PHILOSOPHICAL TRANSACTIONS B

Research

CrossMark
click for updates

Time for a change: addressing R&D and commercialization challenges for antibacterials

David J. Payne[1], Linda Federici Miller[1], David Findlay[2], James Anderson[3] and Lynn Marks[4]

[1]Infectious Diseases Therapeutic Area Unit, GlaxoSmithKline, 1250 South Collegeville Road, Collegeville, PA 19426, USA
[2]Immuno-inflammation and Infectious Diseases Franchise, GlaxoSmithKline, 980 Great West Road, Brentford, Middlesex TW8 9GS, UK
[3]Government Affairs, Public Policy and Patient Advocacy, Communications and Government Affairs, GlaxoSmithKline, 980 Great West Road, Brentford, Middlesex TW8 9GS, UK
[4]Projects, Clinical Platforms and Sciences, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA

The antibacterial therapeutic area has been described as the perfect storm. Resistance is increasing to the point that our hospitals encounter patients infected with untreatable pathogens, the overall industry pipeline is described as dry and most multinational pharmaceutical companies have withdrawn from the area. Major contributing factors to the declining antibacterial industry pipeline include scientific challenges, clinical/regulatory hurdles and low return on investment. This paper examines these challenges and proposes approaches to address them. There is a need for a broader scientific agenda to explore new approaches to discover and develop antibacterial agents. Additionally, ideas of how industry and academia could be better integrated will be presented. While promising progress in the regulatory environment has been made, more streamlined regulatory paths are still required and the solutions will lie in global harmonization and clearly defined guidance. Creating the right incentives for antibacterial research and development is critical and a new commercial model for antibacterial agents will be proposed. One key solution to help resolve both the problem of antimicrobial resistance (AMR) and lack of new drug development are rapid, cost-effective, accurate point of care diagnostics that will transform antibacterial prescribing and enable more cost-effective and efficient antibacterial clinical trials. The challenges of AMR are too great for any one group to resolve and success will require leadership and partnerships among academia, industry and governments globally.

1. Introduction

There is an urgent need for new antibacterial agents. The spread of antibacterial resistance has become a global threat to public health, reducing the options available to healthcare providers to manage life-threatening infections. Additionally, many modern medical procedures such as chemotherapy, acute cardiac interventions, elective surgery, transplantation and some specialized care of neonates require antibacterial agents to be effective. Society must change the way that current and new antibacterials are used, both in human and animal health, in order to prolong their utility. Challenges in three key areas have caused a number of pharmaceutical companies to discontinue research and development (R&D) investment in this area which has contributed to a lack of new antibacterials in development:

(1) unique scientific challenges associated with antibacterial discovery research;
(2) regulatory and clinical challenges; and
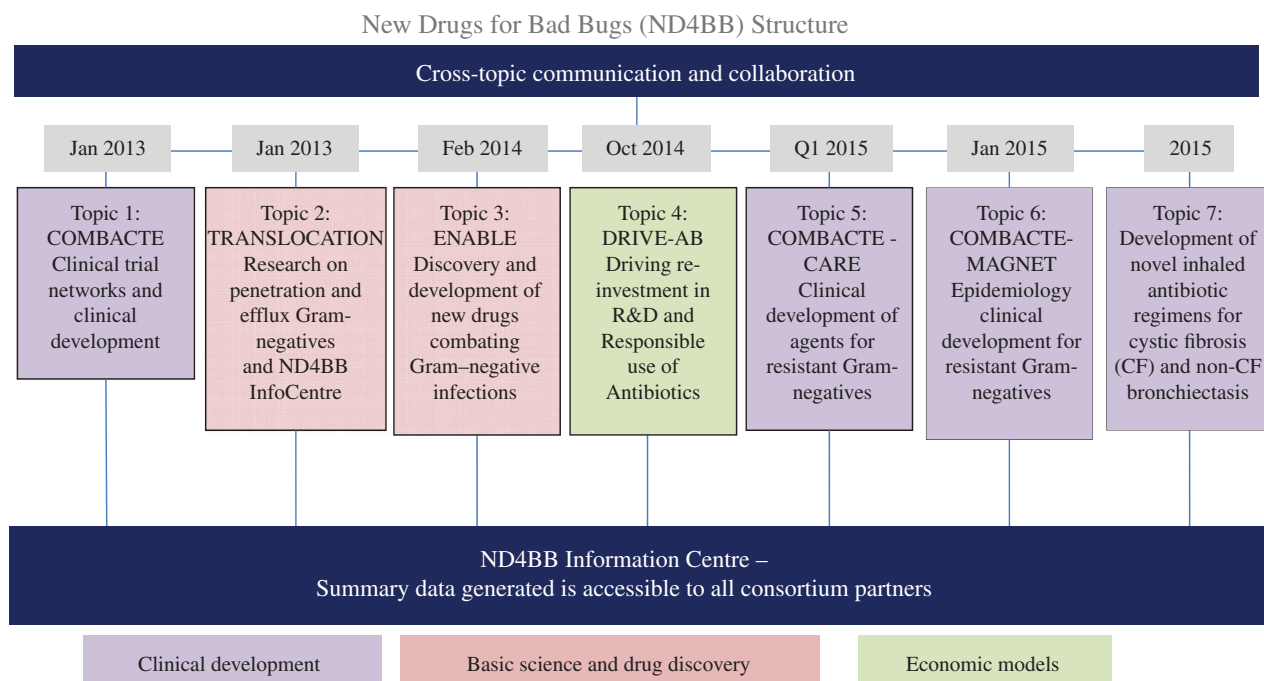(3) commercial challenges due to limited economic attractiveness of investing in antibacterial R&D.

