COMBACTE-CARE	COMBACTE - Carbapenem Resistance
COMBACTE-MAGNET	COMBACTE - Molecules Against Gram-Negative Infections
CTTI	Clinical Trials Transformation Initiative
cUTI	complicated urinary tract infection
DFG	German Research Foundation
DG RTD	Directorate-General for Research and Innovation
DG SANTE	Directorate-General for Health and Food Safety
DG-RTG	Directorate-General for Research and Innovation
DISARM	Developing an Innovative Strategy for Antimicrobial Resistance
DMID	Division of Microbiology and Infectious Diseases
DNDi	Drugs for Neglected Diseases initiative
DZIF	German Centre for Infection Research
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EDCTP	European and Developing Countries Clinical Trials Partnership

EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Authority
EIB	European Investment Bank
EMA	European Medicines Agency
ENABLE	European Gram-Negative Antibacterial Engine
EU	European Union
FDA	US Food and Drug Administration
FNIH	Foundation for National Institutes for Health
FP6	Sixth Framework Programme
FP7	Seventh Framework Programme
GAIN	Generating Antibiotic Incentives Now
GUARD	Global Union for Antibiotics Research and Development Initiative
HAP	Hospital acquired pneumonia
iABC	Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis
IDFF	InnovFin Infectious Disease Finance Facility
IDSA	Infectious Disease Society of America
IMI	Innovative Medicines Initiative
IMMI	Inserm's Institute for Microbiology and Infectious Diseases
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMIC	Low- and middle-income countries
LPAD	Limited Population Antibacterial Drug Program
NAA	Novel Alternative to Antibiotics
ND4BB	New Drugs for Bad Bugs
NIAID	National Institute for Allergies and Infectious Diseases
NIH	US National Institute for Health
NPV	Net Present Value
OECD	Organisation for Economic Co-operation and Development
OHE	Office of Health Economics
OMA	Options Market for Antibiotics
PDP	Product development partnership
QDIP	Qualified Infectious Disease Product Designations
R&D	Research and Development
RCT	Randomised controlled trials
ROI	Return on Investment
SME	Small and medium sized enterprises
SRC	Swedish Research Council
TATFAR	Transatlantic Task Force on Antimicrobial Resistance
UK	United Kingdom
UK-MRC	UK Medical Research Council
UKCRC TIRI	UK Clinical Research Collaboration Translational Infection Research Initiative

USA	United States of America
WHO	World Health Organisation
ZonMw	Netherlands Organisation for Health Research and Development

List of Figures and Tables

Figure 1 Deaths attributable to AMR every year compared to other major causes of death…….....12
Figure 2 Critical tasks required for effectively combatting AMR as identified by TATFAR…….....13
Figure 3 Antibiotic pipeline for the last 20 years…….....14
Figure 4 Patent applications (families and total) relating to antibiotic research.....15
Figure 5 Overview of the antibiotic development value chain.....17
Figure 6 Success rate of antibiotic development from Phase I to Market……..18
Figure 7 European national level funding of therapeutic-related antibacterial resistance projects between 2007-13 by therapeutic sub-category.....22
Figure 8 Venture capital investment (millions) for antimicrobial R&D, 2004-08 vs. 2009-13.....23
Figure 9 The list of organizations that provided expert input on the compilation and basic assessment of identified antibiotic R&D initiatives.....25
Figure 10 The list of organizations that did not respond in time to provide expert input on the compilation and basic assessment of identified antibiotic R&D initiatives.....25
Figure 11 Member organizations of TATFAR.....28
Figure 12 Breakdown of the New Drugs for Bad Bugs projects.....33
Figure 13 NIH research spending on AMR research, United States, Fiscal Years 2010-15.....36
Figure 14 Distribution of incentives used by antibiotic R&D initiatives.....49
Figure 15 Estimated annual public funding of R&D of antibiotics and related products, Europe and the USA, Millions of Euros.....52
Figure 16 Partial picture of the current antibiotic development pipeline of antibiotics and related products as compiled from data provided by the PEW Charitable Trusts and the BEAM Alliance.....53
Figure 17 Distribution of international, EU, and select European national antibiotic R&D initiatives across the antibiotic value chain.....56

List of Tables

Table 1 Basic push and pull incentives for encouraging and fostering antibiotic R&D.....20
Table 2 Total committed public funding to antibacterial resistance research by JPIAMR countries and the EU.....21
Table 3 Total committed public funding from 2007-13 to therapeutic and diagnostic antibacterial research by JPIAMR countries and the EU.....21
Table 4 Global venture capital investment (millions) in antimicrobial research and development between 2004 and 2013.....22
Table 5 Outline of analysis framework applied to each identified antibiotic R&D initiative.....26

Table 6 Tabulation of initiatives that fulfill the six incentive evaluation criteria.....47
Table 7 Tabulation of the number of active initiatives that used only push incentives, only outcome-based pull incentives, only lego-regulatory incentives, or hybrid push-pull incentives.....48

1. Objectives

The 2016 Dutch Presidency of the European Union has named antimicrobial resistance (AMR) a top priority in their upcoming policy agenda and has planned a Ministerial Conference on this issue in February 2016. In preparation for this conference, the Dutch Ministry of Health, Welfare and Sport has commissioned the London School of Economics' health research centre, LSE Health, to submit a report that will provide a platform for discussion among the attending European Ministers of Health and Ministers of Agriculture. More specifically, this report will review current policy instruments aimed at incentivizing the innovation of novel antibiotics, alternative therapies, and diagnostic devices that support the rapid assessment of bacterial infections. This report builds on LSE Health's previous research commissioned by the Swedish government.[1] One follow up implication of this previous report was the establishment of the Transatlantic Taskforce on Antimicrobial Resistance.

Antimicrobial resistance is a complex, multi-factorial problem requiring a global solution that tackles the issue from multiple different angles. One key aspect of a global solution is the development of novel antibiotic drugs to support or replace the increasingly ineffective set of antibiotics currently available. However, the pipeline for antibiotics is limited because there are numerous scientific, regulatory and economic barriers that prevent adequate investment in antibiotic research and development (R&D). In response to this growing crisis, multiple R&D initiatives have been implemented at international, European, and national levels to reinvigorate the antibiotic development pipeline. These are an excellent first step, however, it appears that the current programs are not sufficient to repair the pipeline; additional intervention is necessary.

The primary objective of this report is to identify gaps in the European R&D agenda for antibiotics, as well as to recommend solutions to identified policy gaps. Through an extensive review of literature and input from experts in the field, we first seek to identify the existing set of initiatives that incentivize R&D of antibiotics and related medical products. We will review international and pan-European R&D initiatives, and additionally national programs in the USA, Canada, UK, France, Germany, Sweden and the Netherlands. Following this mapping exercise, we will discuss the most important initiatives and apply an analytical framework to assess these programs. Finally, based on our research we will identify key policy questions that deserve further discussion. This discussion will ultimately inform our set of policy recommendations on how to improve the European R&D agenda for antibiotics.

2. Background

2.1 Combating the rise of antimicrobial resistance

Antibiotics are essential to modern medical care. They are used routinely as prophylaxis in elective surgeries, as well as lifesaving measures in critically ill patients. However,

AMR is a constant threat to antibiotics in the ever-shifting landscape of infectious disease.[i] Microorganisms targeted by antimicrobial drugs evolve and naturally select for immunity to these medical weapons. This process is accelerated by the widespread and often inappropriate use of antibiotics in human and veterinary contexts.

AMR has spread so rapidly that it has been identified by the World Health Organization (WHO) as one of the greatest current threats to global health.[2] Numerous lethal pathogens have resistance levels exceeding 25% within EU states and other threatening microorganisms are surpassing 50% resistance rates throughout the world.[2] The recent emergence of MCR-1, a plasmid-mediated colistin resistance mechanism, marks the final breach of antibiotics by plasmid-mediated resistance.[3] Studies conducted by RAND Europe and KPMG for the UK's Review on Antimicrobial Resistance estimated that global antibiotic resistance is responsible for over 700,000 deaths each year.[4] Global deaths due to AMR are predicted to exponentially rise above 10 million deaths per year by 2050 (Figure 1).[4] They further estimate that the economic costs of such a rise in mortality and morbidity would likely be $100 trillion.[5]

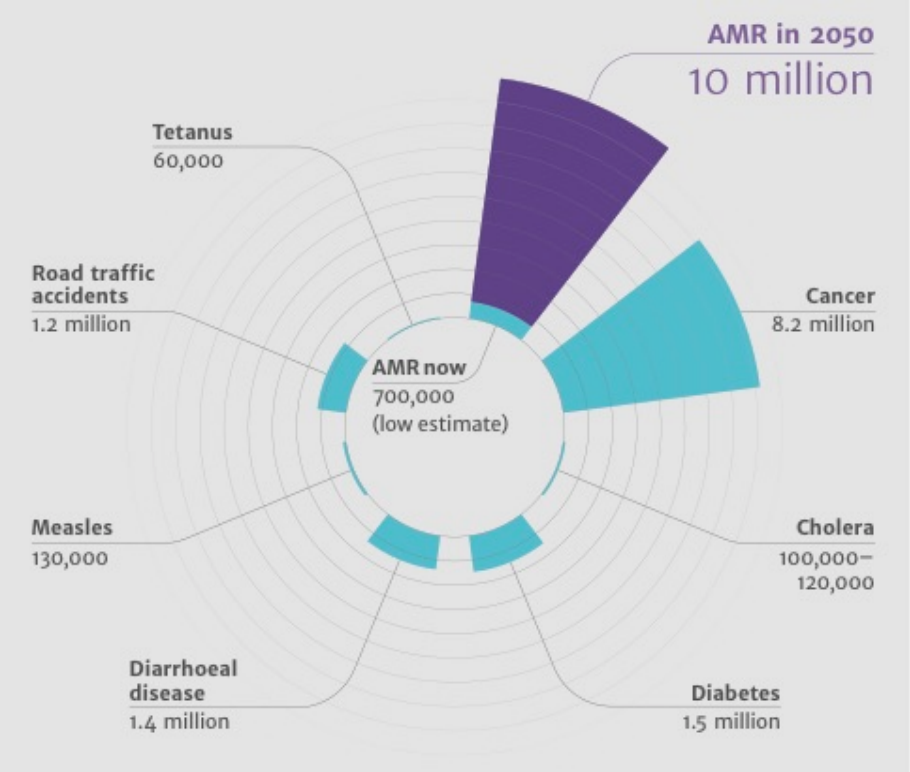

Figure 1. Deaths attributable to AMR every year compared to other major causes of death.[4]

[i] We recognize that the terms antibacterials, antibiotics, and antimicrobials are different and have specific medical terminology. However, they are often used interchangeably in the relevant literature. For the purposes of this report they are used interchangeably to refer to natural and synthetic compounds that target various pathogens, including bacteria.

A comprehensive strategy is necessary to address the challenges that accompany the rising threat of AMR. The Transatlantic Task Force on Antimicrobial Resistance (TATFAR) outlined three critical tasks that must be undertaken to effectively fight AMR (Figure 2).[6] First, therapeutic use of antibiotics needs to be conducted appropriately in medical and veterinary contexts. Second, drug-resistant infections need to be controlled and prevented. Third, strategies are necessary to preserve existing antibiotics and improve the development pipeline for new antibiotics, alternative therapies, and diagnostic devices. A crucial aspect of this third task, and the focus of this report, has been the design and implementation of reforms that facilitate R&D of AMR products.

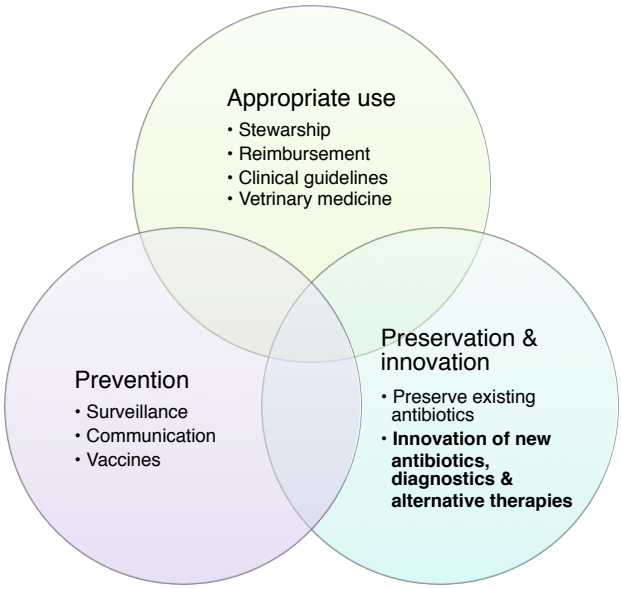

Figure 2. Critical tasks required for effectively combatting AMR as identified by TATFAR.[6]

While not further discussed in this report, preventing the spread of resistance and facilitating appropriate use of antibiotics are being addressed by multiple European directorates and agencies including: the European Commission's Directorate-General for Health and Food Safety (DG SANTE), the European Commission's Directorate-General for Research and Innovation (DG RTD), the European Medicines Agency (EMA), the European Food Safety Authority (EFSA), and European Centre for Disease Prevention and Control (ECDC). A comprehensive mapping and assessment of these public health programs is a worthy research topic and would aid in the improvement of the European AMR agenda.

2.2 The lagging antibiotic development pipeline

There is clear demand for new generations of antibiotics to replace the increasingly ineffective ones, however the development pipeline is strained. Since 2000, only five novel classes of antibiotics have been marketed (Figure 3).[7,8] Unfortunately, none of these target gram-negative bacteria, which are often deadly and known to more readily

adapt to antibacterial drugs. The well-known "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*, and *Enterobacter*) are gram-negative and cause the majority of hospital acquired infections, yet few drugs in the pipeline target these bacteria.[9]

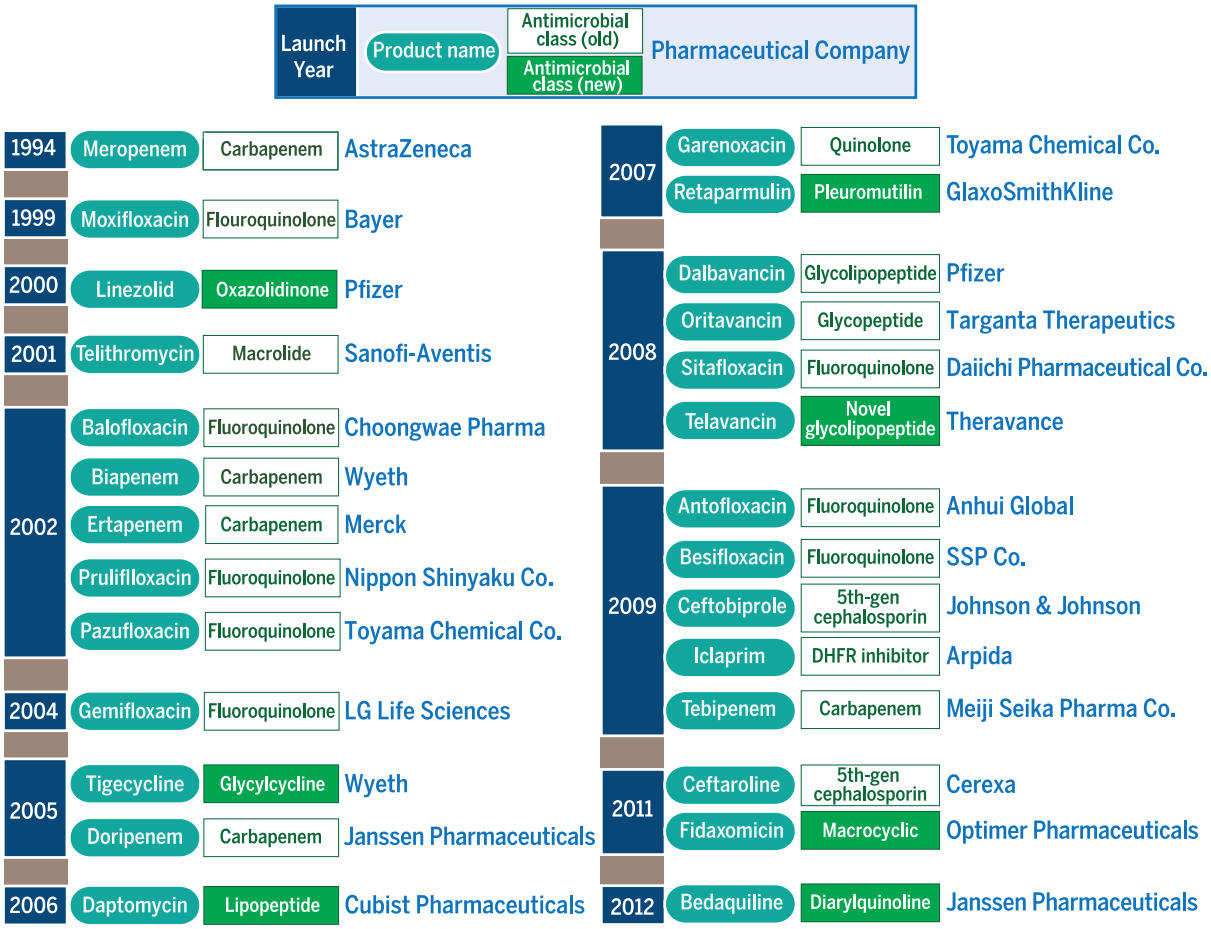

Figure 3. Antibiotic pipeline for the last 20 years.[8]

It would also seem that the development pipeline is not accelerating at the needed rate despite calls to actions, as pharmaceutical companies continue to divest from antibiotics. A life sciences report by Marks & Clerk found that the total number of patent applications worldwide related to antibiotic research has dropped considerably.[10] In 2007, a total of 8565 antibiotic patents were filed across the globe and in 2012 this number plummeted to 5586, a 34.8% decrease (Figure 4). In contrast, the number of patent families[ii] in the field of antibiotics filed over the same period stayed quite constant. This combination of decreasing total patent filings and stable patent family filings may be a result of consolidations in antibiotic patent filings or, more worryingly, it may indicate general apathy and uncertainty in antibiotic development.

[ii] Patent families are a set of patents covering a single invention.

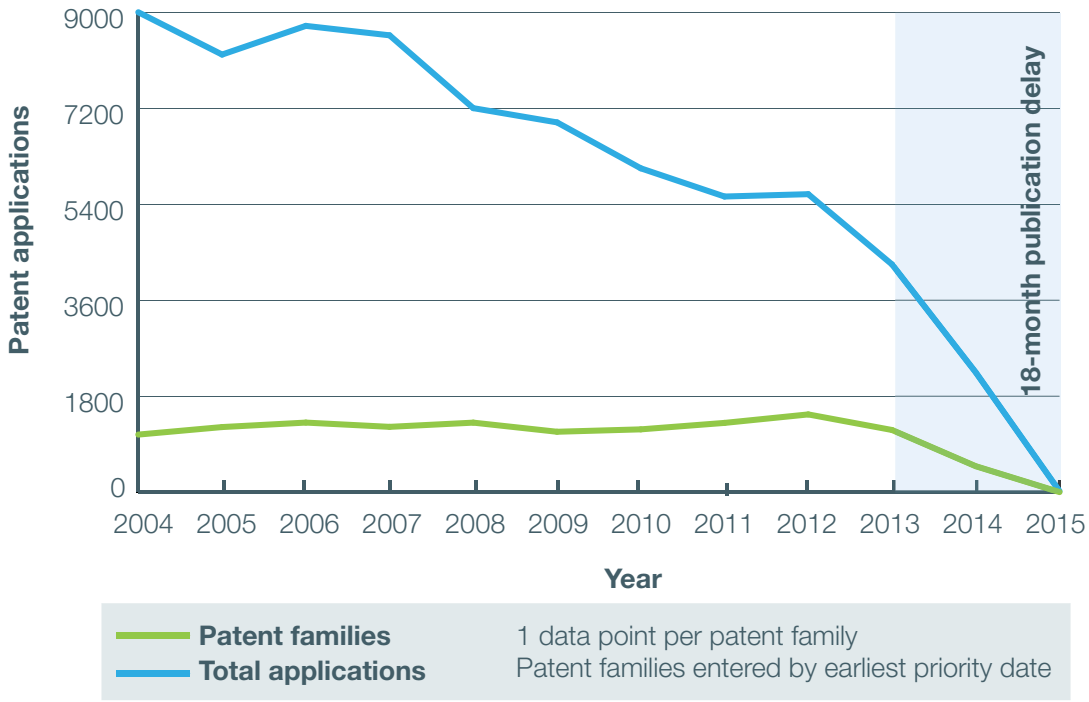

Figure 4. Patent applications (families and total) relating to antibiotic research.[10]

Currently, GlaxoSmithKline, Novartis, AstraZeneca, and Sanofi-Aventis are the major large-capital pharmaceutical companies that are actively developing antibiotics.[7] This number has shrunk significantly since 1990 when there were at least 18 big pharmaceutical companies active in the field.[7] This recent decade has also been a period of substantial commercial restructuring, as many pharmaceutical companies have either established or closed antibiotic R&D subsidiary firms. As a result, small and medium sized enterprises (SMEs) have attempted to fill any void created by the fluidity in the infectious disease sector. This is a trend that is common throughout the pharmaceutical industry. Munos found that, between the early 1980s to early 2000s, the proportion of new drugs attributable to SMEs had increased from 23% to 70%.[11] Regrettably, these SMEs often lack the capital to undertake R&D of novel antibiotics and have resorted to redeveloping existing compounds.[12] This trend of divestment is perhaps not surprising given that there are significant scientific, economic and regulatory barriers in the development of antibiotics relative to other medical technologies.[13,14] These barriers are discussed further in the following section.

The situation is not entirely hopeless as there are promising antibiotics currently in development, some of which target the lethal ESKAPE pathogens. PEW Trusts maintains an updated list of current US antibiotics in the clinical stages of development (Appendix 1).[15] As of September 2015, there are an estimated 39 systemic antibiotics in varying clinical phases. It is important to recognize that this US pipeline assessment does not capture the global or even European antibiotic pipeline. Since 2014, the FDA

approved 6 new antibiotics.[16] However, they are within existing classes of antibacterial mechanisms and lack high-priority clinical applicability.

According to additional analysis of Pew's work, 32 of the antibiotics in the pipeline target the "Big 5" indications: complicated urinary tract infection (cUTI), complicated intraabdominal infection (cIAI), acute bacterial skin and skin structure infection (ABSSSI), community acquired bacterial pneumonia (CABP), and hospital acquired pneumonia (HAP) (personal communication, Dr. John Rex, Senior Vice President and Chief Strategy Officer of the Infection Business Unit at AstraZeneca, 2016).

Furthermore, 20 of the antibiotics in the US pipeline target gram-negative bacteria, 13 of which target the ESKAPE pathogens. Dr. Rex estimated this current pipeline could translate to 7 marketable drugs. It should be further noted that 6 candidate antibiotics solely target *C. difficile* and only one candidate has an entirely novel mechanism of action, although limited to *Pseudomonas*.

A position paper by the BEAM Alliance, a consortium of European SMEs developing antibiotics and alternatives, provides a snapshot of the development pipeline of the participating 40 companies (Appendix 2).[17] There is wide variation in the types of therapies in their development pipeline including antibiotics, antibiotic combinations, monoclonal antibodies, bacteriophages, and bioproducts. The majority of these therapies are in Phase I or II, with only one therapy in phase III.

Also, critical discoveries have recently been made in antimicrobial research such as Ling et al.'s novel method of developing antibiotics that may avoid progress of resistance.[18] These advancements in our basic understanding of bacteria and antibacterial mechanisms might help facilitate development of new antibiotic classes.