THE ROYAL SOCIETY
PUBLISHING

New Drugs for Bad Bugs (ND4BB) Structure

Figure 1. Overview of the ND4BB project funded by the IMI.

These challenges will each be explored and relevant examples from GlaxoSmithKline's perspective and experiences will be provided. Some potential solutions to these challenges will be proposed. In addition, we will discuss the need for rapid, cost-effective, accurate point of care diagnostic tests and how these will help resolve both the problem of antimicrobial resistance (AMR) and lack of new drug development. Many of these ideas require a multi-stakeholder approach and one central theme of our strategy has been to establish public–private partnerships (PPPs) and these partnerships will be discussed and their role in each of these challenges explained.

2. Critical role of public–private partnerships

The challenges of antibacterial R&D are too great for any single entity to resolve, therefore, since 2007 an integral component of GlaxoSmithKline's strategy has included PPPs. These partnerships have expanded our knowledge base in antibacterial R&D via sharing information and knowledge with academia and other companies. Additionally, these PPPs have helped assume some of the cost of developing antibacterials which in turn helps to improve the return on investment (ROI). New Drugs for Bad Bugs (ND4BB, funded by the Innovative Medicines Initiative (IMI)) is an example of a broad-based partnership among a variety of European academic groups and several pharmaceutical companies. This PPP has consortia that focus on many of the key bottlenecks in antibacterial R&D (figure 1). A key objective of the COMBACTE [1] consortium is to resolve clinical trial challenges, the ENABLE [2] consortium is addressing lead optimization hurdles, TRANS-LOCATION [3] goals are to solve early discovery challenges and DRIVE-AB [4] plans to find solutions to the commercial challenges, and other consortia are under discussion. These projects will be discussed in more detail throughout the paper. In addition, GlaxoSmithKline has a novel partnership with the Biomedical Advanced Research and Development Authority (BARDA) which is part of the US Government's

Department of Health and Human Services and shares the cost of progressing a portfolio of antibacterials and is governed by a joint operating committee made up of representatives from both GlaxoSmithKline and BARDA. We also have a contract with the Defense Threat Reduction Agency (the US Army agency concerned with protection of the military). This US government funding is being used to develop compounds for their utility at treating both biothreat and conventional infections. GSK2140944 is an example of the type of antibacterial that is receiving this funding which exhibits activity against both biothreat pathogens and conventional pathogens [5] (tables 1 and 2). In the past, we have also had agreements with the Wellcome Trust's Seed Drug Discovery initiative. GlaxoSmithKline's R&D effort benefits from these partnerships in multiple ways and we have had to implement new procedures to adhere to distinct processes associated with the external funding. However, these partnerships have been integral to our continued antibacterial R&D effort as without this support the economics of antibacterial R&D are not sustainable.

3. Addressing the scientific challenges

(a) Scientific challenges facing antibacterial discovery

The vast majority of R&D effort that has been applied to this therapeutic area for the last 50 years has been based on the traditional model of designing small molecules that inhibit essential processes required for the bacterial cell to survive. These agents thereby kill the bacteria or prevent it from growing (i.e. the 'small molecule—kill the microbe' paradigm). There are some considerable challenges with this approach and in many instances we lack rational mechanisms to improve our chance of success.

To start such a program, a small molecule 'lead' is required. This is a compound that has some encouraging attributes such as selective inhibition of a target(s) or process, some antibacterial activity and proof that the 'lead' can kill or inhibit bacteria via inhibition of a defined target or process.

Table 1. MIC90s of GSK2140944 for skin and respiratory pathogens [5]. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; NT, not tested; PVL, Panton-Valentine leukocidin.

organism (*n*)	MIC$_{90}$ (μg/ml)[a]		
	GSK2140944	levofloxacin	moxifloxacin
all *Streptococcus pneumoniae* (549)	0.25	1	0.12
penicillin-resistant (167)	0.25	2	0.25
erythromycin-resistant (161)	0.25	>4	2
levofloxacin-resistant (22)	0.5	>4	>2
Haemophilus influenzae (981)	1	0.03	0.03
β-lactamase positive (183)	1	0.03	0.03
Moraxella catarrhalis (158)	≤0.06	0.12	0.03
Escherichia coli (1013)	4	>4	>4
levofloxacin-resistant (283)	4	>4	>4
all *S. aureus* (1008)	0.5	>2	>1
MSSA (518)	0.5	1	0.25
MRSA (490)	0.5	>2	>1
azithromycin-resistant (470)	0.5	>2	>1
levofloxacin-resistant (424)	0.5	>2	>1
MRSA PVL+ (58)	0.5	8	NT
linezolid-resistant (2)[b]	0.25	>2	>1
VISA and VRSA (12)	0.25	>2	>1
Streptococcus pyogenes (201)	0.25	1	0.25
Mycoplasma pneumoniae (5)[b]	0.006 to 0.0125	NT	NT
Chlamydophila pneumoniae (3)[b]	>64	0.5 – 2	NT
Legionella pneumophila (7)[b]	0.25 – 0.5	≤0.25	NT

[a]MIC90 is the Minimum Inhibitory Concentration that inhibited the growth of 90% of the collection of isolates tested.
[b]Results reported as a MIC range when $N \leq 10$.