2.3 Barriers within the antibiotic development value chain

In order to target policy that sparks antibiotic innovation, it is important to understand the key scientific, regulatory, and economic barriers that underpin the current development pipeline. In late 2015, the German Federal Ministry of Health, in support of the G7's Global Union for Antibiotics Research and Development (GUARD) Initiative, commissioned an advisory consortium to examine the key barriers of antibiotic development.[19] This report uses a useful conceptual framework that identifies the public and private barriers to development across the five major stages of the antibiotic value chain (Figure 5): (1) basic research, (2) preclinical development, (3) clinical development, (4) market approval and (5) commercialization.

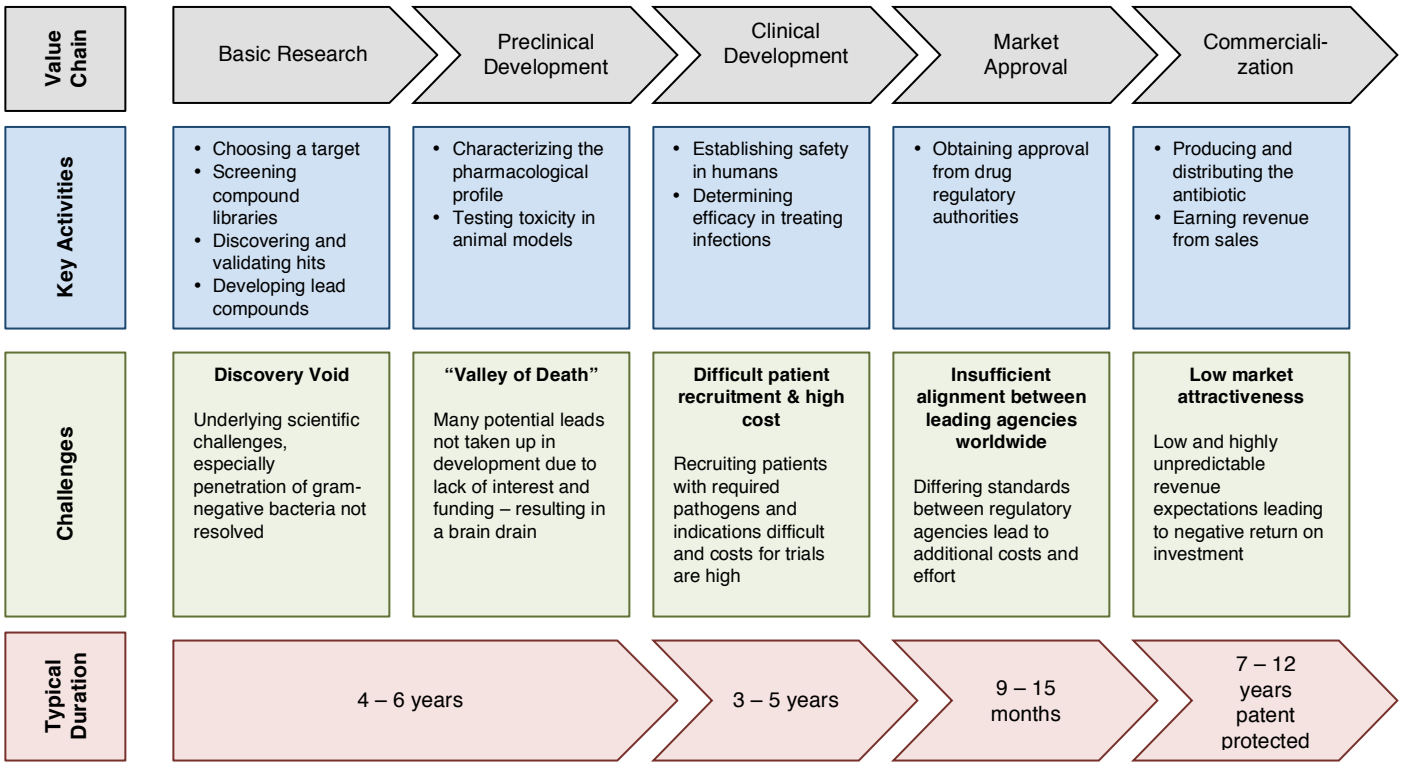

Figure 5. Overview of the antibiotic development value chain.[19]

2.3.1 Barriers to basic research

In the basic research phase of antibiotic development there seems to be what has been termed a '"discovery void".[19] It appears that big pharmaceutical companies are leaving the critical early stages of drug discovery because basic research tends to be a high-risk phase that will often not result in a marketable drug. A 2006 study examined the success rates of high intensity throughput (HIT) screening for discovery of antibacterial drugs and found that success rates were on average 2.6% from initial HIT screening to reaching phase I clinical trials.[20] While HIT screening is rarely used now for antibiotic discovery, experts still find that early research success rates are quite low.

High failure rates are in part attributed to the difficulty of applying existing drug discovery strategies to the field of infectious disease, which is constantly morphing. Instead of investing in basic research, large pharmaceutical companies are favouring investment in later stage clinical phases of drug candidates that have been validated by preclinical studies.[1] The divestment of pharmaceutical companies in human and physical resources from basic research activities has lowered the number of dedicated experts in this particular field of antibiotic discovery, a so-called brain drain. The realm of basic research has heavily fallen onto academic institutions, which struggle to find suitable researchers.

2.3.2 Barriers to preclinical development

The 'valley of death' describes the preclinical phases of transitioning a lead compound to a drug candidate ready for human testing.[19] It straddles basic research and clinical development where there are often weak translational links between academia, non-profits, and industry. Preclinical development is considerably more expensive than basic research and thus many academic and non-profit institutions are unable to afford moving their lead compound to further development. Meanwhile, pharmaceutical companies determine preclinical development based almost solely on commercial viability. As a result, there is an inefficient silo effect created among key antibiotic players often resulting in a duplication of efforts in the preclinical realm.[21]

2.3.3 Barriers to clinical development

Once an antibiotic has reached the clinical phases, success rates for marketability significantly increase (Figure 6) and are actually relatively higher compared to other drugs.[19,22] However, there is still a high cost required to properly test an antibiotic product through the three phases of randomized controlled trials (RCTs). The UK AMR Review estimates that the clinical development cost for one marketable antibiotic costs €120 million.[5] However, this figure does not include the cost of the many failed candidates. The Review further estimates the true cost of developing one antibiotic, from basic research to commercialization, is approximately €700 million to €1.1 billion. A significant portion of this substantial cost is from clinical development.

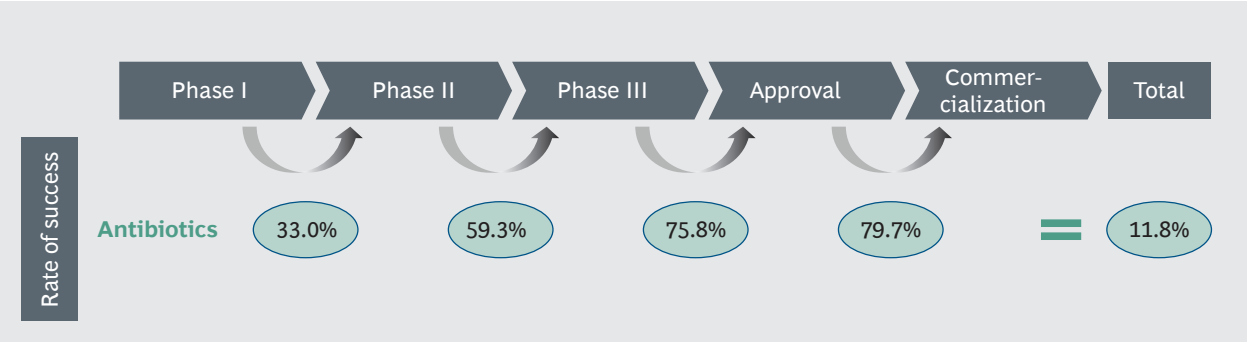

Figure 6. Success rate of antibiotic development from Phase I to Market.[19]

These development costs are prohibitively high for many SMEs, which may not have the available capital to invest in promising candidates.[1,17] Despite this disadvantage, small pharmaceutical firms and biotechnology companies are the primary investors in antibiotic development. In 2014, the top 25 pharmaceutical companies maintained only 15% of the share of antibiotics in clinical development.[5] In stark contrast, the top 25 pharmaceutical companies spend 67% of the global pharmaceutical R&D budget.[23]

Lastly, the combination of few rapid point-of-care diagnostic tools and short treatment times for acute bacterial infections makes recruiting patients logistically challenging.

Until only recently, there has been no centralized database to identify patients suitable for participation in an antibiotic RCT. However, as part of the Innovative Medicines Initiative (IMI) a clinical trials network for antibiotic development has been established across Europe (this initiative, known as COMBACTE, is discussed in more detail below). Moreover, there is an undersupply of expert practitioners in a particular bacterial disease that can adequately lead an RCT.

2.3.4 Barriers to market approval

The European Medicines Agency (EMA) and The US Food and Drug Administration (FDA) recognize that there is regulatory uncertainty and differences between the two market authorization processes for antibiotics.[6] These differences pertain to patient selection criteria, definition of clinical endpoints, specification of statistical parameters, and rules regarding expedited approvals.[19] Consequently, companies spend significant portions of their R&D budgets ensuring that they meet the clinical requirements for both drug agencies. Greater harmonization between the EMA and FDA is a key goal of TATFAR.[6]

2.3.5 Barriers to commercialization

An Office of Health Economics (OHE) report calculated that the average net present value (NPV) for an antibiotic project is -$50 million USD.[22] The estimated NPVs for musculoskeletal drugs and neurological drugs is +$1.15 billion and +$720 million respectively.[22] The low NPV for antibiotics particularly stems from low revenue potential after it has been marketed. This arises because antibiotic sales volumes and prices are low.[19] First, there are low expected sales volumes for new antibiotics as there is an established set of competitors in the market, antibiotics are typically used for only short durations, and stewardship programs encourage restricted use of antibiotics. Sales are further threatened by upcoming diagnostic tests that could decrease the inappropriate use of antibiotics.[24] Second, prices of antibiotics tend to be low despite their high value in health care.[19] Many antibiotic treatments can cost less than €40 for a week-long treatment course in contrast to cancer therapies which can reach prices of over €90000 for a year-long treatment.

As a result, many experts consider the antibiotics business model to be broken. Multiple new models have been posited such as the Antibiotic Conservation Effectiveness (ACE) program, the Options Market for Antibiotics (OMA), the Antibiotic Health Impact Fund (AHIF), and the Antibiotic Innovation Funding Mechanism (AIFM).[25-28] Many new antibiotic business models build on the concept of ‘delinkage’, the separation of revenues from sales volume in order to ensure that developers are not pushing sales and increasing the potential for further resistance development.[24]

2.4 Incentives to spark innovation in the antibiotics market

Research and development of neglected drugs, such as antibiotics, can be incentivized through two broad strategies known as push and pull mechanisms (Table 1).[1,29] Push methods reduce the cost of researching and developing new drugs. This is accomplished through increasing access to scientific resources, providing research grants, offering tax incentives, and establishing public-private partnerships for dividing R&D costs. In contrast, pull mechanisms reward successful development of a drug by increasing or ensuring future revenue. Pull mechanisms can be outcome based as seen with monetary prizes, advanced market commitments, and patent buyouts. Alternatively, they may invoke lego-regulatory policies such as accelerated drug assessment pathways, market exclusivity extensions, anti-trust reforms, and value-based reimbursement. These push and pull strategies understandably have distinct advantages and disadvantages, as well as target different barriers in the antibiotic value chain. Experts tend to agree that a combination of complimentary incentives will be needed to effectively stimulate R&D in antibiotics.

Push incentive strategies	
• Supporting open access to research	• Funding translational research
• Grants for scientific personnel	• Tax incentives
• Direct funding	• Refundable tax credits
• Conditional grants	• Product development partnership
Outcome-based pull incentive strategies	
• End prize	• Research tournament
• Milestone prize	• Advanced market commitment
• Pay-for-performance payments	• Strategic Antibiotic Reserve
• Patent buyout	• Service-availability premium
• Payer license	
Lego-regulatory pull incentive strategies	
• Accelerated assessment and approval	• Anti-trust waivers
• Market exclusivity extensions	• Sui generis rights
• Transferable intellectual property rights	• Value-based reimbursement
• Conservation-based market exclusivity	• Targeted approval specifications
• Liability protection	• Priority review vouchers

Table 1. Basic push and pull incentives for encouraging and fostering antibiotic R&D.[30]

In late 2014, the UK Economic and Social Research Council, on behalf of Jim O'Neill's AMR Review, commissioned Renwick, Brogan, and Mossialos to conduct a systematic review of existing push and pull incentive strategies for encouraging development of novel antibiotics.[30] This review identified 47 different strategies, ranging from single push or pull incentives to complex proposals combining multiple incentives that restructure the entire antibiotic business model. Furthermore, this paper puts forward a framework that can be used by policy makers to design a comprehensive incentive package that encourages and fosters development of novel antibiotics.

The framework can be broken down into three successive steps. The first step involves choosing a core incentive package that addresses key economic criteria necessary for rebalancing the market. This core incentive package must: improve the net present

value of antibiotic project development; make antibiotic development possible for small and medium sized enterprises; encourage participation of large firms; and foster synergy among all stakeholders in the market. The second step requires the core market incentive package to be amended to attain public health goals pertaining to antibiotic stewardship and patient access to necessary antibiotics. The last step considers the package's implementation and operational feasibility, which is distinct to national context.

2.5 Funding landscape for the development of antibiotics

The funding landscape can be looked at from the perspective of both public and private investments. A comprehensive study by Kelly et a. published in 2015 in *The Lancet Infectious Disease* assessed public funding for AMR research in 19 JPIAMR countries, the European Commission, and related EU agencies between 2007 and 2013.[31] Data from this study highlights that total public investment in 1243 projects was €1.3 billion for this time period (Table 2).

	Total number of projects, 2007-13	Total funding (€), 2007-13	Proportion of total funding (excluding EC contributions to IMI)	Proportion of total funding
19 JPIAMR countries	1129	646,646,541	67.3%	49.5%
EU level	114	659,201,418	NA	50.5%
EU level (excluding IMI)	105	314,128,438	32.7%	24.1%
IMI (EC contribution only)	9	345,128,438	NA	26.4%
Overall	1243	1,305,847,959	100%	100%

Table 2. Total committed public funding to antibacterial resistance research by JPIAMR countries and the EU.[31]

Funding was assessed across six priority areas: therapeutics, diagnostics, surveillance, transmission, environment, and interventions. In the present report, we are concerned with the categories of therapeutics, which includes antibiotic and alternative therapy R&D, and diagnostics (Table 3). In total €626 million was invested between 2007 and 2013 at national and European levels (excluding the IMI) in antibacterial therapeutics and €129 million was invested in diagnostic tools. The IMI is composed of 9 projects and makes up a significant portion of total antibacterial funding and is primarily dedicated to therapeutics.

	19 JPIAMR Countries		EU Level (excluding IMI)		Total	
	No. Projects	Funding	No. Projects	Funding	No. Projects	Funding
Therapeutics	763	€ 428,199,158	71	€ 197,432,615	834	€ 625,631,773
Diagnostics	131	€ 90,353,417	13	€ 38,266,222	144	€ 128,619,639

Table 3. Total committed public funding from 2007-13 to therapeutic and diagnostic antibacterial research by JPIAMR countries and the EU.[31]

Therapeutics can be sub-categorized as follows: (I) basic research in antibacterials, (II) basic research in alternative therapies, (III) research in optimizing existing therapies, (IV) pre-clinical and clinical development, and (V) multi-component (i.e. projects focusing on more than one of the above sub-categories). Figure 7 highlights the breakdown of national level funding across these therapeutic subcategories. Notably, only 5% of national level funding was dedicated to research with preclinical and clinical trials and only 3% was dedicated to multi-component research projects that may include preclinical and clinical studies. This may be due to the IMI taking the lead on category IV therapeutic projects on behalf of European countries.

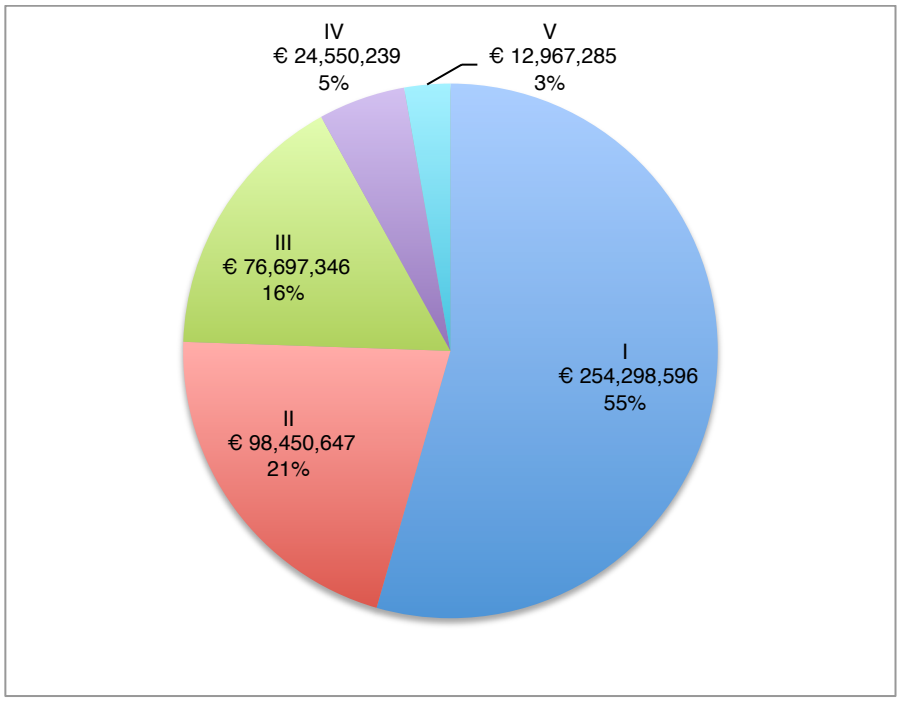

Figure 7. European national level funding of therapeutic-related antibacterial resistance projects between 2007 and 2013 by therapeutic sub-category: (I) basic research in antibacterials, (II) basic research in alternative therapies, (III) research in optimizing existing therapies, (IV) pre-clinical and clinical development, and (V) multi-component therapeutic projects[iii]

Providing a picture of private sector funding for antibiotics, the Biotechnology Industry Organization (BIO) conducted an analysis of four major venture capital databases over the ten-year period, 2004 to 2013.[32] These databases capture $38 billion in venture capital invested in over 1,200 drug companies across the world. According to this BIO report, approximately $1.8 billion in venture capital was invested in the R&D of antimicrobials between 2003 and 2013 (Table 4). Venture capital investment in all antimicrobials declined by 28% across the two five-year windows in this timeframe. The

[iii] Figure 7 data is based on publicly available data that will soon be hosted on the JPIAMR website. However, this data has yet to be officially verified and may have some inconsistencies in relation to the Kelly et al. paper.

report further noted that venture capital appears to have increased by 51% in the field of gram-negative antimicrobial R&D, yet still only captures 12% of total investment (Figure 8). In contrast, the field of broad-spectrum antimicrobial R&D declined by 61%. Gram-positive antimicrobial R&D remained steady.

	2004-08	2009-13	2004-13	Change % between 2004-08 & 2009-13
Antimicrobial Gram-positive	$386	$394	$780	2%
Antimicrobial Gram-negative	$89	$134	$223	51%
Antimicrobial Broad Spectrum	$578	$225	$803	-61%
Antimicrobial All	$1,053	$753	$1,806	-28%

Table 4. Global venture capital investment (millions) in antimicrobial research and development between 2004 and 2013.[32]

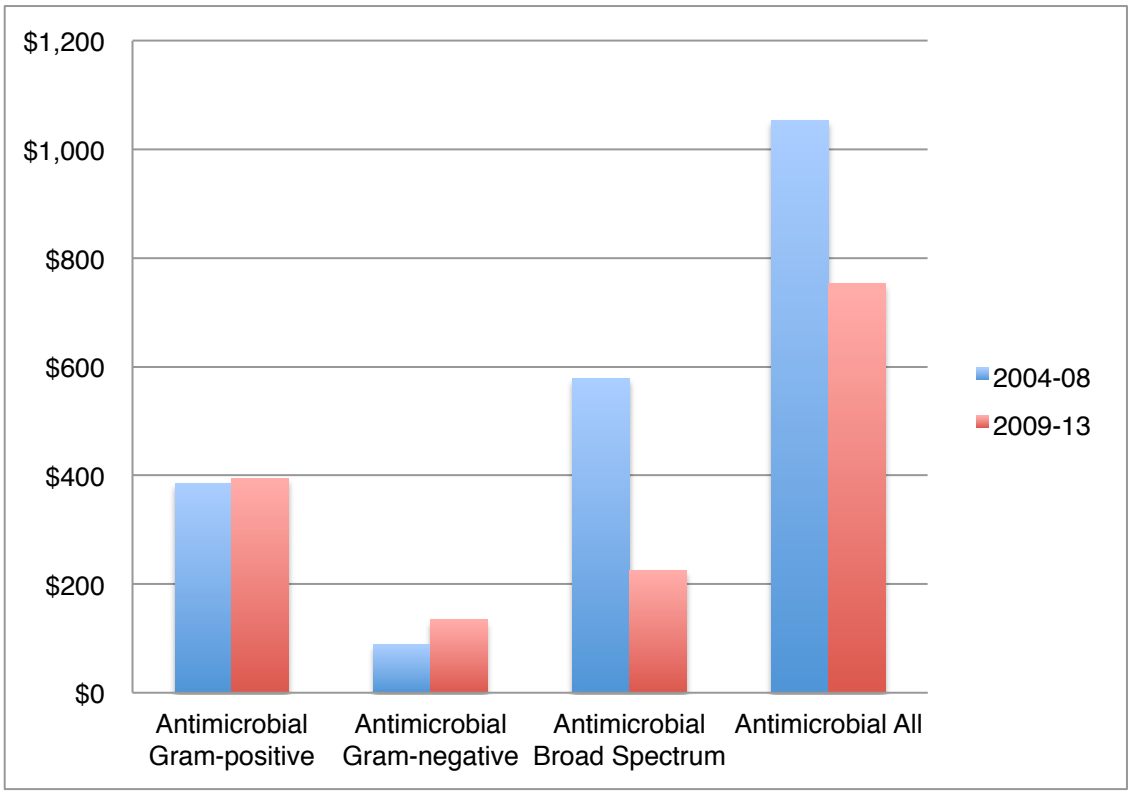

Figure 8. Venture capital investment (millions) for antimicrobial R&D, 2004-08 vs. 2009-13.[32]

It is important to appreciate that this venture capital data does not provide insight into how much of their internal capital individual firms are investing in antibiotic R&D. Additionally, this data does not indicate what types of companies were being funded (i.e. big pharmaceutical companies vs. SMEs) through external private financing.

3. Research Methodology

Our research methodology can be divided into three phases. The first phase involved collecting information and evidence on the existing set of initiatives that support R&D of human antibiotics, alternative therapies, and diagnostic devices. This step involved a semi-systematic literature review complimented by input from experts in the field.[iv] Using this evidence, we constructed case studies for the major antibiotic R&D initiatives. The second phase entailed performing an in-depth analysis of each initiative using evaluation criteria identified from the literature. This analysis supplemented the case studies and provided a basis for policy discussion of antibiotic R&D. The final phase consisted of consolidating a concise set of recommendations that arose from our analysis and policy discussion.

3.1 Literature review

Through a semi-systematic[v] literature search we identified current and proposed policy initiatives that foster R&D of novel antibiotics, alternative therapies, and diagnostic devices. We reviewed relevant peer-reviewed articles with use of MEDLINE (PubMed), Embase (Ovid), and Web of Science. Search terms included: “antibiotic”, “antimicrobial”, “antibacterial”, “resistance”, “resistant”, “alternative”, “diagnostic”, “devices”, “research”, “development”, “incentive”, “policy”, “mechanism”, “business model”, “strategy”, “instrument”. The search was restricted to papers published in the last five years, in English, and either comments, editorials, journal articles, reviews, or systematic reviews. Additional non-peer reviewed literature was included in this report and identified through a Google search, and from citations in several key papers and publication archives on relevant websites.

3.2 Expert input

Once an initial compilation of initiatives had been established, we solicited expert input to ensure that we had correct information and had not missed pertinent initiatives (Figure 9). In collaboration with the Dutch Ministry of Health, Welfare, and Sport, we selected experts that were associated with the major initiatives identified in our initial literature review. Experts related to an initiative provided feedback regarding their initiative’s priorities, operational programs, R&D incentive mechanisms, and funding. Further phone interviews were conducted with select experts to learn more about particular major initiatives. Due to the timeline of the project, some experts were not able to respond in time for this report’s publication (Figure 10).

3.3 Country case studies

[iv] We limited the scope of our research to only antibiotic products for humans, however we recognize that R&D of veterinary antibiotics is an important aspect of the One Health approach to AMR.

[v] A semi-systematic literature review or rapid literature review follows a predetermined structured format for compiling and identifying relevant information from peer-reviewed and non-peer-reviewed sources. However, it does not include the same degree of review repetition and external review input that would be associated with a complete systematic literature review. Due to time constraints, a semi-systemic review structure was used instead of systematic review structure.

Using a combination of our primary and secondary research, we drafted short case studies of the major antibiotic R&D initiatives at international, pan-European, and national levels. These case studies provide an overview of the various initiatives and each one is complimented by a brief analysis based on the framework discussed in the following section.

- Antibiotic Research UK
- Antimicrobial Resistance and Health Acquired Infections Program, European Centres for Disease Control and Prevention
- Astellas
- AstraZeneca
- BEAM Alliance
- Broad Spectrum Antimicrobials Program, Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
- Canadian National Research Council
- European Federation of Pharmaceutical Industries and Associations
- European Medicines Agency
- GlaxoSmithKline
- Innovative Medicines Initiative
- Institute of Infection and Immunity, Canadian Institutes of Health Research
- Joint Programming Initiative on Antimicrobial Resistance
- Health Directorate, Directorate General Research and Innovation, European Commission
- Merck
- Ministry of Health, Welfare and Sport, Dutch Government
- National Institutes of Allergy and Infectious Diseases, US National Institute of Health
- Office of Antimicrobial Resistance, US Centers for Disease Control and Prevention
- Office of Life Sciences, UK Government
- Organization for Economic Co-operation and Development
- Pew Charitable Trusts
- Public Health Agency of Canada
- The Review on Antimicrobial Resistance
- Swedish Research Council
- UK Medical Research Council
- Vinnova

Figure 9. The list of organizations that provided expert input on the compilation and basic assessment of identified antibiotic R&D initiatives.

- Office of Antimicrobial Products, US Food and Drug Administration
- World Health Organization

Figure 10. The list of organizations that did not respond in time to provide expert input on the compilation and basic assessment of identified antibiotic R&D initiatives.

3.4 Framework for initiative analysis and discussion

Initiatives were analyzed based on their underlying incentives used to facilitate discovery and development of antibiotics and related medical products (Table 5). We first identified:

1. The type of incentives used (i.e. push vs. pull)
2. The antibiotic value chain barriers targeted by these incentives (i.e. basic research, preclinical development, clinical development, market approval, and commercialization)
3. The amount of funding backing the antibiotic R&D incentives

Following this, we analyzed the initiatives according to the critical actions required of a comprehensive and effective incentive package as proposed by Renwick et al.[30] Therefore, we examined whether a particular initiative as a whole fulfilled the following:

1. Improved antibiotic R&D NPV
2. Supported SMEs throughout the antibiotic value chain
3. Enticed large pharmaceutical companies to participate in the antibiotics market
4. Encouraged stakeholder synergies
5. Promoted antibiotic stewardship and patient access
6. Addressed specific high-priority medical needs (e.g. antibiotics targeting Gram-negative bacteria)

First-tier assessment	• What types of push and pull incentives are used under this initiative? • Which barriers are targeted in the antibiotic value chain by this initiative? • How much funding is available to this initiative?
Second-tier assessment	• Does this initiative improve antibiotic project NPV? • Does this initiative enable SMEs to participate in antibiotic R&D? • Does this initiative engage large-cap pharmaceutical companies to participate in antibiotic R&D? • Does this initiative facilitate any form of collaboration and synergy among relevant stakeholders? • Does this initiative promote the goals of antibiotic conservation and patient access? • Does this initiative target specific high-priority medical need?

Table 5. Outline of analysis framework applied to each identified antibiotic R&D initiative.

Based on our evidence collection and analysis, we compiled a set of key policy questions that deserved further discussion. This discussion ultimately informed our final recommendations, in Section 6, regarding further enhancing global and European antibiotic R&D.

Our initiative analyses, discussion, and recommendations are founded on our own views and do not explicitly reflect the opinions of the numerous experts that provided input on this report.

4. Results

The following results section explores the most impactful initiatives identified at international, pan-European, and national levels. We first provide an overview of each initiative's agenda and programs. Then we provide a brief analysis of each initiative

according to the framework discussed above. A comprehensive table of all the initiatives identified in our research can be found in Appendix 3 as well as an assessment of these initiatives in Appendix 4.

4.1 Key International initiatives that foster R&D of antibiotics

4.1.1 Joint Programming Initiative on Antimicrobial Resistance

Overview:

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) is an international collaboration effort focused on streamlining and coordinating research in the field of AMR.[33] Established in 2011, the JPIAMR is now comprised of 22 member countries including numerous EU states, Switzerland, Canada, Israel, Turkey and Japan. The JPIAMR directs national funding from these countries towards research projects that fill key knowledge gaps in AMR. In addition, the JPIAMR aims to support research through establishing a biobank for clinical specimens, establishing a database compiling veterinary and human AMR research, collaborating with key stakeholders, and raising public awareness of AMR. Their strategic research agenda outlines six key areas of future investment in AMR research priorities: therapeutics, diagnostics, surveillance, transmission, environment, and interventions. The JPIAMR's first joint call for transnational research was published in early 2014 and the research projects started in early 2015. This €8.1 million first call, known as InnovaResistance: Innovative approaches to address antibacterial resistance, is composed of 7 research projects that address key issues such as infection, treatment development, target identification for antibacterial drug development, and pharmacokinetics. The JPIAMR also has three other research calls in various preparatory stages that focus on translational research, transmission dynamics, and research networks.

Analysis:

The JPIAMR provides antibiotic R&D incentivization in the form of direct research funding (push) and by providing an international forum for collaboration between researchers (push). The targeted value chain barrier of this initiative is basic research and thus academic groups are the primary benefactors. In fact, all the research partners listed for the first joint research call were universities or non-profit research organizations such as the Pasteur Institut. An international forum for AMR research collaboration such as the JPIAMR has the potential to disseminate novel research, minimize duplications in research, assemble expertise in AMR, and pool funding resources from its national partners. In addition, the JPIAMR is helping identify key research priorities in AMR and then allocating research responsibilities to various academic institutions. The early stage focus on basic research means that these incentives do not particularly reinforce stewardship programs or patient access to developed antibiotics down the line.

4.1.2 Transatlantic Task Force on Antimicrobial Resistance

Overview:

Created in 2009, The Transatlantic Task Force on Antimicrobial Resistance (TATFAR) is a cooperative agreement between the EU and US to harmonize government strategies combatting AMR.[34] Members of TATFAR include the key health regulatory, funding, and administrative bodies from the EU and USA (Figure 11). The TATFAR has 15 ongoing recommendations across three priority areas: "(1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, (2) prevention of healthcare and community-associated drug-resistance infections, and (3) strategies for improving the pipeline of new antimicrobial drugs." Of particular relevance to this report are the recommendations made regarding development of new antibiotic drugs. Broadly they call for greater financial incentives for private firms, improved communication between US and EU drug regulatory and research bodies, increased basic research funding, harmonized regulatory pathways for antibiotics, and open sharing of information on drug development. It is the responsibility of the relevant member organizations to implement these recommendations.

US Member Organizations:
- Department of Health and Human Services
- Centers for Disease Control and Prevention
- Food and Drug Administration
- National Institute for Allergy and Infectious Disease, National Institutes of Health

EU Member Organizations:
- Directorate General for Health and Consumers, European Commission
- Directorate General for Research and Innovation, European Commission
- European Centre for Disease Prevention and Control
- European Medicines Agency
- European Food Safety Authority
- Council of the European Union

Figure 11. Member organizations of TATFAR.[6]

Analysis:

TATFAR does not provide any direct incentives for the R&D of antibiotics given that it's mandate is to facilitate inter-organization & international communication, discussion, and harmonization. However, TATFAR brings together the critical government agencies involved in making decisions on antibiotic R&D funding, drug approval requirements, and market policies and regulations. TATFAR has the potential to implement incentives indirectly through it member organizations.

4.1.3 European & Developing Countries Clinical Trials Partnership

Overview:

Formed in 2003, the European and Developing Countries Clinical Trials Partnership (EDCTP) is an evolving public-private partnership between 16 European countries, 14 African countries, NGOs, and pharmaceutical companies to enable research collaboration and accelerate the clinical development of drugs for neglected infectious diseases.[35] HIV/AIDS, tuberculosis, malaria, and other infectious diseases of Sub-Saharan Africa are the primary targets for the EDCTP. Drug resistance is a major factor in treating many of these diseases, thus antibiotic development is an important part of the EDCTP's strategic agenda. The original EDCTP, spanning 2003 to 2013, had funding of approximately €800 million, half of which was sponsored through the EC's FP6 and FP7. The second generation of the EDCTP, EDCTP-2, is currently being implemented as another 10-year program (2014 – 2024). The European Commission is providing a contribution of up to €683 million with the expectation that member states will match contributions. The total funding for the new program, including private, NGO, and other third party contributions, is estimated to be €1.36 billion.[35]

EDCTP's funding is concentrated on clinical trials for treatment drugs, vaccines, alternative therapies like microbicides, and diagnostic tools that target HIV/AIDS, tuberculosis, malaria, and other poverty-centered infectious diseases that are susceptible to AMR. The EDCTP-2 will augment this current program by expanding to include all clinical trial and post-marketing phases (I to IV).[35] In addition, EDCTP supports the ongoing networking and capacity building required for developing an international system of clinical trial sites and which actively includes developing countries. Consequently, the EDCTP is responsible for establishing 4 African Regional Networks of Excellence for clinical trials that coordinate treatment development. Finally, the EDCTP provides ongoing access to research grants and scholarly fellowships to promote training and career development as well as the scientific contribution of individual researchers.[35]

Analysis:

The EDCTP forms one of the three key pillars of the European Commission's strategy to fight AMR – the other two being the JPIAMR and the IMI program. The EDCTP is highly successful in regards to incentivizing R&D of antibiotics and related products. It provides direct funding and access to the R&D resources and infrastructure required to move a drug candidate from basic research to market approval. In addition, it does an excellent job of engaging developing countries in the R&D process as well as industry partners. However, it does appear that EDCTP's industry partnership tend to heavily weighted towards the big pharmaceutical companies such as GSK, Sanofi, and Merck. It is unclear how, or if at all, the EDCTP pulls potential novel antibiotics through the market approval stages and eventual commercialization process. The EDCTP's ultimate goal of improving access to effective treatments for its target neglected infectious diseases

aligns well with current public health priorities. However, patient access and antibiotic stewardship are difficult to balance, particularly in developing countries where appropriate use of antibiotics is difficult to control. Thus, it is unclear how the EDCTP aims to facilitate appropriate use of any novel antibiotics that are produced through the initiative.

4.1.4 World Health Organization's Global Action Plan on Antimicrobial Resistance

Overview:

The WHO Global Action Plan on AMR was endorsed at the 68th World Health Assembly in May 2015.[36] It is a global call to action among all WHO member states, the Secretariat, international organisations, and other partners. The overriding goal is to "treat and prevent infectious diseases with effective and safe medicines."[36] It focuses on using a One Health approach as well as aiming for access for those in need. In order to achieve its goal, one of its strategic objectives is to make an economic case for sustainable investment. The aim is to increase investment in new medicines, diagnostic tests, vaccines, and other interventions.

The WHO Global Action Plan called for the creation of a new partnership to foster the development and conservation of antibiotics. The Global Antibiotic R&D Facility was planned to implement this part of the Action Plan.[37] The WHO and the Drugs for Neglected Diseases Initiative (DNDi) are working in collaboration on this partnership to develop novel antibiotics, as well as promoting their responsible use and ensuring equitable access. This partnership model is based on previous experience with neglected diseases. It encourages close collaboration with the public and private sector, including pharmaceutical companies and academia. It aims to address global public health needs. Three million euros in seed funding is required for the initial two-year start-up phase.

Analysis:

The WHO Global Action Plan is designed to encourage the development of novel antibiotics. It focuses on the latter stages of the value chain. It encourages an integrative approach. It is a plan, offering no monetary incentives, which details strategic objectives in order to achieve its overriding goal. The Global Antibiotic R&D facility aims to implement part of this plan.

While this facility is still in the planning phases it aims to target all levels of the antibiotic value chain from the basic research level to the commercialization phase. DNDi has successfully developed a pipeline of drugs and treatments for the most neglected diseases, and thus it seems like a valuable collaborator to work with in the fight against AMR. Possible incentives include the use of milestone prizes, which will act as pull incentives to encourage antibiotic development. In addition the strong emphasis on

collaboration with all stakeholders encourages synergy across the antibiotic market. It may play a complementary role to other initiatives such as JPIAMR, BARDA, and IMI, which will encourage further synergy across the antibiotic market.

4.1.5 G7 Global Union for Antibiotics Research & Development Initiative

Overview:

The Global Union for Antibiotics Research and Development (GUARD) arose from the 2015 Berlin Conference of G7 Health Ministries.[19] GUARD is an agreement among G7 nations that a collaborative approach among countries is required to effectively fight AMR. It is recognized that continued efforts are needed to stimulate the antibiotic R&D pipeline.

This initiative proposes priority areas for action and recommendations to stimulate antibiotic research and development. It explores how economic incentives can contribute to antibiotic research and development and it targets incentives along all areas of the antibiotic value chain, recommending levers at each stage.[19]

Analysis:

GUARD recognizes that individual countries have created incentives to encourage R&D but also recognizes that a global response is necessary to fully effect change. An international approach is required to encourage engagement of the pharmaceutical industry with antibiotic development and to coordinate research to avoid duplication. This initiative recommends a global antibiotic collaboration platform to foster research and development. While this initiative has important implications in global coordination of antibiotic R&D action, as of now, there are no concrete incentives that back its calls to action.

4.2 Key European initiatives that foster R&D of antibiotics

4.2.1 Directorate-General for Research and Innovation, European Commission

Overview:

The European Commission's Directorate-General for Research and Innovation (DG-RTD) funds numerous R&D projects related to AMR. These projects range in size from single research endeavours to multifaceted and coordinated programs. The DG-RTD's funding for AMR projects comes from the Sixth Framework Programme (FP6), Seventh Framework Programme (FP7) and Eighth Framework Programme, known as Horizon 2020. Altogether, the FP7 has provided $1.08 billion in European Commission funding

for 147 AMR projects. Starting in 2014, Horizon 2020 has funded 145 AMR projects so far with a budget of €316 million.[vi]

The Innovative Medicines Initiative (IMI) and the European & Developing Countries Clinical Trials Partnership (EDCTP) are two of the largest drug R&D programs operating under governance of the DG-RTD and funded with FP6 and FP7. Both these programs have dedicated significant resources to R&D of antibiotic products. The DG-RTD is now beginning is roll out the second iterations of the IMI (IMI2) and EDCTP (EDCTP2), funded through Horizon 2020.

The DG-RTD funds numerous individual projects related to antibiotic development separate from the IMI and EDCTP. Many of these individual projects target innovation in SMEs. Funded within FP7, 7 SME-focused research projects on novel antibiotics, vaccines, and alternative medicines were launched in 2013, each with a budget of over €90 million. As of 2014, Horizon 2020 is funding 28 AMR projects through the new H2020 SME instrument, which will fund SME antibiotic R&D. Of additional interest is the H2020 Better Use of Antibiotics Prize, which is a €1 million prize for developing a rapid point-of-care test to identify patients with upper respiratory tract infections that can be treated without antibiotics.[38]

Analysis:

The DG-RTD is one of the largest funding bodies supporting R&D in antibiotics, alternative medicines, and diagnostic tools. The DG-RTD is able to bring together many of the key stakeholders throughout the antibiotic value chain and allocate significant resources pooled from European member states. However, the complexity of project networks and sheer size of some of these programs makes it difficult to accurately assess the effectiveness of the DG-RTD in terms of AMR R&D. The diagnostics prize (pull) is an interesting departure from the R&D push funding typically offered by the DG-RTD. Alas, the €1 million reward is a relatively small denomination.

4.2.2 New Drugs for Bad Bugs, Innovative Medicines Initiative

Overview:

Launched in 2008, the IMI is a joint program between the European Commission under their FP7 and the European Federation of Pharmaceutical Industries and Associations (EFPIA).[39] The IMI is a public private partnership that brings together key stakeholders involved in healthcare research and development: universities, pharmaceutical companies, SMEs, patient organizations, medicines regulators, and health research companies. The IMI has a budget of €2 billion funded equally by the EC and EFPIA. The Initiative currently has over 60 projects that tackle various areas of unmet medical and social need such as Alzheimer's disease, schizophrenia, depression, chronic pain,

[vi] The EC contribution to IMI is not included in the budget figures presented for the FP7 and Horizon 2020.

autism, and AMR. Beneficiaries of the IMI are selected through a competitive call process and determined by an expert committee representing important stakeholders.

The New Drugs for Bad Bugs (ND4BB) Program is an IMI partnership established in 2012 and tasked with improving the discovery and development of novel antibiotics.[40] There are seven core ND4BB projects with a total committed budget of €606M, of which €317M is contributed by the EC's FP7.[41] These seven projects have been tailored to target different R&D barriers to the marketing of novel antibiotics (Figure 12). The projects TRANSLOCATION and ENABLE are focused on assisting early stage antimicrobial drug discovery; COMBACTE facilitates drug development of antibiotics targeting gram-positive bacteria; COMBACTE-CARE, COMBACTE-MAGNET, and iABC aim to tackle the drug development barriers of antibiotics targeting gram-negative bacteria; and finally DRIVE-AB looks at the economic and stewardship aspects of AMR. The largest project within ND4BB is COMBACTE, which has built four key pillars in AMR R&D: a clinical trial network (CLIN-Net), a microbial surveillance database (LAB-Net), a clinical trial design suite (STAT-Net), and an epidemiological network (EPI-Net). These pan-European platforms have created a core information centre that facilitates antibiotic R&D and makes findings accessible to all ND4BB partners. In addition to these core 7 ND4BB programs, the IMI also has the ongoing RAPP-ID program, which is developing a rapid point-of-care test for infectious diseases.[40]

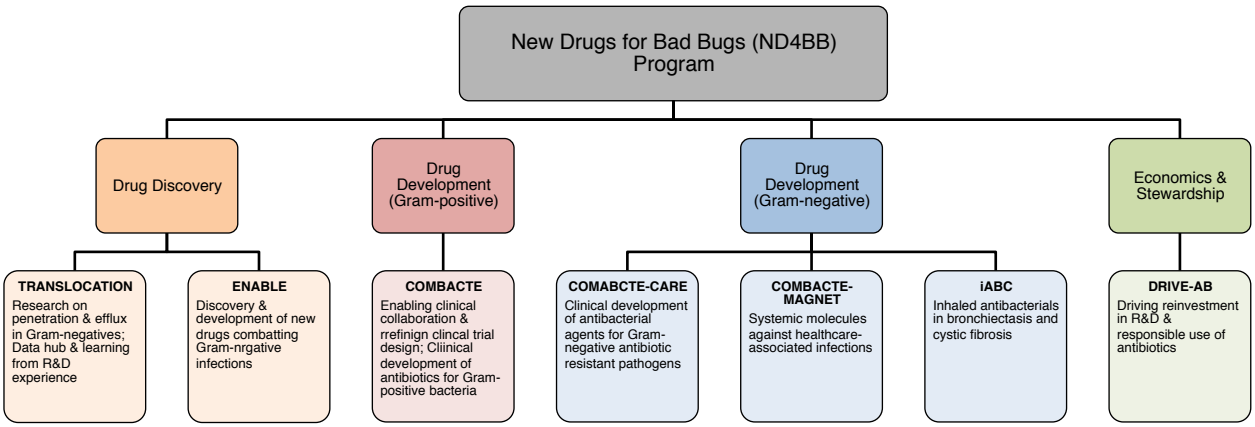

Figure 12. Breakdown of the New Drugs for Bad Bugs projects.[41]

The second iteration of the IMI – IMI2 – is currently being rolled out with funding from Horizon 2020. IMI2 aims to build on the successes of the IMI and will run for the period of 2014 to 2024 with a joint EC/EFPIA budget of €3.276B.[42] The IMI2's strategic research agenda outlines AMR as a key research priority and the IMI2 is expected to build on the ND4BB program (personal communication, Dr. Angela Wittelsberger, Scientific Officer at IMI, 2016).[43] Many of the ND4BB projects have only just been started and are slated to run until 2020.

Analysis:

The ND4BB Program is a comprehensive and well-established mechanism for supporting antibiotic R&D. It targets all aspects of the antibiotic value chain. The COMBACTE program is particularly commendable and has established key R&D resources in Europe (e.g. CLIN-NET, LAB-Net, and EPI-Net) that form the basis for additional drug discovery and development programs. The public-private partnership model employed throughout ND4BB seems to be effective at pooling resources, facilitating collaboration among key stakeholders in the development process, and sharing the financial risk of R&D outlays across both the private and public sectors. Save the ENABLE program, the majority of ND4BB seems to primarily fund larger pharmaceutical companies at the expense of SMEs (personal communication, Florence Séjourné, CEO of Da Volterra, 2016). In addition, the DRIVE-AB program has not produced significant results despite the considerably high funding of €11 million.

4.2.3 InnovFinn Infectious Disease Finance Facility

Overview:

"InnovFin: EU Finance for Innovators" is a joint project launched in 2014 by the European Investment Bank Group and the European Commission under its Horizon 2020 framework programme.[44] InnovFin builds on its FP7 predecessor, the Risk-Sharing Financing Facility, and is comprised of a series of financing tools and advisory services for innovative enterprises of all sizes. By 2020 it is expected that InnovFin will provide over €24 billion in debt and equity financing to research and innovation focused European companies. One of the core financial facilities offered is the InnovFin Infectious Diseases.[45] The InnovFin Infectious Disease Finance Facility (IDFF) provides access to loans of €7.5 million to €75 million to companies active in researching and developing medical products related to combatting infectious diseases. These financial products range from standard debt instruments to risk sharing agreements. InnovFin Infectious Diseases targets validated projects that have moved beyond the preclinical stages of development and are looking to progress through the clinical stages.

Analysis:

InnovFinn IDFF incentivizes antibiotic R&D through late-stage push funding in the form of low-risk loans and risk sharing programs. The IDFF primarily targets SMEs in the clinical phases of antibiotic development, but can also provide funding to large pharmaceutical companies as well. The IDFF is an innovative mechanism for providing access to funding by private developers that also tries to minimize public financial risk. The IDFF funds up to half of the project costs with the recipients funding at least 25% and third parties funding the remainder. Should the project fail, the loan essentially becomes a grant.

However, the condition that firms must have surpassed the preclinical phase of development may hinder the participation of SMEs, which often struggle to reach the clinical phases.[46] Furthermore, the loan sizes may be insufficient support for smaller firms who may not be able to raise enough additional capital to cover the high costs of clinical tests. As noted above, clinical development often costs upwards of €120 million. Another aspect to consider is that by funding proposals put forward by industry there is a risk that development goals may diverge from public health goals. Thus, a more collaborative approach may be required.