Table 2. MIC90s of GSK2140944 for biothreat pathogens [5].

pathogen	no. of isolates	GSK2140944 MIC$_{90}$ (μg/ml)
Yersinia pestis	30	0.5
Francisella tularensis	30	1
Bacillus anthracis	30	1
Burkholderia mallei	30	>8
Burkholderia pseudomallei	30	>8

These leads can be obtained either from screening natural products or synthetic libraries against purified targets or whole cell assays. The genomic era came early for bacteria and the late 1990s saw the first bacterial genomes being sequenced. For the first time, it was possible to assess the essentiality of hundreds of different bacterial enzymes for their role in bacterial survival *in vitro* and during the infection process. This provided a wealth of targets that were believed to be valid and were then progressed to high-throughput screening. In addition, a large number of well-funded biotechnology companies were set up that focused on various areas such as quorum sensing (Quorex), aromatic amino acid biosynthesis (Arrow), fatty acid biosynthesis (Affinium), tRNA synthetases, efflux pump inhibitors (Microcide), metallo enzymes (Versicor), pathogenesis (Microcide), isoprenoid biosynthesis (GPC Biotec), ribosomes (Ribotargets, RibX), Coenzyme A biosynthesis (Pantherix) and riboswitches (Biorelix). The result of the bacterial genomic era was that it created a vibrant and well-funded biotech, academic and big pharma effort in antibacterial discovery.

(i) Poor success at identifying novel leads for novel targets

However, the output from this effort was very disappointing. GlaxoSmithKline's experience was that 70 high-throughput screens were run between 1995 and 2001 on a variety of novel targets as well as some whole cell screens but only 7% of the screens resulted in leads [6]. Others have experienced similar disappointments. For example, Pfizer ran a similar number of screens which were largely whole cell screens but interestingly their success rate was similar at 6.5% (P. Miller 2011, now AstraZeneca, personal communication). Considering other therapeutic areas have approximately a 10-fold greater success in this phase [7] and the cost of running and deconvoluting each screen was in the order of a £1 million (approx. $1.6 million), these were very costly initiatives with poor success.

4

(ii) Challenge of optimizing leads to development candidates

The discovery challenges do not stop at identifying leads. The next step is the optimization of those leads to increase antibacterial activity and decrease safety and or tolerability issues. In the majority of cases, this can be a very long process for two reasons. Firstly, optimizing antibacterial activity is challenging. If we consider the case of Gram-negative pathogens, if the target is intracellular then the compound needs to be designed to penetrate the outer membrane, cell wall and inner membrane plus avoid being ejected by bacterial efflux pumps. Each of these barriers has slightly different properties and lipophilicity, therefore designing small molecules so they optimally penetrate all these barriers is very challenging. There are no rational ways of doing this and often it is optimized by a chemist's intuition and trial and error. Secondly, antibacterials require higher blood levels than almost all other medicines. For example, the maximum serum concentration ($C_{\max}$) of amoxicillin in Augmentin (875 mg amoxicillin + 125 mg clavulanic acid) is 12 µg ml^{-1} [8]; the $C_{\max}$ of Lipitor (a cholesterol-lowering drug) is 13–55 ng ml^{-1} [9]. These high levels of antibacterial are needed to prevent rapid bacterial growth and suppress emergence of resistance during treatment. This requirement for high doses and high exposures often results in high attrition for experimental antibacterials due to tolerability and safety problems. When safety liabilities are observed in an antibacterial lead optimization program, the chemistry program takes a step back to re-think the strategy and optimize new molecules to avoid the liability and this can take considerable resources and time to achieve. An example that illustrates these challenges is a series that GlaxoSmithKline has been working on since 1998—this series inhibits bacterial gyrase via a novel mechanism [10] but several pre-clinical liabilities (e.g. cardiovascular, genotoxicity and eye toxicity) had to be addressed in an iterative process and there was only confidence to progress the lead molecule (GSK 2140944 [5], tables 1 and 2) once it had passed extensive three-month toxicity studies which are not normally conducted until much later in development.

(b) Approaches for addressing scientific challenges

(i) Optimizing the traditional discovery model ('small molecules to kill the microbe')

It is relatively straight forward to find selective inhibitors of bacterial proteins/enzymes. The challenge is to rationally optimize such molecules so they effectively penetrate bacterial membranes and avoid being effluxed. A consortia (TRANSLOCATION) has been established in ND4BB funded by the IMI to further our knowledge in this area. Five companies (AstraZeneca, GlaxoSmithKline, Basilea, Janssen and Sanofi) are actively involved in this, along with 14 academia groups and eight small/medium enterprises [3]. The goal of this consortium is to merge the diverse science of microbiology, structural biology and biophysics to further our understanding of porin and efflux pump structure/function. The consortium will also pursue the development of new assays that will eventually enable rapid measurement of the propensity of small molecules to be effluxed as well as their ability to penetrate the various barriers in Gram-negative bacteria. In addition, the potential to use bacterial uptake pathways as a mechanism to actively penetrate bacterial pathogens is being explored. For example, bacteria have complex pathways to ensure they can sequester sufficient Fe from the host where Fe concentrations can be as low as approximately 10^{-24} M. Antibacterials have been designed that are recognized by the bacterial Fe uptake pathways and consequently hijack these systems resulting in significantly improved penetration and thus greater antibacterial activity [11]. Designing antibacterials to be recognized by other bacterial uptake pathways will be also investigated to understand the broader applicability of this approach. The fact that five companies are active in TRANSLOCATION illustrates that rational design of compounds to optimally penetrate bacterial cells is an industry-wide bottleneck to our delivery of new antibacterials. Furthermore, we think more research funding needs to focus on improving our understanding of the fundamental science that underpins the design of antibacterials and this is also one of the recommendations in the report from the President's Council of Advisors on Science and Technology (PCAST) on combating antibiotic resistance [12].