4.2.4 European Medicines Agency

Overview:

As the central drug regulatory body for the European Union, the EMA is responsible for the market authorization of antibiotics submitted through their centralized procedure on behalf of the European member states. As a core TATFAR member, the EMA is working closely with the US FDA to standardize an effective protocol for the market approval of high priority antibiotics, alternative medicines, and rapid diagnostic tools.[47] The EMA is able to employ a number of regulatory tools to expedite the market approval of novel antibiotic drugs such as: offering scientific advice and protocol assistance to pharmaceutical companies, accelerating assessment of new drug applications, and granting conditional market authorization for drugs that meet unmet medical needs.[47] Furthermore, the EMA has released an "addendum to the guideline on the evaluation of medical products indicated for treatment of bacterial infections."[48] Under this revision the EMA can authorize new antibiotics that address an unmet medical need related to AMR based on abbreviated, but targeted clinical development scenarios. Finally, it is interesting to note that the EMA is currently exploring the scientific and regulatory issues of bacteriophage therapy, which is not currently authorized in Europe as a medicinal product.[49]

Analysis:

The EMA can use multiple lego-regulatory pull mechanisms to facilitate market approval of antibiotic drugs that address AMR. Expedited approval pathways as well as access to the EMA's scientific resources can help lower the cost of developing antibiotics.[1] In addition, earlier market entry may improve the revenue potential of a novel antibiotic as the developer can take advantage of a longer effective market exclusivity period. From a public health perspective, faster approval periods for antibiotics can increase access to needed antibiotics. However, it is important that this authorization speed is balanced with maintaining an adequate standard of safety and efficacy in approved drugs.[30] SMEs often find that these lego-regulatory pull mechanisms do little to help them move through the expensive clinical phases of development.[1,30]

4.3 Key national initiatives that foster R&D of antibiotics

4.3.1 United States of America

4.3.1.1 National Institute for Allergies and Infectious Disease, National Institutes for Health

Overview:

The National Institute for Allergies and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and prevent infectious, immunologic, and allergic disease. The NIAID is the primary government agency within the US National Institutes for Health (NIH) that funds AMR R&D. In 2015, the NIAID had a budget of approximately $4.4 billion.[50] The Division of Microbiology and Infectious Diseases (DMID) is the department within the NIAID that is responsible for providing funding opportunities and resources for researchers that support basic research, preclinical development, and clinical evaluation of antibiotics. In a 2015 Health Affairs article, Outterson et al. note that annual NIH funding for AMR research has been steady since 2010 at roughly $350 million (Figure 13).[14] Unfortunately, this figure cannot be further separated to show how much goes towards antibiotic R&D.

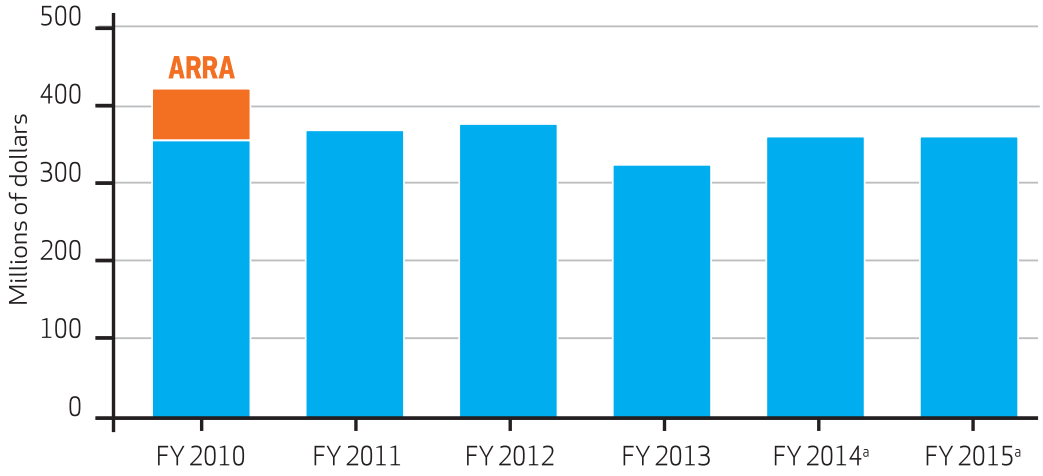

Figure 13. NIH research spending on AMR research, United States, Fiscal Years 2010-15.[14vii]

In 2013, the NIAID provided a $62 million grant over 6.5 years to establish the Antibacterial Resistance Leadership Group (ARLG).[51] Led by the Duke Clinical Research Institute, ARLG develops, designs, implements, and manages a clinical research agenda to increase knowledge of AMR. The Group is particularly focused on

[vii] FY 2014 and FY2015 are estimated by Outterson et al.

building transformational trials that will change clinical use of antibiotics. Some of their approaches involve earlier clinical evaluation of new antibacterial drugs and modernization of clinical trial testing strategies.

Another interesting initiative is the Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge.[52] Co-sponsored by the NIH and the Biomedical Advanced Research and Development Authority, the 2015/2016 Challenge is a prize competition of up to $20 million for the delivery of a diagnostic tool that can quickly identify bacterial infections in a clinical setting. The FDA and the Centers for Disease Control and Prevention (CDC) will provide the required technical and regulatory expertise for the evaluation process.

Analysis:

The NIAID is the largest US government funding body for antibiotic R&D from basic research through clinical development. The vast majority of funded projects seem to be individual basic research projects through university grants and academic fellowships. In addition, the NIAID provides access to its vast network of R&D infrastructure, scientific expertise, and public and private partners. The ARLG is an example of a smaller faculty within the NIAID that coordinates the use of these resources and has multiple projects in the pipeline. The NIAID's pipeline levers are heavily push based, which is particularly appealing to smaller private firms, academic research groups, and NGOs. The diagnostic prize is a notable step towards using outcome-based pull mechanisms to entice firms with the resources and capital to successfully develop a diagnostic product through to commercialization. However, it remains to be seen if the prize of $20 million is a large enough incentive to overcome the significant development costs.

4.3.1.2 Broad Spectrum Antimicrobials Program, Biomedical Advanced Research and Development Authority

Overview:

The Biomedical Advanced Research and Development Authority (BARDA) is a government organization within the US Department of Human and Health Services. BARDA is tasked with enhancing development and purchasing of critical vaccines, drugs, therapies, and diagnostic tools intended for public health emergencies. Arising from the growing concern for AMR and the lack of antibiotic innovation, BARDA established the Broad Spectrum Antimicrobials (BSA) Program in April 2010. The BSA Program's mission is "to help revitalize the antimicrobial pipeline by forming innovative public-private partnerships with companies engaged in antimicrobial therapy development."[53] Much like other initiatives within BARDA, the BSA Program provides non-dilutive funding and expert support throughout the stages of a drug's clinical

development. The BSA Program's budget is determined annually. Their 2016 fiscal year budget has been awarded $182M, over double the previous year's budget of $79M.

Since the Program began five years ago, they have assisted four candidate antimicrobials from preclinical stages to Phase III clinical trials, and another candidate to late stage Phase I clinical trials.[53] The program's success is reflected in expected new drug applications from these projects; one is to be filed in April 2016 and another in 2017 (personal communication, Dr. Joe Larsen, Chief of the BSA Program at BARDA, 2016). In addition, the BSA Program has setup flexible cost-sharing partnerships with GlaxoSmithKline and AstraZeneca that encompass a portfolio of candidate antimicrobials. The GSK/BSA partnership has funding of $200M over 5 years ending in 2018 and has so far resulted in one candidate being progressed to Phase II clinical development, and another lead clinical candidate that targets gram-negative bacteria being identified.[53,54] The AstraZeneca/BSA partnership, started in 2015, has funding of up to $170M over its 5-year contract.[55] This partnership currently has one candidate in its portfolio and is in Phase III. Notably, the IMI-ND4BB is contributing funding for the EU clinical trials for this drug through their COMBACTE-CARE program.

In the US National Action Plan for Combatting Antibiotic Resistant Bacteria, one of the strategic objectives was to create the Antibiotic Resistance Biopharmaceutical Incubator to improve the number of candidate molecules in the development pipeline.[56] This incubator, operated by BARDA and the NIH, would build on the BSA Program's flexible portfolio partnership model that would create a consortium of key stakeholders that could pool funding, expertise, and resources into the higher risk initial stages of drug development. The idea would be to further de-risk innovative research necessary to produce candidates with novel approaches to combatting resistant gram-negative bacteria. Providing early stage funding allows innovative research to be validated enough for other sources of investment to participate: venture capital funds, governmental organizations like BARDA, or non-governmental organizations and charities. The development of the biopharmaceutical incubator is still in the early stages however the National Action Plan calls for it to be operational by 2018.

Analysis:

BARDA's public-private partnership incentive model is particularly targeted at the preclinical and clinical development barriers of antibacterial drugs. This synergistic approach appears to be effective given their success in progressing several drug candidates to market authorization assessment. The significant committed funding behind the GSK and AstraZeneca partnerships is promising and the flexible nature of these two collaborative portfolios is a welcome departure from the more bureaucratic process of typical government R&D funding. The portfolios allow the BSA and major pharmaceutical companies to quickly determine the viability of a particular project and either add or drop the project from the portfolio, thus reducing risk exposure and cost. The biopharmaceutical incubator program will help BARDA apply its model to earlier

basic research and hopefully provide a transitional link to the clinical phases of antibiotic development. This incubator may allow BARDA to appeal more readily to SMEs, which have not been well integrated into BARDA's partnerships. Finally, it is important to recognize that BARDA's focus on defensive and emergency related drugs may limit the scope of its antibiotic R&D agenda.

4.3.1.3 Food and Drug Administration

Overview:

The US FDA is a federal agency of the US Department of Health and Human Services. It collaborates with partners to address the issue of antibiotic resistance. It aims to ensure development of new strategies including novel antibiotic development and diagnostic devices. The US FDA collaborates with external partners to advance clinical trials.

The agency is responsible for the market authorization of antibiotics in the US and uses a number of regulatory tools to support their development. Some of these levers are available through the implementation of the GAIN Act, which was ratified in 2012 as part of the Food and Drug Administration Safety and Innovation Act.[47,57] The GAIN Act allows Qualified Infectious Disease Product Designations (QIDP) to be granted to unique molecules. These QIDPs allow priority review of molecules as well as fast-track designation, allowing early consultation between the FDA and antibiotic sponsors. They may also allow an additional five years of market exclusivity.

The FDA has also created a multidisciplinary antibacterial Task Force to prioritise antibiotic development. This is a collaborative approach involving researchers within the FDA and as well stakeholder groups involved in antibiotic development.[58] Within the Task Force there is a focus on improving efficiency of clinical trials to aid antibiotic development.

A further initiative proposed is a Limited Population Antibacterial Drug Program (LPAD) under the 21st Century Cures Act.[59] This would provide the FDA with a new approval pathway to streamline the process of antibiotic development to allow access to antibiotics to patients with serious bacterial infections who lack appropriate treatment options. These antibiotics would be studied in smaller clinical populations and would establish safety and effectiveness for a limited population and are not generalizable to the patient population as a whole[60]

Analysis:

These initiatives described are acting as pull incentives, specifically lego-regulatory strategies, to accelerate novel antibiotic development. By granting QIDPs to unique molecules, the GAIN Act encourages alignment between regulatory agencies and

industry and improves the market attractiveness of antibiotic development. This targets the latter stages of the antibiotic value chain (market approval and commercialization).[19] Overall this aims to speed up the antibiotic development process, accelerating access to novel antibiotics. While this should encourage participation by large pharmaceutical companies and improve the NPV, it may not benefit SMEs who may lack the capital reserve of reaching the clinical trial assessment stages.

The option of offering an additional five years of market exclusivity may further encourage participation of large pharmaceutical companies who can recover R&D costs. The high prices associated with extended intellectual property rights may, however, burden the health system and limit patient access.[30]

By focusing on efforts to improve clinical trial efficiency the multidisciplinary Task Force can target the clinical development stage. It also aims to facilitate synergy and cooperation between stakeholders.

The accelerated approval pathway offered by LPADs under the 21st Century Cures Act would speed up the process of antibiotic development and access for those with urgent need, but there is a possibility that this could compromise safety and efficacy.[30] Some criticisms of this proposal include concerns regarding the methods used to speed up this process.[61] The FDA would need to consider non-traditional study design and data analysis methods in order to accelerate drug approval. This leads to concerns regarding efficacy and safety as data may be drawn from different sources including small studies or phase II clinical trials. While the antibiotics would be labelled accordingly with disclaimers, there is no guarantee that they would only be prescribed to the limited group of patients they are intended for.

These initiatives certainly offer incentives to accelerate the process of developing antibiotics for clinical use by targeting the latter stages of the value chain and encouraging large pharmaceutical companies to participate. However, as they only materialize in the final stages of antibiotic development, SMEs may be unable to participate if they lack the capital reserve to reach the later clinical study phases.

4.3.2 Canada

4.2.2.1 Institute of Infection and Immunity, Canadian Institutes of Health Research

Overview:

The Canadian Institute of Health Research (CIHR) offers opportunities for funding within health research.[62] The CIHR has invested $93.8 million CAD, between 2009/2010 and 2013/2014, in AMR research, of which $15 million CAD was in 2013/2014. There has been a focus towards investment in innovation. Within the CIHR, the Institute of Infection and Immunity (III) supports research and helps to build capacity in the areas of

infectious diseases and the body's immune system. The CIHR-III 2013 -2018 Strategic Plan has made AMR a priority area for research. Previous projects have included the development of a surveillance program, monitoring bacterial infections and antibiotic use.

Several initiatives have been developed specifically targeting the area of antibiotic resistance. The Novel Alternative to Antibiotics (NAA) Funding Opportunity Initiative aims to increase research funding available.[62] This initiative started in 2006 and is currently ongoing with total funding of $13 million CAD. Through open competitions it aims to encourage applications that are focused on novel approaches to antibiotic resistance. It combines input from 26 different partners including academia, industry, government, and NGOs. As a result of this initiative, new antibiotics have been identified and several patents have been filed. A further initiative includes a partnership between Canada and the UK's Medical Research Council, which was established in 2007. Under this collaboration, a 4-year joint grant on antibiotic resistance was launched in 2010. The CIHR contributed $4 million CAD. This grant allowed the funded teams to create partnerships and secure additional funding.

Analysis:

The initiatives offered by the CIHR-III act as push incentives, targeting the antibiotic value chain at the basic research level. By offering scientific grants and fellowships it promotes antibiotic resistance as a priority area. In addition, by combining input across the private and public sector, the NAA Funding Opportunity may help to translate research into the preclinical development stage. The collaborative approach, both across the public and private sector and between Canada and the UK, does facilitate synergy and cooperation within the antibiotic market.[19]

4.3.3 United Kingdom

4.3.3.1 UK Medical Research Council

Overview:

The Medical Research Council (MRC) is a publicly funded governmental organisation, which coordinates and funds research in the UK. The MRC had a total budget of £771.8 million in 2014/2015.[63] It is working to address the key challenges in AMR in a multidisciplinary approach through three key initiatives: the Antimicrobial Resistance Funders Forum (AMRFF), the Tackling AMR – UK Cross Council Initiative, and the UK Clinical Research Collaboration/ Translational Infections Research Initiative.

First, The Antimicrobial Resistance Funders' Forum (AMRFF) coordinates research councils, health departments, government bodies and charities and provides a forum to share information on AMR.[64] Second, The Tackling AMR - UK Cross Council Initiative is

a new inter-disciplinary program initiative started in 2014 that focuses on cross-resistant bacteria of humans and animals.[65] The Cross Council Initiative has four main themes to its strategy: (1) understanding resistant bacteria, offers grants to improve basic knowledge of this area; (2) accelerating therapeutic and diagnostics development aims to stimulate research to encourage antibiotic development, with collaboration between academia and industry; (3) understanding the real world interactions aims include delivering new surveillance networks across different environments; and (4) understanding behaviour within and beyond the health care setting assesses how to ensure a viable antibiotic market. Finally, The UK Clinical Research Collaboration Translational Infection Research Initiative (UKCRC TIRI) aims to promote infection research by encouraging multi-disciplinary collaboration, improve research infrastructure, and promote human resource development.[66] With funds of up to £16.5M, the UKCRC TIRI offers consortium grants to support new research partnerships and strategy development grants to foster new partnerships and improved research bids.

Analysis:

These initiatives act as push incentives to encourage infection research and to improve access to research. They predominantly target the early stages of the antibiotic value chain (basic research, preclinical and clinical development levels). The collaborative approach encourages the sharing of information and the partnership between academia and industry encourages synergy across the market. This allows a coordinated approach to the issue of antibiotic resistance. This collaboration may encourage participation of pharmaceutical companies if they have the necessary capital reserve.

4.3.3.2 Review on Antimicrobial Resistance

Overview:

The Review on Antimicrobial Resistance by Jim O'Neill was commissioned by the UK Prime Minister, David Cameron, in 2014 to explore global solutions to AMR.[5] It is also funded by and supported by the Wellcome Trust, an independent global charity. To date numerous reports have been published encouraging innovation in antibiotic development and in the development of rapid point-of-care diagnostic tests. The review recommends greater funding to support early-stage R&D activities. They suggest a Global Innovation Fund for AMR of $2 billion over 5 years with support from the global pharmaceutical industry.

The AMR Review recommends market entry rewards for successful new drugs, which meet priority indications. It estimates that $15-35 billion is required to achieve about 15 licensed new drugs over the next 10 years. This would include two new broad-spectrum classes of antibiotic and two newly targeted therapeutic classes every decade. It works with key stakeholders to determine R&D pipeline lever solutions. The final package of recommendations will be available by the summer of 2016.

Analysis:

Initiatives proposed by the O'Neill Review could act as both push and pull incentives.[46] By recommending early stage investment as well as later stage lump payments, these initiatives target all stages of the value chain. The investments are realistic in scale for antibiotic development. Offering market rewards would target the later stages of market approval and commercialization and these late stage payments would help to delink the volume of antibiotics sold from industry revenues. These investments could improve the NPV of antibiotic projects and as such could encourage participation of pharmaceutical companies.

A global innovation fund, with contributions from the pharmaceutical industry, would help to support early stage research and may encourage participation of SMEs in the antibiotic development market.[46] The $2 billion fund suggested is a realistic proposal for the costs that would be required. A further proposal is for the harmonization of the regulatory approval process across countries, which would encourage synergy and cooperation in the antibiotic market. The AMR Review also recommends increasing information sharing during the early development stage and this could be of benefit to both SMEs and large pharmaceutical companies by reducing the regulatory burden and the overall costs of antibiotic development. SMEs and larger pharmaceutical companies may be willing to share information to differing degrees. While the AMR Review offers a framework of how to tackle the issue of AMR on a global scale, the initiatives may be challenging to implement across a global market and may require considerable political effort to coordinate regulatory requirements across countries.

4.3.3.3 Longitude Prize

Overview:

The Longitude Prize is a monetary reward offered by Nesta, a British lottery funded charity.[67] It was announced by the UK Prime Minister David Cameron in 2012 and opened for submissions in 2014. There is a £10 million prize to develop a new diagnostic tool.

Analysis:

This R&D end-prize is a pull incentive that rewards the development of a successful diagnostic test. It targets the commercialization stage of the value chain and offers a substantial monetary prize. It remains to be seen whether this sum is an adequate incentive to pull a diagnostic tool to market.

4.3.4 France

4.3.4.1 French National Research Agency

Overview:

The French National Research Agency (ANR) was established by the French Government in 2005 to fund basic and applied research projects in all science fields.[68] It provides funding via grants to public research organisations, universities and private companies including SMEs. In the field of antimicrobial research it closely collaborates with the JPIAMR.

Analysis:

By providing funding via grants to both public and private companies, the ANR is utilising push incentives to encourage antimicrobial resistance R&D. This also may allow participation of SMEs that have limited capital reserve to enter the antibiotic market.

4.3.4.2 French National Institute of Health and Medical Research

Overview:

The French National Institute of Health and Medical Research (Inserm) was founded in 1964 as the only French public research institute to focus entirely on human health.[69] It has forged close partnerships with other public and private research establishments. Inserm's Institute for Microbiology and Infectious Diseases (IMMI), with support from AstraZeneca (€500,000), launched a call for two proposals on antibiotic resistance, in January 2014.[70] One focus was on the ultra-rapid diagnosis of resistance and the other was the identification of novel targets for antibiotics. Two projects have been selected.

Inserm (Transfert), an incorporated subsidiary of Inserm, focuses on adding value and reducing risk for innovative projects at pre-commercial stages, bridging the valley of death.[69] Inserm (Transfer) can provide developers with high-potential antibiotic candidates access to expert partners and an international R&D consortia to help push the project through the clinical phases of development.

Also, Inserm cofounded, with other research institutes, the National Alliance for Life and Health Sciences to strengthen coordination between national research institutes, universities and hospitals. Since January 2015, it has been coordinating research in areas of infectious disease and microbiology.[53]

Analysis:

The initiative by IMMI, with its support from AstraZeneca, focuses on basic research but also there is the possibility of translating this research into the preclinical development stage. Inserm (Transfert) focuses on reducing risk at pre-commercial stages and offers

a variety of push incentives to early-stage life sciences companies that need support across the preclinical valley of death. This encourages greater participation from SMEs. The development of strong collaboration between public and private partners, and the support of a large pharmaceutical company, facilitates cooperation and synergy across the antibiotic market. The National Alliance for Life and Health Sciences encourages collaboration with industry, which facilitates synergy across the antibiotic market and may encourage participation with pharmaceutical companies.

4.3.5 Germany

4.3.5.1 German Research Foundation

Overview:

The German Research Foundation (DFG) is a research-funding organisation serving all branches of science and humanity.[71] It currently supports a number of research projects on the subject of antibiotics within the field of basic research, providing funding through individual grants.

Analysis:

Funding basic research acts as a push incentive, which targets the value chain at the basic research level and may allow specific priorities to be targeted. An issue with these types of incentives is that tangible results are not always realised and it can be difficult to translate research into drug development.

4.3.5.2 German Centre for Infection Research

Overview:

The German Centre for Infection Research (DZIF) was established in 2011 by the German Federal Ministry for Education and Research (BMBF).[72] It aims to tackle the most urgent challenges in infection via an integrative approach. The aim is to ensure collaboration between universities, university medical centres, Leibniz and Max Planck institutes, Helmholtz centres, and other government research establishments. In total it is an affiliation of 35 research institutes located at seven sites distributed throughout Germany. DZIF has formed Thematic Translational Units of scientists, each dedicated to one specific pathogen or infectious disease. There are specific research areas focused on faster molecular diagnostics and the development of new vaccines and drugs.

InfectControl 2020 is a consortium of representatives from academia and enterprises, which encourages cooperation between scientists and industry in collaboration with patient associations and the general public. It aims to develop solutions regarding the

threat of antimicrobial resistance on a national and global level. BMBF heads the funding program.

Analysis:

Both DZIF and InfectControl 2020 aim to provide a collaborative approach to overcoming AMR. This may bridge the gap between basic research and antibiotic drug development and may go some way to overcoming the challenges at the preclinical development level or the 'valley of death'. This integrative approach should encourage the participation of larger pharmaceutical companies and also facilitate synergy across the antibiotic market.

4.3.6 Netherlands

4.3.6.1 Netherlands National Centre for One Health

Overview:

Utrecht University, UMC Utrecht and Wageningen UR founded the Netherlands National Centre for One Health.[73] It pursues basic and clinical research and allows collaboration between academia, research institutes, industry, policymakers, and NGOs. It forms the basis for a high-quality consortium with top expertise in the field of antimicrobial resistance. It aims to better understand the emergence, transmission, and dynamics of AMR and to improve and expand tools for AMR prevention and intervention.