We also propose that we think differently about how to address the challenges of the lead optimization process for new antibacterials. The ENABLE consortium (also part of ND4BB) is working to re-think the process and introduce a more collaborative approach integrating academia and smaller companies or organizations [2]. ENABLE provides a drug discovery capability for interested groups to use for their antibacterial drug discovery programs and Sanofi, GlaxoSmithKline and multiple public partners (both universities and smaller companies) have included drug discovery programs into the consortium. New programs and partners will also be able to join ENABLE through a series of Open Calls during the course of the project. The bacterial Topoisomerase Inhibitors program in ENABLE is based on novel topoisomerase inhibitors leads from both GlaxoSmithKline and Sanofi who are pooling leads and resources to work on the program together. By running this program in ENABLE, there is the added benefit of input from a variety of different companies along with intellectual input and bench work from academic experts. Data on this program is shared among all the participants of ENABLE in a way we never have before. An innovative collaboration agreement ensures that the original program owner retains full control of active antibacterial compounds and value added through the work of the wider consortium, ensuring the original program owner, whether GSK and Sanofi or an academic or small company, is able to fully exploit any success achieved within ENABLE. This focused input and more open innovative way of working could help overcome some of the bottlenecks faced by antibacterial lead optimization programs. New ways of working and sharing science, we believe, are required to find success.

(ii) Exploring and validating new paradigms

The current research paradigm for antibacterial R&D has not changed substantially for the last 50 years with the majority of effort focused on the traditional paradigm of designing small molecules to inhibit essential processes and targets that result in killing the microbe. However, there are other compelling approaches for treating bacterial infections. We consider below three groups of non-traditional approaches that could be pursued (table 3):

— *Alternative approaches for targeting the bacteria.* Examples include novel delivery systems such as inhaled delivery where technology and know-how that has been developed to deliver inhaled medicines for other diseases

Table 3. Three areas of alternative approaches and examples that require further exploration and validation.

alternative approaches to tackle the bacteria	different modalities	host targets
— zwitterionic prodrugs	— bacteriophage	— inhibition of human targets to prevent bacterial adhesion/invasion
— targeting pathogenesis, virulence, persisters	— antibody–drug conjugates	— modulation of inflammation
— lipsomal delivery	— antibody recruiting molecules	— modulation of innate immunity and immunomodulators
— inhaled delivery	— bacterial delivery systems	— repurposing of established therapeutics targeting human targets that may have a role in bacterial infection
— biofilm disrupters	— monoclonal antibodies	
	— micobiome	

could be applied to antibacterials. This approach has already been applied to established antibacterials but it could be applied more broadly to novel mechanism antibacterials that are insufficiently tolerated as systemic agents. New delivery systems for inhaled agents may broaden the disease scenarios where these agents could be used to treat or augment traditional therapies. Other formulations such as liposomal delivery could also be explored and should be coupled with new science in this area to target the liposomes to interact with the outer membranes of Gram-negatives [13,14]. These new delivery approaches will have to prove that adequate drug can be delivered to the site of infection. Alternative strategies also include targeting virulence/pathogenesis orbiofilm disrupters instead of essential targets. However, there needs to be caution with such approaches that still target bacterial enzymes as these are still dependent on securing quality leads which can be a substantial bottleneck to success as discussed above.

— *Other modalities.* The majority of R&D in antibacterials has focused almost entirely on progressing small molecules but there are other modalities that could be pursued. For example, the concept of using bacteriophages is appealing as it could provide rapidly cidal action with sustained dosing, while the bacteriophage multiply within the infecting organism. This concept has been around for a considerable time but work is now starting towards more definitive experiments that will enable a better assessment of the approach. In addition, monoclonal antibodies are beginning to be applied to the antibacterial therapeutic area as both prophylaxis and treatment approaches. Furthermore, some of the advances in this area such as dual targeting monoclonal antibodies, antibacterial : monoclonal conjugates and antibody recruiting monoclonals could also be applied [15]. In addition, there is a wealth of microbiome research that has shown how manipulating the microbiome could be used to treat infections such as *Clostridium difficile* [16] and perhaps there is a broader application of this approach to other bacterial infections. In addition, innocuous species of bacteria could be used to integrate into the microbiome to deliver therapeutic agents for bacterial infections.

— *Targeting human target 'host targets'.* Up to now, our approach for treating bacterial infections has largely focused on interacting directly with the bacterial cell to inhibit essential processes and only limited research has been conducted on exploring the modulation of host (human) targets as a way of halting a bacterial infection or blocking its pathogenic effects [17]. Areas of pursuit would be to investigate targets that could enhance the immune response to a bacterial infection or reduce the inflammation response, which can be the most devastating effect of a bacterial infection. Furthermore, identifying human targets and receptors required for bacterial toxins or bacterial adhesion could also open up approaches to block the pathogenic effects of bacteria. This is a complex area as modulating human targets would be expected to have some undesirable consequences but these approaches have been successfully pursued by other therapeutic areas for example immune-therapeutics for treating cancer [18] and should be further explored for bacterial infections. Development of sophisticated rapid diagnostic tests to monitor and change therapies that modulate the immune system will be crucial to the success of this approach.

Many of these areas have preliminary and compelling data but have not been pursued as mainstream approaches due to the lack of evidence that the approach has a good probability of successfully treating bacterial infections in humans and robust 'target validation' experiments are needed. In addition, many of these approaches have complex challenges associated with them that would need new assays and animal models. We propose that this could be an area of better integration between academia and industry with a focused effort on conducting critical target validation of these new approaches in a precompetitive environment. Such integration would combine the breadth and depth of knowledge from academia with the pharmaceutical approach to target validation to create validated alternative approaches for treating bacterial infections that could be further pursued by the antibacterial R&D community. This suggestion is similar to the biopharmaceutical incubator proposed in the US National Strategy for Combating Antibacterial Resistance [19].

4. Addressing regulatory and clinical challenges

(a) Regulatory and clinical challenges

Prior to 2010, the US Food and Drug Administration (FDA) regulatory guidance for antibacterial drug development was creating major obstacles to the conduct of clinical trials for serious infections, including requirements that did not align with common patient standards of care. For example, patients with ventilator-associated bacterial pneumonia (VABP) were required to have no prior antibacterial treatments within 24 h of being enrolled in a clinical trial, yet higher survival

6

rates had been demonstrated for patients started on antibacterials as soon as possible. With this new standard of care, the enrollment process, which involves many steps before randomization and dosing, presented a barrier to recruitment, as patients could not wait for their antibacterials and study logistics stalled. Furthermore, study designs evolved to accommodate the greater FDA regulatory need to justify a non-inferiority margin for the primary endpoint. As placebo studies have not been conducted in the era of modern medical management, there was no obvious way to demonstrate a historical evidence of sensitivity to drug effect in patients with ventilator-associated pneumonia. In short, the FDA found that all-cause mortality was the only endpoint where a non-inferiority margin could be justified. European regulators did not demand such a restrictive approach to endpoint justification so the generally acceptable test of cure based on clinical signs of symptom improvement remained in effect. Nonetheless, the clinical trials required to achieve indications in both the US and EU for hospital-acquired bacterial pneumonia (HABP) and VABP remain large and challenging to conduct. As an example, telavancin was approved for nosocomial pneumonia (also referred to as HABP and VABP) in the European Union, Norway and Iceland in September 2011, based on two international studies of nosocomial pneumonia comprising a total of 1503 subjects [20]. In today's environment, it is estimated that it would take in excess of 4 years and cost more than £100 million to deliver a similar package to support a novel therapy aimed at Gram-negative nosocomial pneumonia.

(b) Approaches for addressing regulatory/clinical challenges

More recently, there have been encouraging discussions about new and more accelerated approaches to developing antibacterials. The FDA has issued a 2013 draft Guidance to Industry entitled, 'Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases' in which options for more streamlined development are described [21]. Since 2013, the FDA has also issued updated guidance documents for skin (ABSSSI) infections, community-acquired bacterial pneumonia (CABP), HABP/VABP and uncomplicated gonorrhoea. The updated 2014 FDA Draft Guidance for HABP/VABP reflects a more accommodating approach, e.g. minimal antibacterials within 24 h are permitted, as well as a 10% non-inferiority margin. The primary analysis is based on the difference between treatment groups on the all-cause mortality with no disease-related complications outcome measure. The agency have dropped the odds ratio approach when the control mortality was less than 20% and allow the treatment difference measure even when all-cause mortality is in the 15% range. This allows for a smaller sample size.

The European Medicines Agency (EMA) has also recently updated guidance to industry with a 2011 update to the Guideline entitled, 'The Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections' [22]. In October 2013, an addendum to the 2011 guidance was issued, which provided detailed advice on issues such as patient selection criteria, primary endpoints, suggestions for non-inferiority margins and criteria for streamlined development.

There have been innovative regulatory paths such as the Limited Population Antibacterial Drug (LPAD) approach proposed by the Infectious Diseases Society of America (IDSA) which calls for limited clinical development but with a label that will limit use only to high unmet need situations [23]. This has also been referred to as a Special Medical Use (SMU) pathway. Essentially, this would expedite approval for drugs that target infections caused by resistant pathogens where there are few therapeutic options. The LPAD approach would require smaller trials to assess safety and effectiveness (with a higher dependence on pharmacokinetics/pharmacodynamics) and provide a special clear label that would inform patients and doctors on limitations of the dataset to ensure informed decision-making about benefits/risks. LPAD would also include provisions whereby new data can be generated to broaden the intended use post approval.

Major health authorities have moved towards a more flexible approach, as reflected in the FDA 2013 Guidance for Antibiotics for Unmet Medical Needs, and the EMA's 2013 Addendum, which discuss limited evidence of clinical efficacy/safety to support approval for treatment of infections caused by multidrug-resistant (MDR) organisms for which there are limited treatment options. However, the IDSA proposed pathway has not yet been fully translated to accepted evidentiary standards. As reflected in the recent PCAST report on Combating Antibiotic Resistance, the FDA has noted that it is unclear whether it possesses the full legal authority to implement a full SMU (LPAD) pathway and it would prefer that Congress provide explicit endorsement. While there is bipartisan support for pending US legislation (*Antibiotic Development to Advance Patient Treatment*) [24], which is intended to provide this endorsement, it is presently unclear when and if these changes to US Federal law will occur.

Another issue is that it is hard to mobilize a clinical study in time to encompass patients in outbreaks of resistant pathogens. Clinical trial networks with protocols in place would have a major positive impact on identifying and enrolling patients infected with resistant pathogens. Efforts to create such networks in the US via the NIH and in the EU through IMI COMBACTE will help address this challenge. Creating and strengthening effective clinical trial networks is another avenue to explore and $25 million per year is recommended in the PCAST report [12] to create such an infrastructure.

These advances within the legal/regulatory framework are all welcome. However, there remain important differences in the regulatory requirements applied by health regulatory agencies. Where these differences remain, modification of the existing regulatory guidance to industry by major health authorities is urgently needed. Regulatory requirements should define a common set of globally accepted evidentiary standards. As an urgent interim measure, it is recommended that the current mechanism for parallel scientific advice be entered into with the explicit goals of US and EU regulators of providing sponsors with consensus development advice.