Analysis:

By pursuing fundamental research and allowing collaboration between academia and industry the Netherlands National Centre for One Health aims to target many levels of the antibiotic value chain including basic research, preclinical development and clinical development. This collaborative approach encourages participation of the pharmaceutical industry and facilitates cooperation and synergy across the antibiotic market.

4.3.6.2 Netherlands Organization for Health Research and Development

Overview:

The Netherlands Organisation for Health Research and Development (ZonMw) funds and promotes research, development and implementation.[74] In order to help control AMR and to foster the development of new antimicrobials, ZonMw set up the research programme Priority Medicines Antimicrobial Resistance.[75] It will fund basic and applied research over a period of nine years (2009-2018) with a budget of €14.76 million. Five

main research areas have been identified which include mechanisms and targets for new drugs and new technologies, in particular rapid diagnostics.

Analysis:

By funding basic and applied research ZonMw is providing a push incentive, which targets the earliest stage of the antibiotic value chain. This aims to overcome the discovery void with a sizeable budget.[19] The Priority Medicines Antimicrobial resistance programme is funding basic and applied research with no role for the development of new drugs. This may mean there are potential avenues that are not translated into drug development.

4.3.7 Sweden

4.3.7.1 Swedish Research Council, Formas and Vinnova

Overview:

There are three major government agencies in Sweden that play a leading role combatting AMR and are responsible for supporting R&D of antibiotics. First, the Swedish Research Council is a government agency which was established in 2001.[76] It provides funding for basic research in all disciplinary domains; antibiotic resistance is one focus area. It has a leading role within the JPIAMR, with the main secretariat being hosted by the Swedish Research Council. Second, Formas is a national research council, which receives funding from the Ministry of the Environment and Energy and the Ministry of Enterprise and Innovation in Sweden.[77] It provides funding for basic research, with antibiotic resistance being a key priority. Third, Vinnova is a Swedish government agency founded in 2001.[78] It is the expert agency within the field of innovation in Sweden. It funds needs-driven R&D within strategically important areas, including antibiotic resistance.

Analysis:

All three of these government agencies provide funding through scientific grants and fellowships. They provide push incentives that primarily target the basic research; however, Vinnova offers avenues for clinical development of qualified drug candidates. While these incentives encourage research focused on antibiotic resistance, and may help to overcome the discovery void, they may not translate into marketable antibiotics. They can, however, complement other initiatives and benefit from public and private research collaborations.[19]

5. Discussion

Based on our case studies and initiatives analysis we formulated a series of key policies questions that deserved in-depth discussion. These questions are as follows:

1. How do current initiatives measure across the evaluation criteria?
2. What is the current balance between push and pull incentives?
3. What are our knowledge gaps in the antibiotics market?
4. What is the current level of coordination between and within initiatives?
5. What is the distribution of initiative support across the antibiotic value chain?
6. How are SMEs supported through existing initiatives?
7. Are public health needs reflected in the current set of initiatives?

This discussion forms the foundation from which we determined our final recommendations.

5.1 How do the current initiatives measure across the evaluation criteria?

Commendable steps are being taken to reinvigorate the antibiotic R&D pipeline at international, pan-European, and national levels. This is clearly evidenced by the 61 active initiatives that facilitate the R&D of new antibiotics, alternative therapies, or diagnostic devices. In addition, we identified 5 initiatives that have either been proposed or have yet to be fully implemented (e.g. IMI-2, Global R&D Facility, Fleming Fund, etc.). Our criteria-based analysis shows that there are important successes across the current schemes of R&D initiatives (Table 6).[viii] However, these areas of strength can and must be improved on. Our analysis also highlights a number of significant gaps and weaknesses across the current set of initiatives.

	Initiatives that improve antibiotic R&D NPV	Initiatives that enable participation of SMEs	Initiatives that encourage participation of large cap firms	Initiatives that facilitate cooperation & synergy	Initiatives that promote antibiotic conservation & patient access	Initiatives that targets specific high-priority medical needs
International-level	5	2	2	8	5	5
EU-level	13	3	10	11	2	10
USA	15	2	10	11	3	7
Canada	5	0	1	4	1	1
UK	9	3	3	5	2	3
France	4	1	0	3	0	2
Germany	4	1	1	3	2	2
Netherlands	3	1	1	3	2	3
Sweden	3	1	0	3	0	1
Total	**61**	**14**	**28**	**51**	**17**	**34**

[viii] See Appendix 4 for our criteria-based analysis of antibiotic R&D initiatives

Table 6. Tabulation of initiatives that fulfil the six incentive evaluation criteria.[ix]

Firstly, it is promising to see that almost all initiatives are working to improve the NPV of antibiotic R&D in some way. However, additional analysis highlighted that there is an imbalance in the number of push versus pull incentives used to improve antibiotic NPV (discussed in detail in section 5.2). Additionally, we found that there is unequal distribution of incentives across the antibiotic value chain that favours early stage basic research (discussed in detail in section 5.5).

We are also pleased to see that the majority of initiatives recognize that cooperation and synergy is critical to improving the antibiotic development pipeline. But, it appears that there is insufficient coherence and coordination across and within these cooperative initiatives (discussed in detail in section 5.4)

Our analysis has also identified a number of weaknesses within the current set of initiatives. Incentives targeting SMEs are particularly lacking at international, pan-European, and national levels (discussed in detail in section 5.6). It also seems that antibiotic stewardship and patient access policies are not well integrated into R&D initiatives (discussed in detail in section 5.7.1). Lastly, our research team had particular difficultly determining whether many R&D initiatives incorporated specific targeting of high-priority medical needs (discussed in section 5.7.2).

5.2 What is the current balance between push and pull incentives?

5.2.2 Incentives currently being used

Our analysis shows that there is currently an imbalance in how incentives are used to overcome the multitude of barriers facing antibiotic development. The vast majority of initiatives employ only push forms of incentivization (Table 7) and the bulk of funding follows these push-based initiatives. This is problematic given that a combination of push, outcome-based pull, and lego-regulatory incentives are needed to effectively improve the entire antibiotic pipeline.[30]

	Initiatives using only push incentives	Initiatives using only outcome-based pull incentives	Initiatives using only lego-regulatory incentives	Initiatives using a hybrid of push-pull incentives	Initiatives that only coordinate AMR action
International-level	5	0	0	0	3
EU-level	9	1	1	0	1
USA	5	1	2	0	4
Canada	5	0	0	0	0
UK	8	1	0	0	1

[ix] Evaluation criteria that were deemed unclear for a particular initiative were omitted from this tabulation.

France	4	0	0	0	0
Germany	4	0	0	0	0
Netherlands	3	0	0	0	0
Sweden	3	0	0	0	0
Total	**46**	**4**	**2**	**0**	**9**

Table 7. Tabulation of the number of active initiatives that used only push incentives, only outcome-based pull incentives, only lego-regulatory incentives, or hybrid push-pull incentives.

The EU and individual European states are relying on the use of traditional methods of supporting R&D, which may not be sufficient in the case of antibiotics. Figure 14 shows that the top 3 most common incentives are direct project funding, research collaborations, and research grants and fellowships for scientific personnel. These are valuable incentives, however, as discussed in detail below, they heavily support the early stages of the antibiotic value chain. In contrast, end prizes, prize competitions, and advanced market commitments, are rarely used, but effectively support the later commercialization stages required to bring an antibiotic into the market. Organizations such as the Global Alliance for Vaccines and Immunizations, also known as the Gavi Alliance, have successfully used pull mechanisms to incentivize development and marketing of drugs for neglected diseases.[79]

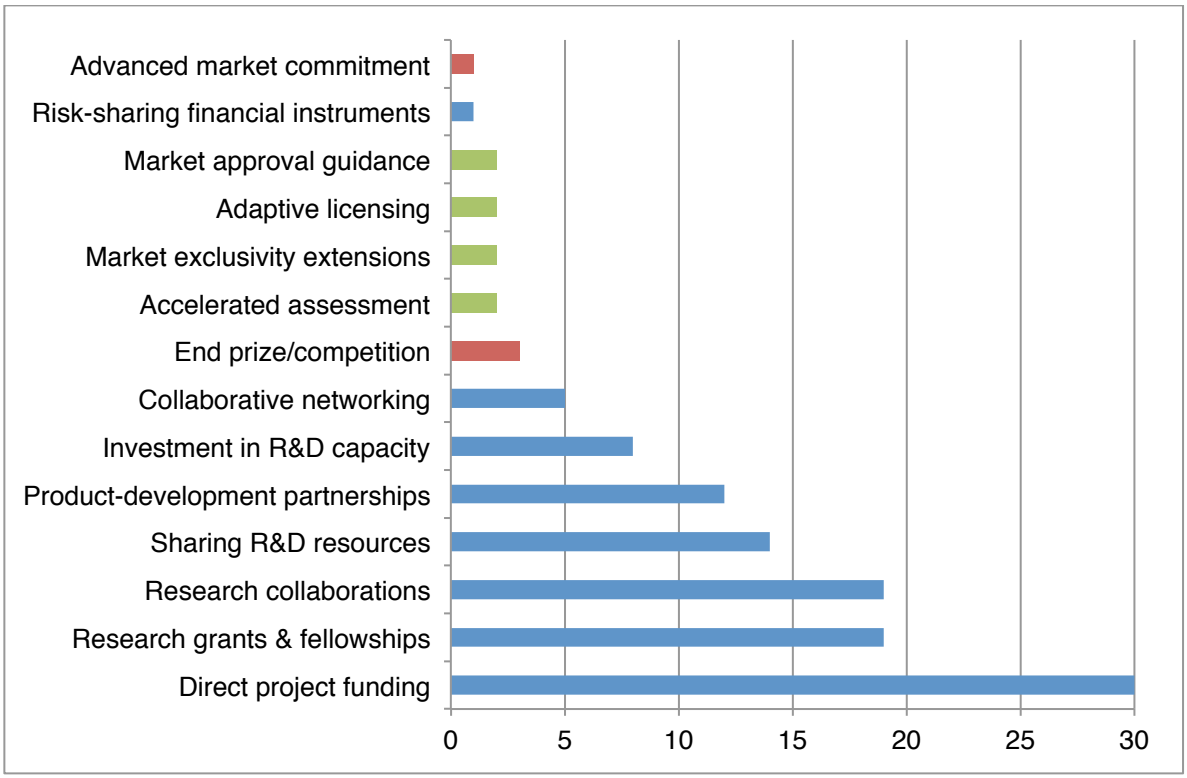

Figure 14. Distribution of incentives used by antibiotic R&D initiatives (Blue = Push incentive; Red = Outcome-base pull incentive; Green = lego-regulatory incentive).

5.2.2 Incentives that are missing

Based on our assessment of the existing initiatives, there are several key incentives that are missing from the current arsenal or are under utilized.[x] First, there are currently only three prizes offered in return for a marketable product. All three prizes target development of a rapid, point-of-care diagnostic tool – none target antibiotic drug development. The EC's prize offers €1 million, the UK's Longitude prize offers £10 million, and the US NIH's prize competition offers up to $20 million. It is unclear to us why there is such a large discrepancy between the prize denominations and why these prizes are independent, despite their common goal.

If an end prize were to target a novel first-in-class antibiotic, the AMR Review team estimated that the prize would need to be in the range of $1 to $1.5 billion.[5] This prize needs to be large due to time discounting and to make antibiotic investment competitive with other therapeutic fields. Given the great size of this prize, it would likely need to be offered and managed by a global or European body. Beyond incentivizing antibiotic development, this prize could be used as a method of purchasing the antibiotic's patent and jointly procuring the drug on behalf of participating countries. Global procurement of novel antibiotics has the benefit of being able to prudently manage the antibiotic's volume and distribution. The AMR Review further estimates that a fund of $15 to $35 billion would be needed to pull 15 new drugs over the next 10 years.

Also, it appears that pricing and reimbursement is missing from current antibiotic R&D initiatives. Aligning pricing and reimbursement schemes with the public health value that antibiotics provide is important to enticing investment in antibiotic R&D.[26] It appears that most countries include antibiotics within their wider pricing and reimbursement policies, which are often specifically tailored to reduce drug costs and procurement inefficiencies. The downward pressure on the prices of antibiotics, which are often lumped together with other drugs, does not reflect their true value. We recognize that national pricing and reimbursement strategies are highly contextual and reflect a country's individual health priorities and ability to pay. Yet, there still may be a role for medicines with high global health value, like antibiotics, to be priced and reimbursed separately from other health technologies. In conjunction, advanced market commitments should be considered as a method of controlling the volume of antibiotics purchased at value-centred prices. Advanced market commitments could be used by multiple nations to jointly procure antibiotics and regulate the antibiotic's consumption. Without consumption controls, value-based pricing and reimbursement may lead to high and unnecessary public cost.

Finally, through our analysis we did not identify any tax incentive policies that specifically benefit firms developing antibiotics and related products. Tax incentives can come in the form of tax credits, allowances, or deferrals that reduce a company's current tax liability.[30] In our opinion, there is a role for coordinated tax incentives in Europe that support firms developing antibiotics and potentially other global high priority

[x] This list is not exhaustive and there are multiple other incentives that have been proposed. See Renwick et al.'s 2015 review for additional insight on other incentives.

medicines. Tax incentives do not require upfront payments by governments and can be tailored to benefit both SMEs and big pharmaceutical companies. Furthermore, these tax incentives could be combined with clawback arrangements that recapture public funding once an antibiotic has successfully made it to market. Such a clawback arrangement makes sense given that the public ultimately deserves a positive return on their financial investment. In the context of taxes, this may take the form of tax deferrals that are recalled once an antibiotic makes it to market. Alternatively, the public could receive a return on their investment through guaranteed lower prices on antibiotics that reach the market. Clawback arrangements such as this could also be linked with push incentives as well.

5.3 What are our knowledge gaps in the global antibiotics market?

Based on our research, we have been able to gather a partial picture of the current antibiotics market. However, to better determine how best to improve the antibiotics pipeline, we need a comprehensive understanding of how much is being invested by private and public entities and what products are currently in development. Ultimately, we want to be able to determine return on investment (ROI) in terms of dollars spent and antibiotic pipeline progress. This will help public and private entities become more efficient with their investments.

5.3.1 Global antibiotic R&D investment

Based on Kelly et al.'s analysis of EU and JPIAMR national funding of AMR research, we can estimate that approximately €147 million was annually invested between 2007 and 2013 by European public agencies into the R&D of antibiotics, alterative therapies, and diagnostics.[31][xi] In contrast, we estimate that US government agencies invested approximately $260 million (~€240 million) in antibiotic R&D in 2015.[53,80][xii] The US investment in antibiotic R&D is expected grow substantially to $413 million (~€382 million) for 2016 with AMR budget increases to both the NIH and BARDA.[xiii] As can be

[xi] This figure was calculated using data displayed in Kelly et al.'s 2015 Lancet Infect. Dis. article. We summed the amounts invested at the EU and national levels into AMR research related to therapeutics and diagnostics over the 7 years of 2007-13. The entire EC contribution to the IMI was also included in this figure, despite the IMI funding projects beyond therapeutics and diagnostics. We subtracted the national contributions of non-EU JPIAMR members (Canada and Israel) pulled from the author's original dataset. Canada contributed ~$68 million to therapeutic and diagnostic AMR projects between 2007-13 ($9.8 million annualized) and Israel contributed $160,000 over the same period.

[xii] This figure was calculated using data from the NIH and BARDA, the two largest US government agencies funding antibiotic R&D. BARDA's FY2015 budget was $79 million. The NIH's FY2015 AMR budget was $361 million, half of which we assumed went towards R&D of antibiotics and related products. This assumption appears conservative given that approximately 84% of European public AMR funding is directed to either therapeutics or diagnostics.

[xiii] BARDA's realized FY2016 budget has increased to $182 million (personal communication Dr. Joe Larsen, Chief of the BSA Program at BARDA, 2016). The NIH has requested an increase of $100 million to its AMR budget in order better support the National Strategy for Combatting Antibiotic-Resistant Bacteria. Again, we estimated that half the NIH's AMR budget would go towards R&D of antibiotics and related products.

seen, there is a significant difference in public funding of antibiotic R&D between Europe and the United States (Figure 15). However, it is unclear how the differences in public funding have affected outcomes in the antibiotic pipeline. Thus, there is a need for an ongoing assessment of ROI from public antibiotic funding. Missing in this picture are the antibiotic R&D investments made by other nations such as Japan, South Korea, China, and India.

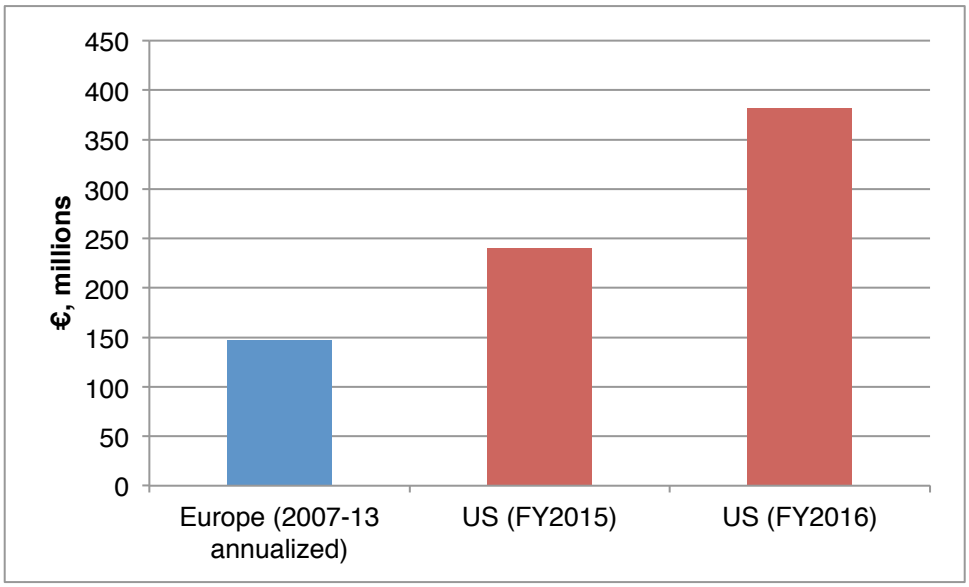

Figure 15. Estimated annual public funding of R&D of antibiotics and related products, Europe and the USA, millions of Euros.[14,31,53]

Private sector funding is the other part of the antibiotic R&D investment equation. However, we know little about how and how much the private sector is investing in antibiotic R&D. Commitments by private companies to public-private product development partnerships such as the IMI and BARDA likely only make up a small portion of private investment. Data on venture capital investment also only provides a snap shot of private investments into R&D projects. Based on 2008-13 data from the BIO report, $181 million was raised annually through venture capital for global antibiotic R&D. It is unclear to which firms (large pharmaceutical firms vs. SMEs) this venture capital money is heading. Further obscuring the picture is the lack of transparency in investments made by big pharmaceutical firms and SMEs into their own R&D operations.

5.3.2 The global antibiotic pipeline

Based on information gathered from the Pew Charitable Trusts and the BEAM Alliance we know that there are at least 19 antibacterial products in clinical development Phase I, 27 products in Phase II, and 6 products in Phase III (Figure 16).[15,17] Using transitional success rates for antibiotic clinical development, this pipeline might translate into approximately 6 systemic antibiotics that have the potential to target gram-negative bacteria. This is promising. However, only one antibiotic in the entire pipeline uses a

novel mechanism of action and it is specific to targeting Pseudomonas. Developing and marketing reiterations of existing classes of antibiotics will not overcome antibiotic resistance. Novel antibiotics are needed to provide more sustainable and effective methods of treating bacterial infections that are increasingly resistant to the current classes of antibiotics.

This pipeline analysis is not an accurate representation of the complete global antibiotic pipeline. We are missing US pipeline data on alternative therapies, European pipeline data from large pharmaceutical firms, and complete pipeline data from other countries such as Japan, South Korea, China, and India. In addition, we have no information on the development pipeline of diagnostic tools.

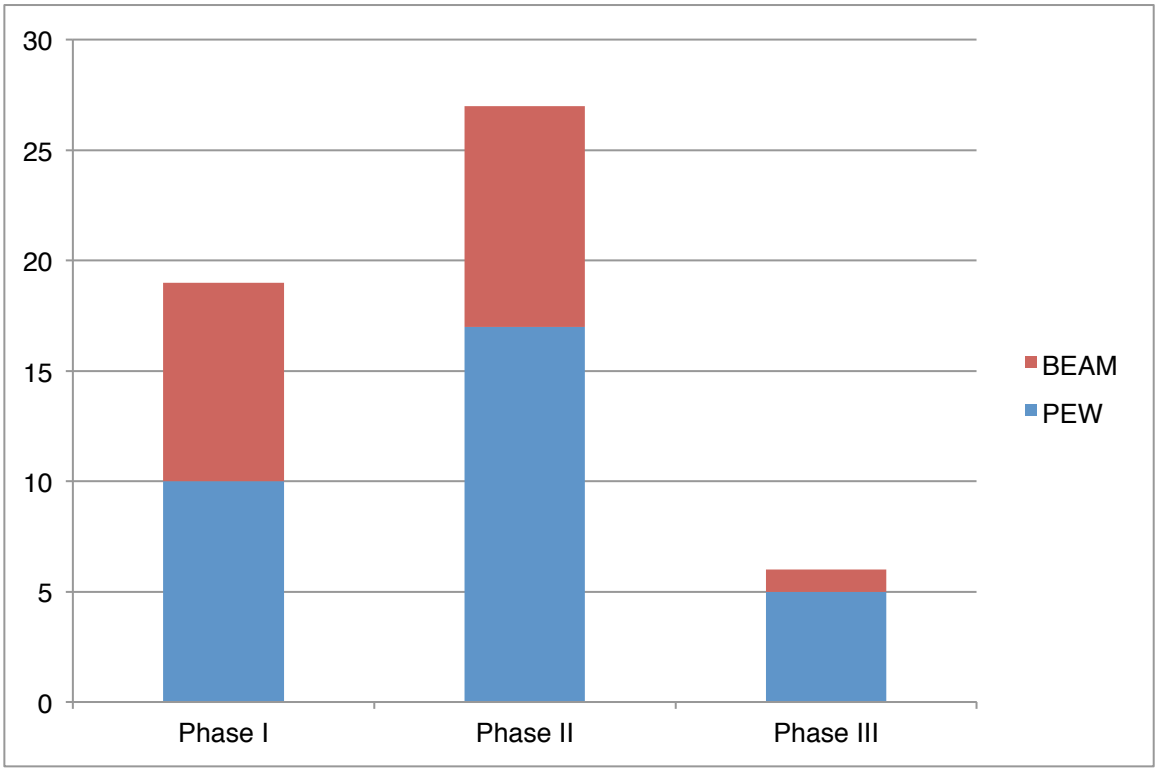

Figure 16. Partial picture of the current development pipeline of antibiotics and related products as compiled from data provided by the PEW Charitable Trusts and the BEAM Alliance.[15,17]

Having a complete picture of the antibiotic pipeline allows us to determine how aligned the current pipeline is with global medical needs. In doing, future investments can be better targeted to support high-priority, high-value antibiotic R&D projects. Moreover, by having a better understanding of the antibiotics pipeline we can more realistically assess the predicted market outcomes from current R&D. For instance, the Infectious Disease Society of America has called for 10 new antibacterial drugs by 2020, yet we do not know how close or far we are to reaching this goal.[81]

5.4 What is the current level of coordination between and within initiatives?

5.4.1 Inter-initiative coordination

The antibiotic R&D initiative environment has become crowded.[82] At just the global level, the JPIAMR, TATFAR, and EDCTP each actively strive to coordinate antibiotic R&D. The WHO Global Action Plan on AMR and the G7's GUARD Initiative are global strategies that plan to additionally coordinate global antibiotic R&D. Thus, there is undoubtedly some overlap in these international initiatives' goals, strategies, and activities.