5. Addressing the commercial challenges

(a) Commercial challenges

For many therapeutic areas, the traditional pharmaceutical commercial model works well. The company makes a substantial investment and takes a risk on the development of a new medicine. Following approval, the returns help fund and sustain the future R&D effort for the area (figure 2a). While there is a widely recognized need for new antibacterials to address AMR, the number of companies undertaking
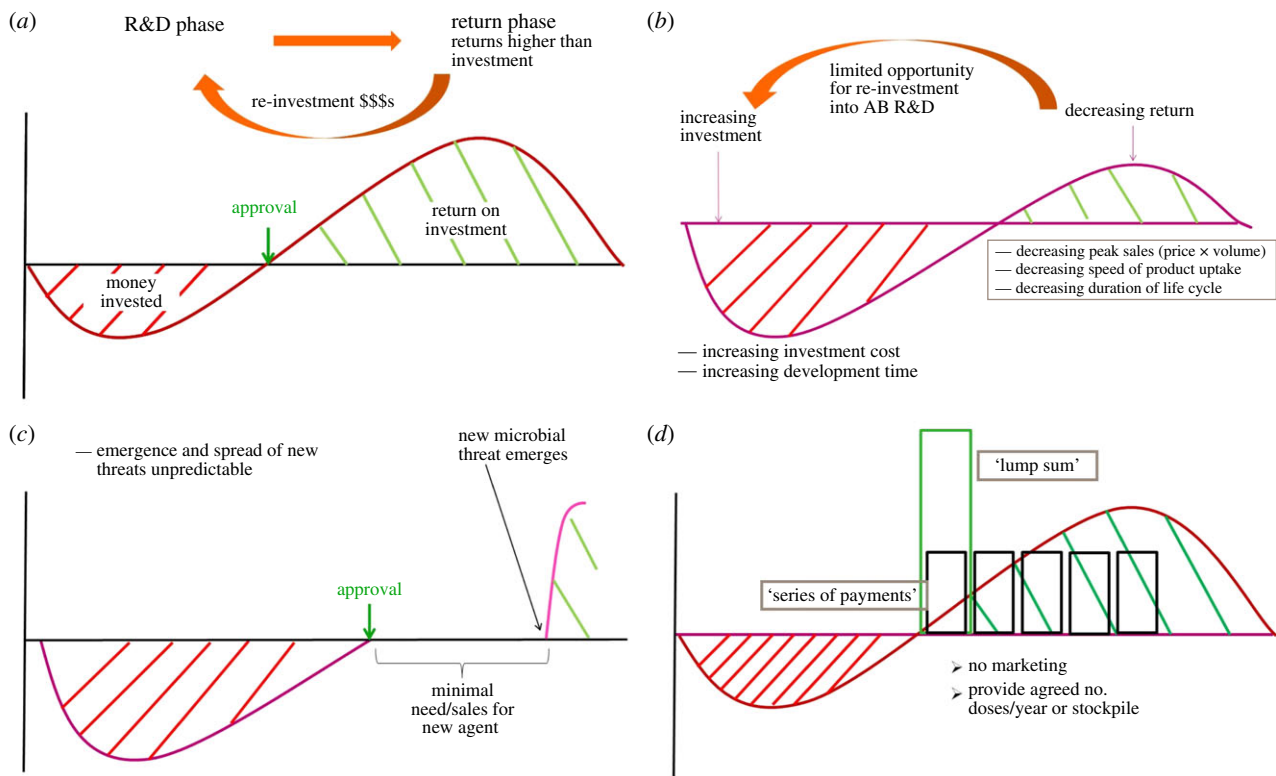
Figure 2. (*a*) The traditional pharmaceutical commercial model. (*b*) Application of traditional commercial model to antibacterials (AB) demonstrating the poor/negative return on investment (ROI). (*c*) Illustration of how the traditional commercial model does not incentivize R&D on antibacterials that could address future potential unmet needs. (*d*) Principles of a de-linked model, where the ROI is provided by either a lump sum or a series of payments provided over several years.

R&D in this area has decreased substantially with a corresponding decrease in both the pipeline and number of approvals for new antibacterial medicines. This trend away from antibacterial R&D seems to be counterintuitive: market forces would be expected to encourage more private investment leading to an increase in the number of antibacterials being developed and approved to meet the high need.

So why are companies reducing investment in this area, or in many cases, exiting completely?

The ROI for antibacterials is below that of many other therapy areas while the risks, both scientific and commercial, are higher. The R&D challenges have been described earlier in this paper. However, many therapy areas have scientifically challenging and expensive R&D programmes, so why are antibacterials different?

The business model for antibacterials is broken: the increasingly expensive challenges of discovery and development are not balanced by the opportunity to make attractive returns (figure 2*b*). In addition, there is little incentive to invest in the development of new antibacterials to address future potential unmet needs that would increase our preparedness to address AMR (figure 2*c*). These facts are increasingly recognized by stakeholders, including those in government, public health and academia as well as the industry. As stated in the recent report prepared by Eastern Research Group, Inc. (ERG), under contract to the Assistant Secretary for Planning and Evaluation which is part of the US Health and Human Services [25, p. vii]:

Despite the potential of new antibacterial products to reduce the social burden associated with resistant infections, some of the large companies have been exiting the markets for antibacterial drugs and vaccines in recent years and have also not responded to the possible social value of opportunities in production of

rapid diagnostic products. These market exits have been driven by the most basic of reasons: insufficient return to capital invested in development of these products.

This ERG report demonstrated that the social value—i.e. the benefit to society in reduction of the social burden of bacterial infection—of a new antibacterial ranged from $486 million (£304 million) for treating acute bacterial otitis media, to approximately $12 billion (£7.5 billion) for treating HABP/VABP (table 4). This is starkly contrasted by their modelled 'private value' (i.e. the value returned to the drug developer), which ranged from negative, −$4.5 million (−£2.8 million) for HABP/VABP (which means the company loses money) to positive, +$37.4 million (+£23.4 million) for CABP. In essence, the developer is getting a negative or very low return for the delivered benefit to society. The models also demonstrated a wide range for the estimates, largely due to unpredictable rates of resistance, unpredictable success in development and the variable time it takes to progress from discovery to a launched product; these uncertainties further reduce the attractiveness for investors.

Why are the returns low? Firstly (and rightly), new antibacterial medicines are reserved so as to preserve their effectiveness in infections caused by resistant pathogens, thus limiting the volume of use. Secondly, the cost of antibacterials, even those for serious hospital infections, is low compared with many new medicines in other therapy areas. The market for antibacterials is dominated by low price generics, which remain effective for many patients. For example, the most commonly used hospital anti-MRSA intravenous antibacterial is vancomycin, widely priced at under £35 a day in the UK. Prices of new antibacterials are often benchmarked against these older generic antibacterials, even when the new agents are active against resistant pathogens and the old agents are not, so there is little scope to increase prices to a level that

8

Table 4. Comparison of mean social ENPVs and mean commercial ENPVs for antibacterials (in US$) demonstrate the life-saving role of antibacterials (adapted from [25]). ENPV, expected net present value; ABOM, acute bacterial otitis media; ABSSSI, acute bacterial soft skin structure infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; CABP, community-acquired bacterial pneumonia. Note: this table shows the mean social ENPVs and as stated in the FDA publication [25], there was a substantial range of values that were calculated. For example for HABP/VABP, the minimum ENPV was $1068 billion, the mean $12.165 billion and the maximum ENPV was $161.335 billion. This range was attributable to, in order of importance, the model parameters for the percentage in disease duration for patients that do not respond to commonly used antibacterial drugs, phase 1 clinical trial success probability, pre-clinical R&D success probability and the real annual social rate of discount. Similarly, a very broad range of values was observed for the private ENPVs, and the primary drivers for the range, in order of importance, were the model parameters for total market size, the real opportunity cost of capital and the total time to market [25].

indication	ABOM	ABSSSI	CABP	cIAI	cUTI	HABP/VABP
private ENPV	−3	27	37	9	22	−4
social ENPV	487	584	9375	1069	6065	12 166

will compensate for the low volume use. This is starkly contrasted by recent innovative treatments for hepatitis C, which can be over £30 000 per patient in the UK.

Thus, the traditional model of revenues being generated as a function of price multiplied by volume does not meet the requirements for adequate returns on antibacterial investment. Additionally, since it takes at least 10 years to develop a new antibacterial, R&D needs to start long before a resistance problem reaches significantly high rates. Even after a drug is developed, manufacturing capacity cannot be cost effectively maintained while waiting for use to increase due to resistance. This adds another layer of investment risk, as future resistance rates can only be estimated, and a predicted increase in need may not even arise. It is also reasonable to propose that companies should be rewarded for the development of antibacterials that could address potential unmet needs of the future. At approval, such agents may not address an immediate unmet need, but will be poised for use to address resistance problems as they arise in the future. Companies need to be compensated for developing such antibacterials as they will increase society's preparedness for future unmet needs.

(b) Approaches for addressing challenges

A new model is urgently needed to address the market failure and increase investment in this area.

The new model should not only address the market failure, but it also needs to reduce the pressure from many stakeholders that drives greater volumes, thereby accelerating the development of resistance. A new economic model that de-links the volume of sales of a new antibacterial from the revenues the company receives would remove incentives for the company to increase volume use beyond what is clinically and microbiologically optimal, while rewarding them for a high risk investment where volume use is low.

We recommend a de-linked model based on one, or a series of fixed payments to the innovator, that reflects in commercial terms, the societal 'insurance' value of a new antibacterial (figure 2d). This would potentially de-risk returns and provide sufficient income to generate an attractive ROI while aligning with public health goals. We believe it is important that the model facilitates access to all patients with resistant infections caused by bacteria resistant to other antibacterials, no matter where they are being treated around the world, or their ability to pay.

Another proposal for an increasing ROI is based on higher prices. While clear signals of a willingness to pay higher prices would likely attract investment, we do not believe that price

alone will deliver a sustainable, predictable model for all stakeholders in all global regions. Higher prices and unpredictable use would increase budget unpredictability for companies and payers alike. For example, a resistance outbreak in a local hospital would trigger significant unplanned novel antibacterial expenditure. High prices are also challenging to implement globally within current national Health Technology Assessment and pricing systems, leading to variable access of new medicines when they are needed. Finally, high prices could increase the tension between the desire to drive volume use to generate revenues and public health objectives to limit volume use in order to preserve microbiological effectiveness.

A de-linked model may not be sufficient alone to address the issue of low ROI. A combination of push incentives (e.g. PPPs such as the IMI, tax credits, public support for research and BARDA) to reduce the costs of development are also required. All are important parts of the model and help improve ROI, but the economic market failure remains the critical gap for attracting new investment. The de-linked model would help fill this gap.

(c) Description of a de-linked model

A guaranteed series of payments could be negotiated between the innovating company and payers. The payments could be structured to be paid on regulatory approval to reward successful development, but also should be sufficient to cover the significant cost associated with attrition of molecules that start development but do not make it to market (figure 2d). Value would be created for companies by reducing commercial uncertainty and for payers by reducing budgetary uncertainty, for example ironing out peaks in financial demand in the event of an MDR outbreak. Value would be created for society by increasing the investment in antibacterial R&D, with the aim of filling the pipeline to address future resistance.