There are also many valuable, smaller initiatives that are left out from these global coordinating networks. For instance, the JPIAMR does not leverage support from the UK's ANTUK, Wellcome Trust, and BSAC; Germany's Leibniz Institute and Infect Control 2020; Sweden's Vinnova and Formas; and the Netherland's Centre for One Health. Of particular concern is the degree of coordination in clinical trials globally and across Europe. The EDCTP, BARDA, and IMI are the largest antibiotic clinical trial programs, but there are multiple other initiatives that support clinical trials at a smaller scale. This suggests that there is significant room to build synergies across the existing set of initiatives by further sharing and coordinating resources. One final example of poor coherence across initiatives is the set of three different diagnostic prizes. Given the common goal between these prizes, it would seem efficient and effective to pool the awards together creating a larger incentive. Moreover, if prizes are going to be used as a method of ultimately procuring antibiotics then there needs to be coordination among initiatives offering the prizes.

Therefore, there is a need for a single global governing body for antibiotic R&D. This entity would: set globally accepted priorities and targeting for antibiotic R&D; coordinate all existing and new initiatives, build synergies between all stakeholders; minimize global inefficiencies arising from overlapping antibiotic R&D work; and integrate antibiotic R&D efforts within the broader global AMR strategy. Additionally, a global governing body will be essential to any strategy that involves joint procurement of antibiotics for multiple nations.

5.4.2 Intra-initiative coordination

Our analysis shows that a large number of initiatives are partnerships between two or more organizations, which benefit from sharing the risks and costs of antibiotic R&D. These partnerships vary substantially based on the number and type of organizations involved.

Public-private partnerships are the most common form and tend to be supported by significant funding. They can be single partnerships between a public agency and a pharmaceutical firm such as that of the BARDA/GSK joint portfolio program.

Alternatively, they may be multi-partnerships that bring together public agencies, academic institutions, NGOs, and industry, such as the IMI. In our analysis, we have also observed private-private partnerships such as ANTUK and public-public partnerships such as the JPIAMR.

However, it is unclear which method of partnership is most effective for differing purposes. Single partnerships boast adaptability to changing scientific discoveries and market conditions. In contrast, large multi-organization partnerships can draw on a wide array of resources, but may be less flexible. Moreover, the various public and private organizations that could participate in such partnerships bring varying benefits and drawbacks. Therefore, we suggest that the role of antibiotic R&D partnerships be further explored in the near future.

5.5 What is the distribution of initiative support across the value chain?

Our assessment shows that there is an unequal distribution of initiatives across the antibiotic R&D value chain (Figure 17). The following discussion section will explore this issue.

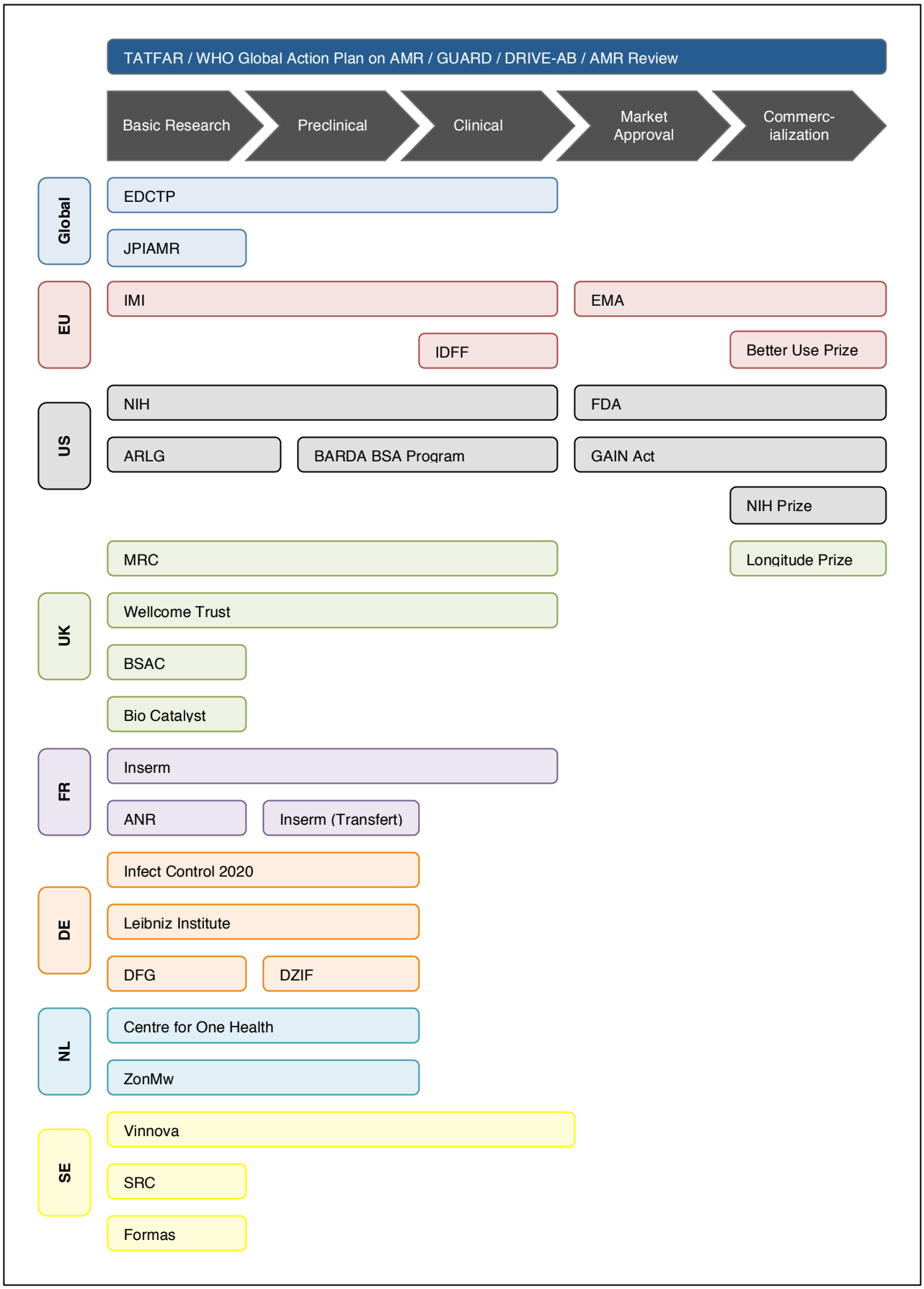
TATFAR / WHO Global Action Plan on AMR / GUARD / DRIVE-AB / AMR Review
Basic Research
Preclinical
Clinical
Market Approval
Commerc-ialization
Global
EDCTP
JPIAMR
EU
IMI
EMA
IDFF
Better Use Prize
US
NIH
FDA
ARLG
BARDA BSA Program
GAIN Act
NIH Prize
MRC
Longitude Prize
UK
Wellcome Trust
BSAC
Bio Catalyst
FR
Inserm
ANR
Inserm (Transfert)
DE
Infect Control 2020
Leibniz Institute
DFG
DZIF
NL
Centre for One Health
ZonMw
SE
Vinnova
SRC
Formas

Figure 17. Distribution of international, EU, and select European national antibiotic R&D initiatives across the antibiotic value chain.

5.5.1 Basic research

A majority of European initiatives identified in this report target basic research of antimicrobials. This finding is reiterated in Kelly et al.'s analysis of European public funding of AMR research, which found that 71% of national-level public funding in antibiotic therapeutics was for basic research (therapeutic sub-categories I & II).[31] Basic research lends itself to being subdivided into multiple small projects that require lesser monetary commitments. In comparison, preclinical and clinical research tends to require far larger investments that cannot be easily parsed. Thus, from a political feasibility standpoint it is understandable why the majority of public funding goes towards basic research. While basic research is important in the development process, an overemphasis of funding towards early discovery stages might inhibit R&D progress of existing antibiotic candidates that could reach the market.

5.5.2 Preclinical and clinical trials

The majority of European public funding towards preclinical and clinical trials appears to come from the IMI. Despite having only 9 active projects, the IMI has invested €312 million in European Commission public funding and €294 million in in-kind private sector contributions towards antibiotic clinical studies. The IMI has proven to be an excellent model for antibiotic development on multiple fronts.

First, the IMI actively engages with the pharmaceutical industry to combine resources and expertise. The public-private partnership model of the IMI also acts to align private and public priorities. Second, the IMI's investment in European-wide clinical trial infrastructure allows researchers to access a far greater pool of potential study participants than if clinical trials were operating out of one country. This facilitates timely clinical trial studies of antibiotics, while maintaining safety and efficacy standards. Third, the IMI is now engaging with non-European partners such as the BARDA's BSA program. This stands to further mutually improve the clinical capacity of participating initiatives.

However, the IMI's project format does not permit the same flexibility observed in the two portfolio programs within BARDA: GSK/ BARDA partnership and AstraZeneca/BARDA partnership. The BARDA antibiotic portfolios allow the BSA and the major pharmaceutical companies to quickly determine the viability of a particular project and either add or drop the project from the portfolio, thus minimizing risk and cost. By involving the BSA leadership team in the decision process, BARDA can still ensure that public health priorities are at the forefront of the portfolio development pipeline. This flexible partnership model may serve as a good example for some of IMI2's future projects in antibiotic R&D.

It worth noting that there are at least 72 research projects with clinical trial aspects that operate at national levels in Europe.[31] These projects likely have minimal coordination, which can be inefficient, and risks duplicating work.

5.5.3 Market approval

The EMA and FDA have a number of useful regulatory mechanisms to expedite approval of high-priority antibiotics. Both regulatory agencies have the ability to accelerate the approval process as well as approve antibiotics through adaptive licensing pathways. These regulatory tools indirectly improve NPV of antibiotic projects and can result in timely patient access to new antibiotics. However, these mechanisms must be used cautiously in order to not compromise the safety and efficacy of authorized antibiotics.

From a R&D perspective, the primary barrier to antibiotic development seems to be the lack harmonization in approval requirements between the EMA and the FDA. Ensuring an antibiotic meets both sets of standards is time consuming and costly for the developer. Given that both the EMA and FDA have similar goals in terms of antibiotic approval, it would be seem wise for both agencies to have an agreed set of authorization practices. Ideally, both agencies would agree to jointly approve antibiotics, thus providing market authorization to novel antibiotics in both regions at the same time. This could take the form of mutual recognition between the agencies whereby one agency would take the lead on an antibiotic application while the other agency advises and observes; these roles could alternate with each application. Alternatively, a joint approval committee could be established that provides expertise from both agencies.

5.5.4 Commercialization

Presently, there are few antibiotic initiatives that target the commercialization aspect of the antibiotic value chain. These include the three end prizes for diagnostic tools and the market exclusivity extensions offered by drug regulatory agencies to qualified antibiotics. Thus, the additional incentives proposed and discussed above (section 5.2.2) tend to fill this gap in the value chain. The IMI's DRIVE-AB program is also exploring incentive solutions that effect commercialization.

5.6 How are SMEs supported through existing initiatives?

Based on our analysis, it appears that SMEs in particular are lacking support from the existing set of initiatives. As highlighted above, a majority of European public funding is directed to academic institutions for the purposes of basic research. On the clinical end, the IMI's partnerships are with big pharmaceutical companies, except ENABLE (personal communication, Florence Séjourné, CEO of Da Volterra, 2016).

SMEs lack support in the preclinical and early clinical phases of development, which are expensive and necessary for validating access to future venture capital. The InnovFin: IDFF would seem like the perfect mechanism for bridging this barrier, however the IDFF loans require drugs to be already in the clinical phases of development. This substantial requirement may defeat the purpose of having a SME-focused antibiotic R&D initiative. The IDFF's largest available loan of €75 million may still not be enough to help SMEs through the expensive clinical phases that often exceed €120 million.

It would be prudent to have a consulting project that explores industry preferences for different incentives in order to accurately pinpoint how best to support the different market players. We would expect that SMEs and big pharma have quite different incentive wish lists and both need to be respected.

5.7 Are public health needs reflected in the current set of initiatives?

5.7.1 Stewardship and patient access

It is increasingly recognized that the current patent-based pharmaceutical business model does not sufficiently work for antibiotics. Antibiotic developers are rewarded through market exclusivity, which reinforces the over-marketing and over-consumption of antibiotics that contribute to high levels of resistance.[24] In addition, developers are incentivized to distribute antibiotics based on ability to pay instead of need. Therefore, low- and middle-income countries (LMIC) often have reduced access to high-value antibiotics.

As a result, delinkage has been proposed by academics, industry representatives, and policy makers as the basis for a new business model for antibiotics.[24,83] Delinkage occurs when a drug developer's revenues are separated from the volume of antibiotic sold. In theory, this would be accomplished through a value-based payment to the developer in return for control over the marketing and distribution of the new antibiotic. These payments may be in the form of payer licenses, a full patent buyout, or as advanced market commitments.[30]

Delinkage is a global solution to a global problem, however its practical implementation seems to be its largest barrier to fruition. Delinkage forms that allow firms to retain their intellectual property appear to be more favourably reviewed by industry.[30] Promisingly, a recent declaration was signed by 85 companies and 9 industry associations representing global pharmaceutical, diagnostics, and biotechnology development in 18 countries, calling on national governments to work with them in developing a new and sustainable antibiotic market.[84] The envisioned antibiotics market would have improved access to all those in need and a reduced incentive to promote antibiotic consumption.

Antibiotic stewardship and patient access are traditionally addressed through public health programs independent of R&D initiatives. These programs are run by the EU

Commission (i.e. DG SANTE) as well as agencies such as the EFSA and ECDC. Thus, few R&D initiatives have explicit stewardship and access policies. This makes more sense given that most initiatives use push mechanisms that are not tied to any post-approval conditions regarding marketing practices or distribution of the antibiotics. However, it is critical that R&D initiatives are interlinked with and reinforce the other aspects of combatting AMR. If R&D initiatives debase other AMR programs then we cannot have an effective global strategy for tackling this complex and evolving threat. In order to address this issue, the DRIVE-AB program has been tasked with designing and presenting a sustainable new business model for antibiotics that factors in these broader public health priorities. Their final recommendations are expected in 2017.

Another aspect of this issue pertains to developing countries, which suffer a majority of the global AMR health burden.[2] Often developing countries and even development agencies do not recognize AMR as a top health priority. Thus, actively seeking involvement from LMICs will be an important step in aligning antibiotic innovation with global health needs. The EDCTP is a convincing model for accomplishing this as it focuses antibiotic R&D towards LMIC health priorities and actively includes LMIC institutions in the antibiotic R&D process.

5.7.2 Medical needs

Ensuring that global medical priorities are aligned with those of the developer is critical to producing marketable antibiotics that target high-priority medical needs. The US pipeline analysis (Appendix 1) suggests that there is in fact significant alignment between developer goals and public health needs. Gram-negative bacteria and the ESKAPE pathogens are targeted. Moreover, many of the pipeline antibiotics are for the Big 5 indications, which are most commonly affected by resistant bacteria.

However, there are also multiple antibiotics in the pipeline that target lower priority diseases such as gram-positive acute skin infections. Also, there are very few antibiotics in the development pipeline that offer entirely new mechanisms of action that are not marred by cross-resistance. Low-priority antibiotics in the pipeline suggest that current initiatives do not set out clear objectives in antibiotic R&D.[4] This is one of the problems with push mechanisms; it is challenging to control the direction of private R&D to attain public health priorities. Milestone prizes tied to ongoing target product profiles is one possible method of ensuring push funding is allocated to antibiotic candidates pursuing high-priority medical needs. Larger end prizes linked to target specifications would be an alternative.

6. Conclusions & Recommendations

Spurring global innovation of new antibiotics, alternative therapies, and diagnostics tools is integral to effectively combatting AMR. However, demand for new antibiotic products far outweighs supply. Only five novel classes of antibiotics have reached the market

since 2000. None of these target gram-negative bacteria. This is not surprising given that there are a numerous scientific, regulatory and economic barriers that prevent adequate investment in antibiotic R&D.

We have a partial picture of the global antibiotics market. EU and US antibiotic pipeline data shows that are at least 52 antibiotic products in clinical development, the vast majority are in Phases I and II. However, this pipeline may only translate into 15 antibiotic products with varying value; less than half would be systemic antibiotics that could target gram-negative bacteria. Only one antibiotic in the development pipeline uses a novel mechanism of action and it is for a limited purposed.

Europe has invested approximately €147 million annually between 2007-13 in antibiotic R&D while the US has invested roughly $260 million (€240 million) in 2015. US investment in antibiotic R&D is expected to grow to $413 million (€382 million) in 2016 after having been constant for 5 years. However, it is unclear how this difference in EU/US funding has affected outcomes in the antibiotics pipeline. European and US governments do not appear to have any method of clawing back these significant contributions should their funding result in marketable products.

Our only real insight in private investment into antibiotic R&D is from global data on venture capital funding. Global venture capital in antimicrobial R&D has declined by 28% between the two five year windows of 2004-08 and 2009-13. Venture capital investment in gram-negative antimicrobials has increased by 51% during these two periods, but it still comprises only 12% of total venture capital investment in antimicrobials. The amount of internal capital invested by developers into their own antibiotic projects is unknown.

Numerous initiatives have been implemented to reinvigorate the antibiotic R&D pipeline. In total, we identified 61 active initiatives at global, EU, and national levels (UK, France, Germany, Netherlands, Sweden, US, and Canada). Also, there are 5 initiatives that are either proposed or in the introductory stages of implementation.

The antibiotic R&D initiative environment is now crowded. There appears to be weak coherence and coordination between and within initiatives. Various models of partnership often form the basis for many initiatives, which improves the possibilities for stakeholder collaboration, but can further confuse coordination efforts.

While almost all these initiatives can be seen to be improving antibiotic project NPV, our analysis shows that a far greater number of push incentives are used over pull incentives. This imbalance between push and pull incentives has led to an unequal distribution of initiatives across the antibiotic value chain. The most common incentives of direct project funding, research collaboration, research grants and fellowships for scientific personnel, tend to favour the basic research side of the antibiotic value chain. Thus, SMEs often find that they lack support throughout the challenging preclinical and

early clinical phases of development. Surprisingly, taxation policies (a push incentive) were not used to specifically support firms that engage in antibiotic R&D.

In contrast, there are few incentives that support the commercialization end of the value chain such as end prizes, advanced market commitments, and value-based pricing and reimbursement. Moreover, there remains a lack of harmonization between the EMA and FDA, as well as other drug regulatory agencies.

Finally, our analysis suggests that antibiotic conservation and patient access objectives are poorly integrated into the existing schemes. Many initiatives have not explicitly linked their incentives to high-priority medical needs in infectious disease.

Given this research report's key findings, we put forth the following fourteen recommendations:

Recommendation 1: Align existing and new antibiotic R&D initiatives to function within the broader One Health approach to AMR.

AMR must be tackled through a unified approach that respects the diverse actions required to prevent further resistance, facilitate appropriate use of antibiotics in human and animal contexts, preserve the existing arsenal of antibiotics, and stimulate innovation in antibiotic R&D. Antibiotic R&D initiatives must be integrated into a broader AMR agenda that reinforces other aspects of the One Health approach.

Recommendation 2: Consolidate and coordinate existing and new European AMR initiatives and antibiotic R&D initiatives, including clinical tirlas, under a One Europe approach.

In order to be a leader in the fight against AMR, Europe must establish coherence and coordination across its own AMR initiatives in a One Europe approach. This requires alignment of EU policies with member state policies both in terms of tackling AMR and in terms of antibiotic R&D. Of particular relevance to antibiotic development, is the Europe-wide organization of all antibiotic clinical trials.

Recommendation 3: Establish a global AMR policy coordination & governing body that brings worldwide coherence under a One World approach to AMR.

AMR is a global problem that necessitates a global solution. Given the proliferation of AMR and antibiotic R&D initiatives at global, regional, and national levels, there needs to be a governing entity that coordinates their activities under a One World approach. Multiple international AMR strategies have been proposed; now is the time to turn them into action. The upcoming 2016 UN General Assembly presents an opportunity to engage nations in this One World approach.

Recommendation 4: Intensify efforts to coordinate and expand European and global antibiotic clinical trial programs under One Europe and One World agendas.

Due to the nature of infectious disease, conducting clinical trials on antibiotics can often be logistically challenging. Significant efficiencies can be gained through clinical trial coordination. There is an opportunity for Europe to build and expand on the solid clinical infrastructure established under the IMI's COMBACTE program. There are a number of national-level antibiotic clinical trials that could possibly be integrated within the broader EU antibiotic clinical trial network. In addition, expanding collaborative efforts between COMBACTE and BARDA would serve to further strengthen these respective programs. Finally, the EDCTP offers an excellent model for further expanding European clinical trial efforts beyond EU boarders to include more LMICs.

Recommendation 5: Ensure antibiotic incentives are explicitly attached to specific high-priority medical needs in infectious disease.

There is malalignment between the observable antibiotic pipeline and key medical needs in the field of infectious disease. Incentives could be improved by attaching clear target product specifications when possible. Milestone payments can be tied to ongoing target product profiles to ensure that push funding is allocated to antibiotic candidates pursuing high-priority medical needs. Similarly, pull-based end prizes need to outline clear antibiotic characteristics that must be met to qualify for the reward.

Recommendation 6: Launch a global AMR observatory that collects AMR and antibiotic pipeline data, shares knowledge, and disseminates best practices in AMR and antibiotic innovation.

Significant gaps exist in our understanding of AMR and the antibiotics market. From an innovation perspective, there is a need to determine the evolving global antibiotic pipeline and the global investments made into the antibiotic pipeline. Ideally, we will be able to learn from this data, share useful knowledge, and disseminate best practices as they are developed. Ahead of our recommendation, the WHO is already in the process of designing a global health R&D observatory that could include, as well as extend beyond antibiotics. However, in line with the One Health approach, a global antibiotic R&D observatory would need to be integrated with other aspects of AMR data collection such as disease surveillance.

Recommendation 7: Register European and global commitment to antibiotic pull incentives.

Pull incentives are effective tools for enticing antibiotic developers into the market. However, they require significant monetary commitments to adequately reward developers of authorized high-value antibiotics. Thus, global pooling of resources is required to effectively pull high-value antibiotics into the market. The upcoming United

Nations 2016 General Assembly, which will discuss AMR, is an opportunity to pave the way for countries to coordinate and commit to pull incentives.

Recommendation 8: Explore the role for European joint procurement of high-value antibiotics to ensure their conservation.

Joint procurement of antibiotics can provide a method of securing public control of a high-value antibiotic's consumption and distribution across member states. In addition, joint procurement can signal European commitment to purchasing high-value antibiotics at fair prices and can be tailored to reflect differences in countries' ability to pay. The EU is in a unique position to consider developing a joint procurement facility for purchasing high-value antibiotics.

Recommendation 9: Consider the feasibility of European tax policies that encourage antibiotic R&D.

There is a role for coordinated tax incentives in Europe that support firms developing antibiotics and related products. Tax incentives do not require upfront payments by governments and can be tailored to benefit both SMEs and big pharmaceutical companies. Furthermore, tax incentives can leverage tax deferrals as a method of clawing back public investment in antibiotic R&D.

Recommendation 10: Incorporate methods of clawing back public investment in antibiotic R&D into incentive packages.

The public deserves a positive return on their financial investment in antibiotic R&D. Incentives that have clawback arrangements can still support firms throughout development, while also allowing for public purchasers to benefit from their original investment. Clawback policies can supplement both push and pull incentives alike and could take the form of tax deferrals or advanced market commitments on discounted antibiotics.

Recommendation 11: Improve antibiotic harmonization across global drug regulatory agencies and encourage joint antibiotic authorization between the EMA and FDA.

Poor harmonization in approval requirements between drug agencies is a significant barrier to antibiotic developers. Harmonization must extend beyond TATFAR to include other drug agencies around the world. In addition, we support the establishment of joint authorization procedures for novel antibiotics between the EMA and FDA. This could be accomplished through a joint EMA/FDA review committee or mutual recognition in the authorization decisions made by either agency.

Recommendation 12: Address key market weaknesses by enabling SME participation and facilitating preclinical development.

SMEs continue to be under supported in the antibiotics market despite their contribution to the development pipeline. More initiatives must recognize the specific resource barriers faced by SMEs and ensure that their incentives are accessible and beneficial to SMEs. In particular, SMEs require initial capital support through preclinical and early clinical phases of development, which are often characterized as the R&D "valley of death."

Recommendation 13: Explore the incentive preferences of different industry players.

Despite knowing that SMEs and large pharmaceutical companies need to be incentivized to develop antibiotics, we do not know exactly what types of incentives are preferred by either type of industry player. Therefore, we recommend exploring industry preferences for different incentives in order to accurately determine how best to support the different market players.

Recommendation 14: Investigate the value of different partnership models in antibiotic R&D and learn from the experiences of the US Biomedical Advanced Research and Development Authority.

There is now a wide proliferation of initiatives founded on partnerships. These partnerships vary substantially based on the number and type of organizations involved. There are likely advantages and disadvantages to the different partnership models that can provide insight into positively reforming these initiatives. One model that is particularly worth learning more about is BARDA's portfolio partnerships with GSK and AstraZeneca. Therefore, we recommend funding research that investigates the roles of partnerships in antibiotic R&D.

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Appendix 1: Antibiotics currently in development or recently approved in the US market[xiv]

Drug name	Development Phase	Company	Drug class	Expected activity against resistant Gram-neg. ESKAPE pathogens?	Expected activity against a CDC urgent threat pathogen?	Potential indication(s)?
Ceftolozane + Tazobactam (Zerbaxa)	Approved Dec. 19, 2014	Cubist Pharmaceuticals, Inc. (wholly owned subsidiary of Merck & Co.)	Novel cephalosporin + beta-lactamase inhibitor	Yes	No	Approved for complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection); other potential indications: hospital-acquired bacterial pneumonia (HAP)/ventilator-associated bacterial pneumonia (VAP)
Ceftazidime + Avibactam (Avycaz)	Approved Feb. 25, 2015	Allergan plc (formerly Actavis)/AstraZeneca plc	Cephalosporin + novel beta-lactamase inhibitor	Yes	Yes	Approved for complicated urinary tract infections, complicated intra-abdominal infections, acute pyelonephritis (kidney infection); other potential indications: hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, bacteraemia
WCK 771	Phase 1	Wockhardt Ltd.	Fluoroquinolone	No	No	Bacterial infections
WCK 4873	Phase 1	Wockhardt Ltd.	Ketolide (JHR)	No	No	Bacterial infections
WCK 2349	Phase 1	Wockhardt Ltd.	Fluoroquinolone (WCK 771 pro-drug)	No	No	Bacterial infections
TD-1607	Phase 1	Theravance Biopharma, Inc.	Glycopeptide-cephalosporin heterodimer	No	No	Acute bacterial skin and skin structure infections, hospital-acquired pneumonia/ventilator-associated pneumonia, bacteraemia
LCB01-0371	Phase 1	LegoChem Biosciences, Inc.	Oxazolidinone	No	No	Bacterial infections
OP0595 (RG6080)	Phase 1	Meiji Seika Pharma Co., Ltd./Fedora Pharmaceuticals, Inc.	Beta-lactamase inhibitor	Possibly	Possibly	Bacterial infections

		(Roche licensee)				
BAL30072	Phase 1	Basilea Pharmaceutica Ltd.	Monosulfactam	Yes	Yes	Multidrug-resistant Gram-negative bacterial infections
Aztreonam+Avibactam (ATM-AVI)	Phase 1	AstraZeneca/Allergan (formerly Actavis)	Monobactam + novel beta-lactamase inhibitor	Yes	Yes	Bacterial infections
MGB-BP-3	Phase 1	MGB Biopharma Ltd.		No	Yes	*C. difficile* infections
CRS3123	Phase 1	Crestone, Inc.	Methionyl-tRNA synthetase (MetRS) inhibitor	No	Yes	*C. difficile* infections
Zabofloxacin	Phase 2	Dong Wha Pharmaeutical Co., Ltd.	Fluoroquinolone	No	No	Community-acquired bacterial pneumonia
Radezolid	Phase 2	Melinta Therapeutics, Inc.	Oxazolidinone	No	No	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia
Nemonoxacin[8]	Phase 2	TaiGen Biotechnology Co., Ltd.	Quinolone	No	No	Community-acquired bacterial pneumonia,diabetic foot infection,acute bacterial skin and skin structure infections
MRX-I	Phase 2	MicuRx Pharmaceuticals Inc.	Oxazolidinone	No	No	Acute bacterial skin and skin structure infections
Gepotidacin (GSK2140944)	Phase 2	GlaxoSmithKline plc	Novel bacterial topoisomerase inhibitor	No	Yes	Respiratory tract infections, acute bacterial skin and skin structure infections, uncomplicated urogenital gonorrhoea
Debio 1452	Phase 2	Debiopharm Group	FabI inhibitor	No	No	Acute bacterial skin and skin structure infections (staphylococci-specific)
Debio 1450	Phase 2	Debiopharm Group	FabI inhibitor (Debio 1452 pro-drug)	No	No	Acute bacterial skin and skin structure infections (staphylococci-specific)
CG400549	Phase 2	Crystal Genomics, Inc.	FabI inhibitor	No	No	Acute bacterial skin and skin structure infections, osteomyelitis
Brilacidin	Phase 2	Cellceutix Corp.	Defensin-mimetic	No	No	Acute bacterial skin and skin structure infections
Avarofloxacin	Phase 2	Allergan plc (formerly Actavis)	Fluoroquinolone	No	No	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections
S-649266	Phase 2	Shionogo, Inc.	Cephalosporin	Yes	Yes	Complicated urinary tract infections

Ceftaroline + Avibactam	Phase 2	AstraZeneca plc/Allergan plc (formerly Actavis)	Cephalosporin + novel beta-lactamase inhibitor	Yes	Yes	Bacterial infections
POL7080	Phase 2	Polyphor Ltd.	Macrocycle (protein epitope mimetic) LptD inhibitor	Yes (*Pseudomonas*)	No	Ventilator-associated bacterial pneumonia (caused by *Pseudomonas aeruginosa*), lower respiratory tract infection, bronchiectasis
Finafloxacin	Phase 2	MerLion Pharmaceuticals Pte Ltd.	Fluoroquinolone	Yes	Possibly	Complicated urinary tract infections, acute pyelonephritis (kidney infection), complicated intra-abdominal infections, acute bacterial skin and skin structure infections
SMT 19969	Phase 2	Summit Therapeutics, Inc.		No	Yes	*C. difficile*-associated diarrhoea
Ramoplanin	Phase 2	Nanotherapeutics, Inc.	Glycolipodepsipeptide	No	Yes	*C. difficile* relapse prevention
ETX0914	Phase 2	Entasis Therapeutics, Inc.	Spiropyrimidinetrione DNA gyrase inhibitor	No	Yes	Uncomplicated gonorrhoea
Taksta (Fusidic acid)	Phase 3	Cempra, Inc.	Fusidane	No	No	Prosthetic joint infections,acute bacterial skin and skin structure infections
Solithromycin	Phase 3	Cempra, Inc.	Macrolide (fluoroketolide)	No	Yes	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhoea, urethritis
Lefamulin (BC-3781)	Phase 3	Nabriva Therapeutics AG	Pleuromutilin	No	No	Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, osteomyelitis, prosthetic joint infections
Iclaprim	Phase 3	Motif Bio plc	Dihydrofolate reductase (DHFR) inhibitor	No	No	Acute bacterial skin and skin structure infections; hospital-acquired bacterial pneumonia
Delafloxacin	Phase 3	Melinta Therapeutics, Inc.	Fluoroquinolone	Possibly	Possibly	Acute bacterial skin and skin structure infections, hospital-acquired bacterial pneumonia, complicated urinary tract infections, complicated intra-abdominal infections

Plazomicin	Phase 3	Achaogen, Inc.	Aminoglycoside	Yes	Yes	Complicated urinary tract infections, catheter-related bloodstream infections, hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia, complicated intra-abdominal infections, acute pyelonephritis (kidney infection) (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae)
Omadacycline	Phase 3	Paratek Pharmaceuticals, Inc.	Tetracycline	Yes	Possibly	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, complicated urinary tract infections
Imipenem/ cilastatin + relebactam (MK-7655)	Phase 3	Merck & Co., Inc.	Carbapenem + novel beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, acute pyelonephritis, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia
Eravacycline	Phase 3	Tetraphase Pharmaceuticals, Inc.	Tetracycline	Yes	Yes	Complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired bacterial pneumonia
Carbavance (RPX7009+meropenem)	Phase 3	Rempex Pharmaceuticals, Inc. (wholly owned subsidiary of The Medicines Co.)	Meropenem + novel boronic beta-lactamase inhibitor	Yes	Yes	Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia, febrile neutropenia, bacteraemia, acute pyelonephritis (some indications specifically target infections caused by carbapenem- resistant Enterobacteriaceae)
Surotomycin	Phase 3	Cubist Pharmaceuticals, Inc. (wholly owned subsidiary of Merck & Co.)	Lipopeptide	No	Yes	*C. difficile*-associated diarrhoea

Cadazolid	Phase 3	Actelion Pharmaceuticals Ltd	Quinolonyl-oxazolidinone	No	Yes	*C. difficile*-associated diarrhoea

Appendix 2: BEAM Alliance products in clinical development[xv]

Company name	Compound name	Compound category	Product description	Development phase
Alaxia	ALX-009	Bioproduct	Association of 2 endogenous substances with antimicrobial properties compensating the defective innate immune system in Cystic Fibrosis (CF) patients	Phase 1
Ilecra Therapeutics	AAI201	Antibiotic combination	Treatment of suspected or confirmed gram-negative multi drug-resistant infections acquired either in the community or hospital environment	Phase 1
Allecra Therapeutics	AAI202	Antibiotic combination	Treatment of hospital acquired gram-negative multi drug-resistant infections in complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) and respiratory indications	Phase 1
Arsanis Biosciences	ASN100	Antibody	Combination of 2 human monoclonal antibodies against S. aureus toxins and expected to be tested both in prophylactic and therapeutic indications	Phase 1
Fab Pharma	FAB001	Small antibiotic molecule	NC	Phase 1
MGB BioPharma	MGB-BP-3	Small antibiotic molecule (novel antibacterial)	Novel, oral antibiotic potential for superiority over current C. difficile standard therapy	Phase 1
SETUBIO	Phytogynal	Bioproduct	Plant bioproduct enhancing the microbiote to stimulate the immune system and fight against pathogens settlement	Phase 1
SETUBIO	Titroléane	Bioproduct	Large spectrum bioproduct efficient on antibiotic resistant clinical strains	Phase 1
Technophage	TP-102	Bacteriophage	NC	Phase 1
AntibioTx	ATx2.1	Small antibiotic molecule	NC	Phase 1/2
Pherecydes Pharma	PP0121	Bacteriophage	Mix of 13 lytic phages targeting E. coli for burn wound infections	Phase 1/2
Pherecydes Pharma	PP1131	Bacteriophage	Mix of 12 lytic phages targeting P. aeruginosa for burn wound infections	Phase 1/2
Da Volterra	DAV132	Medical device	Oral therapy protecting the intestinal microbiota from antibiotic-induced damage, including the prevention of C. difficile infections	Phase 2

[xv] Data table copied from BEAM Alliance Position Paper

Destiny Pharma	XF-73	Small antibiotic molecule (novel antibacterial)	Anti-staphylococcal drug, addressing Antibiotic Resistance, nasal gel for prevention of infection in At-Risk patients	Phase 2
Helperby Therapeutics	ARB 1-6	Antibiotic combination	Helperby Pipeline combinations for cUTIs (inc. CREs), CF, nasal MRSA, gingivitis, halitosis, skin infections	Phase 2
Morphochem/Biovertis	MCB3837/MCB3681	Small molecule antibacterial	Intravenous narrow spectrum Gram-positive antibacterial for the treatment of C. difficile infections	Phase 2
NAICONS	CB-06-01	Small antibiotic molecule (novel antibacterial)	New chemical class antibiotic highly selective against P. acnes developed in collaboration with Cassiopea SpA	Phase 2
NovaBiotics Ltd	Lynovex	Adjuvant therapeutic	Aminothiol – small molecule initially intended for use in treating respiratory infections associated with CF	Phase 2
Polyphor	POL7080	Macrocyclic antibiotic	Pseudomonas selective, protein epitope mimetic targeting the LptD protein essential for outer membrane biosynthesis. Potential indications include ventilator-associated pneumonia, non-CF bronchiectasis and CF	Phase 2
Immunosystem AB	Anti-Pseudomonas IgY	Antibody	Prevention of lung infections caused by P. aeruginosa in CF patients	Phase 3

Appendix 3: Overview of Antibiotic R&D Initiatives[xvi]

International Antibiotic R&D Initiatives					
Initiative/ agency affecting AB R&D	**Description**	**AB R&D incentives**	**Value chain targeted**	**Timeframe**	**AB R&D Funding**
Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)	JPIAMR coordinates national funding from 20 countries worldwide and supports collaborative action to fill existing knowledge gaps in AMR; Developed strategic research agenda that provides framework for future investment in research priorities; The 1st joint call for transnational research is underway, with 3 others in various preparatory stages	- Direct project funding - Collaborative networking	- Basic research	2011 – ongoing	Yes – see below
1st Joint Call - InnovaResistance: Innovative approaches to address antibacterial resistance	InnovaResistance is the JPIAMR's first joint call for AMR R&D projects; Call is promoted by 14 funding agencies across 12 countries; the 7 chosen projects will address prevention of infection, treatment development, target identification for antibacterial drug development, and pharmacokinetics	- Direct project funding	- Basic research	2015 – 2017	€8.1M
2nd Joint Call	Focus on repurposing of neglected antibiotic & characterizing antibiotics as well as antibiotic/non-antibiotic combinations to overcome bacterial; Call is promoted by 10 funding agencies across 9 countries; 3 projects selected	- Direct project funding	- Basic research	2016 - 2018	€4.5M
3rd Joint Call – JPI-EC-AMR Co-funded Call	Calls for proposals addressing dynamics of transmission and selection of AMR at the genetic, bacterial, animal, human, societal, and environmental levels, in order to design and evaluate preventative and intervening measures for controlling resistance; Call promoted by 22 funding agencies from 19 countries + the European Commission	- Direct project funding	- Basic research - Preclinical development	Open	€30M available for funding projects
European & Developing Countries Clinical Trials Partnership (EDCTP)	EDCTP funds collaborative research that accelerates clinical development of new or improved treatments for key poverty-related infectious diseases; many studies focus on AMR; The second generation of the program, EDCTP-2, is now being implemented; 14 EU countries and 14 African countries are participating in EDCTP-2; EDCTP-2 budget: €1.36B; EC contributing up to €683M over 10 years if matched by member EU countries	- Research grants & fellowships for scientific personnel - Direct project funding - Investment in R&D capacity - Sharing R&D resources - Product-development partnerships	- Basic research - Preclinical development - Clinical development - Commercialization	EDCTP: 2003-2013 EDCTP-2: 2014 – 2024	Unknown
Transatlantic Taskforce on Antimicrobial Resistance	A cooperative program between the USA and EU	- International harmonization	- Basic research	2009 –	No

[xvi] Blue: initiatives that provide direct monetary support for antibiotic (AB) research and development (R&D); Red: initiatives that do not provide direct monetary support for AB R&D, but instead indirectly support AB R&D (e.g. meetings, strategies, action plans, regulatory mechanisms, etc.); Green: initiatives that have been proposed or have not been implemented; Yellow: drug agencies that invoke lego-regulatory mechanisms to incentivize AB R&D

(TATFAR)	in three key areas required for tackling AMR: 1. Appropriate therapeutic use of antimicrobial drugs in medical & veterinary settings 2. Prevention of healthcare and community-associated drug-resistant infections Strategies for improving the pipeline of new antimicrobial drugs	- Collaborative networking - Priority setting	- Preclinical development - Clinical development - Market authorization - Commercialization	ongoing	
World Health Organization's Global Action Plan on Antimicrobial Resistance	A global call to action among all WHO member states, the Secretariat, and international organization and other partners to ensure the continuity of the ability to treat and prevent and prevent infectious diseases with effective and safe medicines; One critical strategic objective of the action plan is to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines, and other interventions	- Priority setting - Collaborative network	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	2015 – ongoing	No
Global Union for Antibiotics Research and Development (GUARD) Initiative	Arising from the 2015 Berlin Conference of G7 Health Ministries, GUARD is an agreement among G7 nations that a joint approach among countries is required to effectively fight AMR; An important aspect of GUARD is the joint recognition that continued efforts are needed to stimulate the antibiotic R&D pipeline	- Collaborative networking	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	October 9 2015	No
Global Antibiotic Research & Development Facility	A proposed joint venture between the World Health Organization (WHO) and the Developing Neglected Drugs Initiative (DNDi) to support all aspects of the antibiotic R&D pipeline; A primary goal of this partnership will be to ensure resource-limited nations have access to any new antibiotics developed through the facility	TBD	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	TBD	TBD

European Union Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D Funding
European Commission's Directorate General for Research and Innovation (EC/ DG RI)	Defines and implements policies that support a research and innovation friendly environment for the purpose of creating needed products and services as well as economic growth and jobs	- Direct project funding - Sharing R&D resources - Research grants & fellowships for scientific personnel	- Basic research - Preclinical development - Clinical development	Ongoing	Exact figure unknown; See below for some initiatives
Innovative Medicines Initiative (IMI) – New Drugs for Bad Bugs (ND4BB)	ND4BB is a program under IMI, a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries & Associations (EFPIA), that is addressing key challenges from early discovery to development of new medicines against AMR; Facilitates collaboration among stakeholders, e.g. Big pharma, SMEs, academic, governmental & non-governmental organizations	- Product development partnership - Public-private research collaboration - Direct project funding (and In-kind contributions) - Sharing R&D resources - Investment in R&D capacity - Development of new economic model for antibiotic R&D	- Basic research - Preclinical development - Clinical development - Market authorization - Commercialization	2013 – 2021	ND4BB: €606M FP7 Contribution: €312M
TRANSLOCATION	Research collaboration aimed at understanding how	- Public-private research	- Basic research	2013 – 2017	Total: €29M

	to get antibiotics permanently into multi-drug resistant (MDR) gram-negative bacteria; 27 public and private partners across 9 countries	collaborations - Direct project funding - Sharing R&D resources - Investment in R&D capacity			FP7 Contribution: €15M
European Gram-Negative Antibacterial Engine (ENABLE)	Discovery platform with an innovative governance model that supports pre-clinical and early clinical research into antibiotics that target gram-negative bacteria; designed to fund only most promising programmes at any given time; 32 public and private partners across 13 countries	- Product development partnership - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Basic research - Preclinical development - Clinical development	2014 – 2020	Total: €101M FP7 Contribution: €59M
Combatting Bacterial Resistance in Europe (COMBACTE)	R&D support project that facilitates clinical trials with new antibiotics; Involves the setting up of a sustainable high-quality pan-European clinical research network of investigators/clinical sites (CLIN-Net) and laboratory surveillance network (LAB-Net); improved clinical trial design/methodology; involves the conduct of clinical trials with innovative anti-infectious agents developed by the pharmaceutical companies participating in the project; 31 public and private partners across 13 countries	- Product-development partnership - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Clinical development	2013 – 2019	Total: €250M FP7 Contribution: €109M
COMBACTE – Carbapenem Resistance (COMBACTE-CARE)	R&D support project that focuses on how to rapidly detect and treat Carbapenem-resistant enterobacteriaceae (CRE); Builds on CLIN-Net and LAB-Net; clinical trials of a novel antibiotic combination product; 21 public and private partners across 10 countries	- Product-development partnership - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Clinical development	2015 – 2020	Total: € 86M FP7 Contribution: €24M
COMBACTE – Molecules Against Gram-Negative Infections (COMBACTE-MAGNET)	R&D support project that will evaluate new approaches to preventing P. aeruginosa infection, particularly in pulmonary infections in ICU patients, and treating patients with MDR infections; Builds on CLIN-Net and LAB-Net and will establish new epidemiological network EPI-Net; clinical trials with innovative anti-infectious agents developed by the pharmaceutical companies participating in the project; 38 public and private partners across 9 countries	- Product-development partnership - Direct project funding - Sharing R&D resources - Investment in R&D capacity	- Basic research - Preclinical development - Clinical development	2015 – 2021	Total: €169M FP7 Contribution: €75M
Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis (iABC)	R&D support project of two inhaled antibiotics for treating respiratory infection in patients with bronchiectasis or cystic fibrosis; 28 public and private partners across 9 countries	- Product-development partnership - Sharing R&D resources - Investment in R&D capacity	- Preclinical development - Clinical development	2015 – 2020	Total: €51M FP7 Contribution: €24M
DRIVE-AB	Collaborative research project aimed at generating and testing alternative economic strategies and reward models that incentivize R&D of new antibiotics, while ensuring antibiotic stewardship and patient access; 23 public and private partners across 11 countries	- Development of new economic model for antibiotic R&D	- Market authorization - Commercialization	2014 – 2017	Total: €11M FP7 Contribution: €6M
IMI – RAPP-ID	Collaborative research project facilitating the development of rapid, point-of-care test platforms for infectious diseases; 18 public and private partners across 7 countries	- Product-development partnership - Direct project funding - Sharing R&D resources	- Basic research - Preclinical development - Clinical development	2011 – 2016	Total: €14M FP7 contribution: €7M
Better use of Antibiotics Prize	Monetary prize awarded for developing a rapid test to	- End prize	- Commercialization	2015 - 2016	€1M

	identify, at the point of care, patients with upper respiratory tract infections that can be treated safely without antibiotics				
Innovative Medicines Initiative 2 (IMI 2)	Second iteration of the IMI, which will be funded by the FP8, also known as Horizon 2020; AMR is a key topic on its strategic research agenda; Additional projects under the ND4BB programme are expected; Total budget: €3.3B (€1.64B from FP8)	TBD	TBD	2014 – 2024	TBD
European Investment Bank (EIB)/ European Commission (EC) – InnovFin – Infectious Disease Finance Facility (IDFF)	Risk-sharing loan schemes offered to EU organizations developing vaccines, drugs, medical and diagnostic devices, and research infrastructures for combatting infectious diseases; Targets projects passed the pre-clinical stage and seeking clinical validation	- Risk-sharing financial instruments	- Clinical development	2014 – 2020	Loan size: €7.5M – €75M
European Medicines Agency (EMA)	European drug agency responsible for the market authorization of antibiotics submitted through their centralized procedure on behalf of member states; Offers a number of accommodations to developers of antibiotics; Key member of TATFAR; Responsible for providing guidance to developers on market authorization of both human and veterinary medicines	- Accelerated assessment - Free protocol assistance & cheaper scientific advice for SMEs - Adaptive licensing - Market exclusivity extensions	- Market approval - Commercialization	Ongoing	No

United States of America: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D Funding
National Institutes for Health (NIH)/ National Institute for Allergy and Infectious Diseases (NIAID)/ Division of Microbiology and Infectious Diseases (DMID)	NIAID conducts and supports basic and applied research to better understand, treat, and prevent infectious, immunologic, and allergic disease. The DMID is the division responsible for providing funding opportunities and resources for researchers that support basic research, preclinical development, and clinical evaluation of antibiotics. NIH budget: US $30.3B (FY14); NIAID budget: US $4.4B (FY14)	- Direct project funding - Sharing R&D resources - Research grants & fellowships for scientific personnel - Investment in R&D capacity	- Basic research - Preclinical development - Clinical development	Ongoing	Unknown
Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge	Prize competition sponsored by the NIH and BARDA for the delivery of a rapid point-of-care diagnostic tool that can be used to identify bacterial infections	- Prize competition	- Commercialization	2015	Prize of up to US $20M
Antibacterial Resistance Leadership Group (ARLG)	Led by Duke Medicine, ALRG develops, designs, implements, and manages a clinical research agenda to increase knowledge of antibacterial resistance; Aims to advance research by building transformational trials	- Direct project funding - Public-private research collaborations - Sharing R&D resources	- Basic research	2013 – ongoing	US $62M grant from NIAID over 6.5 years
Biomedical Advanced Research and Development Authority (BARDA)	Program operating with the US Dept. Health and Human Services (HHS) that provides an integrated, systematic approach to the development and purchase of necessary vaccines, drugs, therapies, and diagnostic tools for public health emergencies; Largely funded through the Project BioShield Act	- Product-development partnership - Direct project funding - Advanced market commitment	- Preclinical development - Clinical development - Commercialization	2006 – ongoing	
BARDA Broad Spectrum Antimicrobials (BSA) Program	Program within BARDA focused on tackling antimicrobial resistance; currently supporting development of 6 prospective antibiotics; Also in partnership with GSK and AstraZeneca	- Product development partnership - Direct project funding	- Preclinical development - Clinical development	2010 - ongoing	FY15: US$79M FY16: US$182M
BARDA/ GSK Partnership	Partnership agreement between BARDA and	- Public-private research	- Preclinical development	2013 – 2018	Up to US$200M

	GlaxoSmithKline to develop a portfolio of drug candidates with dual uses in treating illnesses caused by bioterrorism agents and antibiotic-resistant infections	collaboration - Product-development partnership	- Clinical development		(US$40M initially)
BARDA/ AstraZeneca Partnership	Partnership agreement between BARDA and AstraZeneca to develop a portfolio of drug candidates with dual uses in treating illnesses caused by bioterrorism agents and antibiotic-resistant infections	- Public-private research collaboration - Product-development partnership	- Preclinical development - Clinical development	2015 – 2020	Up to US$170M (US$50M initially)
US Food and Drug Administration (FDA)	Drug agency responsible for the market authorization of antibiotics in the US; Offers a number of accommodations to developers of antibiotics	- Fast track designation - Priority review designation - Qualified Infectious Disease Product (QIDP) designation (fast track, priority review, market exclusivity extension) (GAIN Act) - Breakthrough therapy designation - Limited population antibacterial drug (LPAD) designation (proposed – 21st Century Cures Act) - Market exclusivity extensions	- Market approval - Commercialization	Ongoing	N/A
GAIN Act	Ratified in 2012, the GAIN Act provides a number of regulatory and legal incentives for the development of drugs intended to treat "qualified infectious disease"	- 5 years of additional market exclusivity - Priority review and fast track approval - FDA guidance for antibiotic development	- Market approval - Commercialization	2012 – ongoing	N/A
PEW Charitable Trusts	PEW is a large independent charity that has dedicated resources to tackling AMR; Their Antibiotic Research Project has three priorities: removing the regulatory, scientific and economic barriers to antibiotic innovation, establishing antibiotic stewardship programs, and ending antibiotic overuse in veterinary settings	- Research collaborations	- Basic research - Preclinical development - Clinical development	Ongoing	No
Clinical Trials Transformation Initiative (CTTI) – Antibacterial Drug Development	PPP to identify and promote practices that will increase the quality and efficiency of clinical trials for antibacterial development by generating empirical data on how trials are currently conducted, leading to recommendations for improvement	- Public-private research collaborations	- Clinical development - Market approval	2007 – ongoing	No
Foundation for National Institutes for Health (FNIH) – Biomarkers Consortium	PPP for biomedical research that endeavours to discover, develop, and seek regulatory approval for biological markers to support new drug development, preventative medicine, and medical diagnostics; number of active projects on clinical trials for antibacterial drugs (HABP, VABP, ABSSSI, CABP)	- Public-private research collaborations	- Clinical development - Market approval	2006 – ongoing	No
Infectious Disease Society of America (IDSA)/ 10x'20 Initiative	An NGO advocacy initiative that seeks a global commitment to create an antibiotic R&D enterprise powerful enough to produce 10 new systemic antibiotics by the year 2020	- PPP for legislative, regulatory, and funding solutions to antibiotic R&D	- All	2010 – ongoing	No
21st Century Cures Act	Proposed US bill that is aimed at speeding up the approval of certain high demand drugs and devices; Proposed NIH budget increase: 3% annually, 3 years	- LPAD-like approval for QIDPs - Collaborative research (NIH-funded clinical trial data more	- Basic research - Market approval - Commercialization	Proposed	Unknown

	(~US $1.5B)	accessible) - See below			
NIH Innovation Fund	Part of the 21st Century Cures Act, the NIH Innovation Fund is aimed at incentivizing biomedical R&D and will be used towards 3 areas: precision medicine, young investigators, and "other"; the details of the fund have yet to be delineated through the legislative process; $2B annually, 5 years (US $10B)	- End-prize - Direct project funding	- Basic research - Commercialization	Proposed	Unknown
Developing an Innovative Strategy for Antimicrobial Resistance (DISARM) Act	Proposed bill that would create a new regulatory designation status – DISARM status – which would increase federal reimbursement for certain antibiotics	- Reimbursement	- Commercialization	Proposed	N/A
Canada: Antibiotic R&D Initiatives					
Initiative/ agency affecting AB R&D	**Description**	**AB R&D incentives**	**Value chain targeted**	**Timeframe**	**AB R&D Funding**
Canadian Institutes of Health Research (CIHR)/ Institute of Infection and Immunity (III)	CIHR-III supports research and helps to build capacity in the areas of infectious disease and the body's immune system; AMR is a primary strategic objective of the CIHR-III; Primarily supporting investment in AMR surveillance and antibiotic stewardship; 2010-2015 AMR funding: $96.1M CAD; JPIAMR funding contribution to date: $7.6M CAD	- Research grants & fellowships for scientific personnel - Direct project funding	See below	Ongoing	Unknown
Novel Alternatives to Antibiotics (NAA) Funding Opportunity	Augments existing research CIHR funding opportunities by attracting applications focused on novel approaches to antibiotic resistance; Combines input from 26 different partners spanning government, pharma industry, agricultural industry, academia, & NGOs	- Public-private research collaborations - Research grants & fellowships for scientific personnel - Direct R&D funding	- Basic research	2006 – 2013	$13M CAD
Canada-UK Partnership on Antibiotic Resistance	Partnership between the UK MRC and CIHR that built on existing collaborations between the two countries; Focus on basic research for identifying antibiotic candidates and building research capacity	- Direct R&D funding - Collaborative networking	- Basic research	2009 – 2015	Total: $8M CAD CIHR: $4M CAD
Canadian Foundation for Infectious Diseases	Charitable foundation that supports research, education and advocacy missions of projects tackling issues of infectious disease	- Research grants & fellowships for scientific personnel	- Basic research	Ongoing	Unknown
Canadian Society of Microbiologists	Fosters advancement and collaboration in the field of microbiology, with antibiotic research being on key focus area	- Research grants & fellowships for scientific personnel	- Basic research	Ongoing	Unknown
United Kingdom: Antibiotic R&D Initiatives					
Initiative/ agency affecting AB R&D	**Description**	**AB R&D incentives**	**Value chain targeted**	**Timeframe**	**AB R&D Funding**
Medical Research Council (MRC)	Public research organization that funds research across the biomedical spectrum in all major disease areas; Total budget: £771M (2014/2015)	- Research grants & fellowships for scientific personnel - Public-private research collaborations	- Basic research - Preclinical development - Clinical development	Ongoing	Unknown
UK Clinical Research Collaboration (UKCRC)/ Translational Infections Research Initiative	Partnership of funders (NIH, MRC, Wellcome Trust, and others) to carry out research relevant to AMR and infection control	- Research grants & fellowships for scientific personnel - Public-private research collaboration	- Basic research - Preclinical development - Clinical development	2008 – 2015	£16.5M
Antimicrobial Resistance Funders' Forum	Forum established for sharing information on activities related to AMR by member organizations such as the research councils, health departments,	- Direct project funding - Sharing R&D resources	- Basic research - Preclinical development - Clinical development		Unknown

	government bodies, and charities				
Tackling AMR – A Cross Council Initiative	Interdisciplinary collaboration Initiative focused on four themes to support antibiotic research, encompassing academia, biopharma, diagnostic companies, veterinary and the health service; currently funding Theme 1 (Understand resistant bacteria)	- Product-development partnership - Public-private research collaboration - Research grants & fellowships for scientific personnel - Sharing R&D resources	- Basic research - Preclinical development - Clinical development	2014 – ongoing	Funded through the AMRFF
Longitude Prize	Monetary prize awarded for creating a cost-effective, accurate, rapid and easy-to-use test for bacterial infections	- End prize	- Basic research - Preclinical development - Clinical development	2014 – 2019	£10M
Wellcome Trust	Independent global charity that has provided significant funding and support for research tackling AMR; Fund and support AMR Review & Fleming Fund, among other projects	- Direct project funding - Sharing R&D resources	- Basic research - Preclinical development - Clinical development	Ongoing	Over £200M in last 10 years on AMR
Antibiotic Research UK (ANTUK)	National charity dedicated to finding new antibiotics against resistant bacteria; ANTUK provides funding for basic research with the goal of developing three antibiotic resistance breakers and two new classes of antibiotic	- Direct project funding	- Basic research	2014 – ongoing	£220K as of Oct 2015
British Society of Antimicrobial Chemotherapy (BSAC)	BSAC is a UK-based inter-professional organization that has provided research support and funding in antibiotic innovation, among other important aspects of combatting AMR	- Research grants & fellowships for scientific personnel	- Basic research	1971 – ongoing	1 year project grants: £15K 1 year research grants: £50K
Biomedical Catalyst (Joint Innovate UK and MRC programme)	Available funding to innovative SMEs and researchers looking to work either individually or in collaboration to develop solutions to healthcare challenges	- Research grants & fellowships for scientific personnel	- Basic research - Preclinical development - Clinical development - Commercialization	2011 – ongoing	Unknown
O'Neill Review on Antimicrobial Resistance	Review commissioned by the UK PM David Cameron to explore global solutions to antimicrobial resistance; published numerous reports recommending market entry rewards for successful new drugs meeting priority indications; Estimate that US15-35B is needed to pull 15 new drugs onto the market over the next 10 years; Review will publish final report with recommendations in 2016	- Collaboration among key stakeholders to determine R&D pipeline lever solutions	- All	2014 – ongoing	Request: - AMR Innovation Fund: USD $2B over 5 years
Fleming Fund	In response to O'Neill Review recommendations, the Flemming Fund will be established overseas development aid to build laboratory capacity and surveillance networks in developing countries to address the issues of AMR and infectious disease; Government will work with Wellcome Trust, Bill and Melinda Gates Foundation, and Institut Pasteur International Network and other partners to launch the fund	- TBD	- TBD	2016 - 2021	£195M

France: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D Funding
The French National Research Agency (ANR)	ANR provides funding for project-based research in all fields of science.	- Public-private research collaborations - Direct project funding	- Basic research	2005 – ongoing	Unknown
The French National Institute of Health and Medical	Strategic, scientific and operational coordination of	- Public-private research	- Basic research	2009 –	Unknown

Research (Inserm)	biomedical research	collaborations - Direct project funding - Research grants & fellowships for scientific personnel	- Preclinical development - Clinical development	ongoing	
Inserm (Transfert)	Focus on adding value and minimizing risk for innovative projects at pre-commercial stages; supports researchers establish proof of concept, registering patents, and searching for industrial partners	- Public-private research collaborations - Sharing R&D resources	- Preclinical development	Unknown	Unknown
French National Alliance for Life Sciences and Health (Avenir)/ Action Theratique et Inceitative sur Programme (ATIP)	ATIP-Avenir is a funding program that supports young researchers conduct research in the fields of life and health sciences (including immunity, infection, & microbiology)	- Research grants & fellowships for scientific personnel	- Basic research	Unknown	Unknown
Germany: Antibiotic R&D Initiatives					
Initiative/ agency affecting AB R&D	**Description**	**AB R&D incentives**	**Value chain targeted**	**Timeframe**	**AB R&D Funding**
German Research Foundation (DFG)	Currently supporting a number of research projects on the subject of antibiotics within the field of basic research.	- Direct project funding - Research collaborations	- Basic research	Unknown	Unknown
German Centre for Infection Research (DZIF)	Alliance of universities, university hospitals and federal research institutions with expertise in the area of infectious diseases; Aim to accelerate the transmission of research results into practice; Two out of nine Thematic Translational Units devote their research to antibiotics resistance	- Direct project funding - Research collaborations	- Preclinical development	Unknown	Unknown
Infect Control 2020 (Part of Twenty20 - Partnership for Innovation)	Facilitates cooperation between scientists and industry in collaboration with patient associations and the general public. Aims to develop new strategies for early recognition, containment and combating of infectious diseases	- Research collaborations - Research grants & fellowships for scientific personnel	- Basic research - Preclinical development	2014 – ongoing	Unknown
Leibniz Institute for Natural Product Research and Infection Biology	Private public partnership model with a goal to promote research in new therapies for infectious diseases and the search for new substances for antibiotics	- Public-private research collaborations	- Basic research - Preclinical development	Unknown	Unknown
Netherlands: Antibiotic R&D Initiatives					
Initiative/ agency affecting AB R&D	**Description**	**AB R&D incentives**	**Value chain targeted**	**Timeframe**	**AB R&D Funding**
Netherlands Center for One Health - AntiMicrobialResistance	Forms the basis for a high-quality consortium with top expertise in the field of antimicrobial resistance; Research agenda promotes multidisciplinary, translational research, spanning the entire spectrum from fundamental research to clinical studies on patients.	- Research collaborations	- Basic research - Preclinical development - Clinical development	Unknown	Unknown
Netherlands Organisation for Health Research and Development (ZonMw)	National Organisation that promotes quality and innovation in the field of health research and health care, initiating and fostering new developments.	-Direct project funding	- Basic research - Preclinical development	Unknown	Unknown

Priority Medicines Antimicrobial Resistance	To help control antimicrobial resistance and to foster the development of new antimicrobials ZonMw will fund basic and applied research over a period of 9 years	-Direct project funding	- Basic research - Preclinical development	2009 – 2018	€14.76 M

Sweden: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Description	AB R&D incentives	Value chain targeted	Timeframe	AB R&D Funding
Swedish Research Council (SRC)	Swedish government agency that provides funding for basic research in all research domains; antimicrobial resistance is a key priority for the SRC	- Research grants & fellowships for scientific personnel - Research collaborations	- Basic research	Ongoing	Unknown
Vinnova/ Innovations for Future Health	The aim is to utilise high-quality Swedish research by funding innovative ideas	- Research grants & fellowships for scientific personnel - Research collaborations	- Basic research - Preclinical development - Clinical development	Ongoing	Unknown
Formas	Government agency funding basic research in agriculture, veterinary sciences, & environmental research domains; AMR is a key priority.	- Research grants & fellowships for scientific personnel - Research collaborations	- Basic research	Ongoing	Unknown

Appendix 4: Criteria-based analysis of antibiotic R&D initiatives[xvii]

International Antibiotic R&D Initiatives						
Initiative/ agency affecting AB R&D	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of large cap firms?**	**Facilitates cooperation & synergy?**	**Promotes antibiotic conservation & patient access?**	**Targets specific high-priority medical needs?**
Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)						
1st Joint Call - InnovaResistance: Innovative approaches to address antibacterial resistance	✔	✖	✖	✔	✖	✔
2nd Joint Call	✔	✖	✖	✔	✖	✔
3rd Joint Call – JPI-EC-AMR Co-funded Call	✔	✖	✖	✔	✖	✔
European & Developing Countries Clinical Trials Partnership (EDCTP)	✔	✔	✔	✔	✔	✔
Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)	✖	✖	✖	✔	✔	✖
World Health Organization's Global Action Plan on Antimicrobial Resistance	✖	✖	✖	✔	✔	✖
Global Union for Antibiotics Research and Development (GUARD)	✖	✖	✖	✔	✔	✖
Global Antibiotic Research & Development Facility	✔	✔	✔	✔	✔	✔

European Union Antibiotic R&D Initiatives						
Initiative/ agency affecting AB R&D	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of large cap firms?**	**Facilitates cooperation & synergy?**	**Promotes antibiotic conservation & patient access?**	**Targets specific high-priority public health needs?**
European Commission's Directorate General for Research and Innovation (EC/ DG RI)	✔	✔	✔	✔	✖	✔
Innovative Medicines Initiative (IMI) – New Drugs for Bad Bugs (ND4BB)	✔	✖	✔	✔	✖	✔
TRANSLOCATION	✔	✖	✔	✔	✖	✔
European Gram-Negative Antibacterial Engine (ENABLE)	✔	✔	✔	✔	✖	✔
Combatting Bacterial Resistance in Europe (COMBACTE)	✔	✖	✔	✔	✖	✔
COMBACTE – Carbapenem Resistance (COMBACTE-CARE)	✔	✖	✔	✔	✖	✔
COMBACTE – Molecules Against Gram-Negative Infections (COMBACTE-MAGNET)	✔	✖	✔	✔	✖	✔
Inhaled Antibiotics in Brochiectasis and Cystic Fibrosis (iABC)	✔	✖	✔	✔	✖	✔
DRIVE-AB	✖	✖	✖	✔	✔	✖

[xvii] A question mark indicates that it is unclear whether a particular criterion is fulfilled or not.

IMI – RAPP-ID	✔	✖	✔	✔	✖	✔
Better use of Antibiotics Prize	✔	✖	✖	✖	✔	✖
Innovative Medicines Initiative 2 (IMI 2)	✔	?	?	✔	?	?
European Investment Bank (EIB)/ European Commission (EC) – InnovFin – Infectious Disease Finance Facility (IDFF)	✔	✔	✖	✖	✖	✖
European Medicines Agency (EMA)	✔	✖	✔	✖	✖	✔

United States of America: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation & synergy	Promotes antibiotic conservation & patient access?	Targets specific high-priority public health needs?
National Institutes for Health (NIH)/ National Institute for Allergy and Infectious Diseases (NIAID)/ Division of Microbiology and Infectious Diseases (DMID)	✔	✔	✔	✔	✖	✔
Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge	✔	✖	✔	✖	✖	✔
Antibacterial Resistance Leadership Group (ARLG)	✔	✖	✖	✔	✖	✔
Biomedical Advanced Research and Development Authority (BARDA)	✔	✔	✔	✔	✖	?
BARDA Broad Spectrum Antimicrobials (BSA) Program	✔	✔	✔	✔	✖	?
BARDA/ GSK Partnership	✔	✖	✔	✔	✖	?
BARDA/ AstraZeneca Partnership	✔	✖	✔	✔	✖	?
PEW Charitable Trusts	✔	?	?	✔	✔	✔
US Food and Drug Administration (FDA)	✔	✖	✔	✔	✖	✔
GAIN Act	✔	✖	✔	✖	✖	✖
Clinical Trials Transformation Initiative (CTTI) – Antibacterial Drug Development	✔	✖	✖	✔	✖	✖
Foundation for National Institutes for Health (FNIH) – Biomarkers Consortium	✔	✖	✖	✔	✖	✔
Infectious Disease Society of America (IDSA)/ 10x'20 Initiative	✖	✖	✖	✔	✔	✖
21st Century Cures Act	✔	✖	✔	✖	✔	✔
NIH Innovation Fund	✔	?	?	✖	✖	?
Developing and Innovative Strategy for Antimicrobial Resistance (DISARM) Act	✔	✖	✔	✖	✖	✖

Canada: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation & synergy	Promotes antibiotic conservation & patient access?	Targets specific high-priority public health needs?
Canadian Institutes of Health Research (CIHR)/ Institute of Infection and Immunity (III)	✔	✖	✖	✔	✔	?
Novel Alternatives to Antibiotics (NAA) Funding Opportunity	✔	✖	✔	✔	✖	✔

Canada-UK Partnership on Antibiotic Resistance	✔	✖	✖	✔	✖	✖
Canadian Foundation for Infectious Diseases	✔	✖	✖	✖	✖	?
Canadian Society of Microbiologists	✔	✖	✖	✔	✖	?

United Kingdom: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation & synergy	Promotes antibiotic conservation & patient access?	Targets specific high-priority public health needs?
Medical Research Council (MRC)						
UK Clinical Research Collaboration (UKCRC)/ Translational Infections Research Initiative	✔	✖	✖	✔	✖	✖
Antimicrobial Resistance Funders' Forum	✔	✖	✖	✔	✖	✖
Tackling AMR – A Cross Council Initiative	✔	✖	✖	✔	✖	✖
Longitude Prize	✔	✖	✔	✖	✔	✔
Wellcome Trust	✔	✔	✖	✖	✖	✖
Antibiotic Research UK (ANTUK)	✔	✖	✖	✖	✖	✔
British Society of Antimicrobial Chemotherapy (BSAC)	✔	✖	✖	✖	✖	✖
Biomedical Catalyst (Joint Innovate UK and MRC programme)	✔	✔	✖	✖	✖	✖
O'Neill Review on Antimicrobial Resistance	✖	✖	✔	✔	✔	✔
Fleming Fund	✔	✔	✔	✔	✖	✖

France: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation & synergy	Promotes antibiotic conservation & patient access?	Targets specific high-priority public health needs?
The French National Research Agency (ANR)	✔	✖	✖	✔	✖	✔
The French National Institute of Health and Medical Research (Inserm)	✔	✖	✖	✔	✖	✔
Inserm (Transfert)	✔	✔	✖	✔	✖	?
French National Alliance for Life Sciences and Health (Avenir)/ Action Theratique et Inceitative sur Programme (ATIP)	✔	✖	✖	✖	✖	?

Germany: Antibiotic R&D Initiatives

Initiative/ agency affecting AB R&D	Improves NPV?	Enables participation of SMEs?	Encourages participation of large cap firms?	Facilitates cooperation & synergy	Promotes antibiotic conservation & patient access?	Targets specific high-priority public health needs?
German Research Foundation (DFG)	✔	✖	✖	✖	✖	✔

German Centre for Infection Research (DZIF)	✔	✖	✖	✔	✖	✔
Infect Control 2020 (Part of Twenty20 - Partnership for Innovation)	✔	✔	✔	✔	✔	?
Leibniz Institute for Natural Product Research and Infection Biology	✔	✖	✖	✔	✔	?
Netherlands: Antibiotic R&D Initiatives						
Initiative/ agency affecting AB R&D	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of large cap firms?**	**Facilitates cooperation & synergy**	**Promotes antibiotic conservation & patient access?**	**Targets specific high-priority public health needs?**
Netherlands Center for One Health - AntiMicrobialResistance	✔	✔	✔	✔	✖	✔
Netherlands Organisation for Health Research and Development (ZonMw)	✔	?	?	✔	✔	✔
Priority Medicines Antimicrobial Resistance	✔	?	?	✔	✔	✔
Sweden: Antibiotic R&D Initiatives						
Initiative/ agency affecting AB R&D	**Improves NPV?**	**Enables participation of SMEs?**	**Encourages participation of large cap firms?**	**Facilitates cooperation & synergy**	**Promotes antibiotic conservation & patient access?**	**Targets specific high-priority public health needs?**
Swedish Research Council (SRC)	✔	✖	✖	✔	✖	✔
Vinnova/ Innovations for Future Health	✔	✔	✖	✔	✖	?
Formas	✔	✖	✖	✔	✖	?