Our analysis indicates that payments totalling £200 million a year globally for 10 years, triggered by the approval of a novel antibacterial, would provide a ROI at a level that would be attractive to a major pharmaceutical company. We believe that this is needed to attract sustainable private investment that enables companies to make a return despite the high rates of R&D attrition described earlier in the paper. This model could also be applied to support the development of antibacterials that could address future potential health threats by creating an incentive to develop such antibacterials so they are poised for use when the threat materializes. For example, currently there is lower unmet need for the treatment of

MRSA skin infections and community-acquired pneumonia making it harder to justify investment in developing such drugs. However, unmet needs may occur in the future, so to ensure preparedness for these very common infections it is important to have incentives to progress such antibacterials. Once the payments have been set up, the company should supply the product at cost, according to a manufacturing service agreement. Other important elements of product management need to be considered as part of the agreement (e.g. pharmacovigilance, maintenance of regulatory files, further clinical investigation, and distribution and physician education).

(d) Challenges for implementing a de-linked model

The proposed model of fixed payments draws from elements within and outside current healthcare purchasing systems. Advance market commitments have been negotiated to encourage companies to invest in vaccine development, by guaranteeing a certain level of revenue. Contracts are agreed between Governments and other industries designed to deliver levels of ROI that encourage companies to invest, for example in needed infrastructure such as toll roads and power stations. The vaccines alliance, GAVI, provides a global model for managing appropriate distribution of valuable medical products. Lessons can also be learned from malaria, HIV and TB.

The de-linked model described in figure 2d has not yet been applied to the purchasing of medicines and creates several implementation challenges that need to be resolved between stakeholders. The key areas of challenge for implementation include: roles and governance, geographical scope, funding mechanisms and amounts, product scope and intellectual property issues. The final challenge, given the financial pressure on most governments worldwide, is the need to invest extra money into antibacterials compared with today, but this is needed irrespective of the type of new commercial model that is adopted. Additionally, further work needs to be done to determine the net benefit accrued from a new model, but we propose that without a significant change to the existing business model, we will not see the increase in R&D investment required to address the problem of future AMR.

An increased stakeholder effort to better understand the economics of antibacterial R&D and commercialization is required. The recent announcement in the UK of a detailed review of new models led by the economist Jim O'Neill (former Goldman Sachs chief economist), the DRIVE-AB consortium [4] and the PCAST report [12] are all encouraging signs. However, concrete progress will only be made once these dialogues are turned into clear strategies, gain significant political support and are implemented with a long-term perspective.

In summary, continuing with the present business model is not an option. Antibacterials provide great benefit to society; there are few medicines that are taken for a week or less that can extend life by decades. However, without more attractive returns for investors, the number of new antibacterials reaching the market will continue to decrease and the threat to life posed by increasing antibacterial resistance will grow. There needs to be a rebalancing between the value to society and the value to investors, as without that, investment will continue to decline, and the long-term impact will be a huge societal cost. A solution needs to be found in the short-term to start addressing this issue and we believe that the de-linked model offers the most balanced approach to addressing the current broken business model.

6. Rapid diagnostics: a key solution for addressing both antimicrobial resistance and industry pipeline

There is general agreement that certain rapid, point of care diagnostic tests could have a transformational effect on the appropriate use of antibacterial agents by changing the current widespread practice of empiric prescribing to a practice of prescribing after target pathogens have been identified [26]. Currently, antibacterial therapy is often based on empiric therapy, which is essentially an 'educated guess'. This is often the best choice for an individual patient and it is the most efficient course of action. The empiric therapy model has worked very well, saving lives and supporting modern medical advances. However, empiric therapy has also had a high cost, primarily to the human and animal population as a whole, but also to individual patients. Empiric therapy results in needless courses of antibacterials prescribed to patients who do not even have a bacterial infection. This model has led to increasing resistance, unnecessary side effects and negative impact on the human microbiome that is just recently beginning to be understood. The development and use of simple, cheap, efficient and accurate rapid diagnostics that can identify the infecting pathogen and its susceptibility profile could break the cycle of resistance development exacerbated by empiric prescribing and enable positive transformational change in pathogen/resistance identification and practices for treating bacterial infections.

Rapid diagnostics could also improve the feasibility of running cost-effective clinical trials that target appropriate patient populations, thereby improving the quality of trials and also the sustainability of the antibacterials R&D business. The traditional clinical trial design allows enrollment of patients with a particular infection, such as ventilator-associated pneumonia that can be caused by several different species of bacteria. These bacteria may or may not be resistant to current agents. Without a rapid diagnostic test that can be used to screen for patients that have the target pathogen or pathogens with the target-resistance mechanisms, clinical trials end up including both the target pathogens as well as pathogens that could have been effectively treated by older agents. This process is inefficient and results in large expensive trials [27]. A rapid point of care diagnostic test could be used to only enroll those patients with the target pathogen or resistance mechanism thereby decreasing the number of patients enrolled into a trial and decreasing the cost of development (figure 3).

Rapid diagnostic tests are particularly needed for new agents that may be approved based on limited datasets and that will have regulatory labels that significantly restrict use such as the LPAD approach described previously. In these studies, limited patient populations will be enrolled. It is crucial that patients with the target pathogens are studied, including those with resistance mechanisms that render the pathogen resistant to current agents but susceptible to the new drug under development. Diagnostic tests that can provide accurate results as part of the trial enrollment process can ensure that only those patients with the target pathogen are enrolled.

It is time for a bold vision for new, rapid, simple, inexpensive, efficient and accurate point of care diagnostics that will enable transformational change in pathogen/resistance identification, antibacterial prescribing and antibacterial clinical trial design.
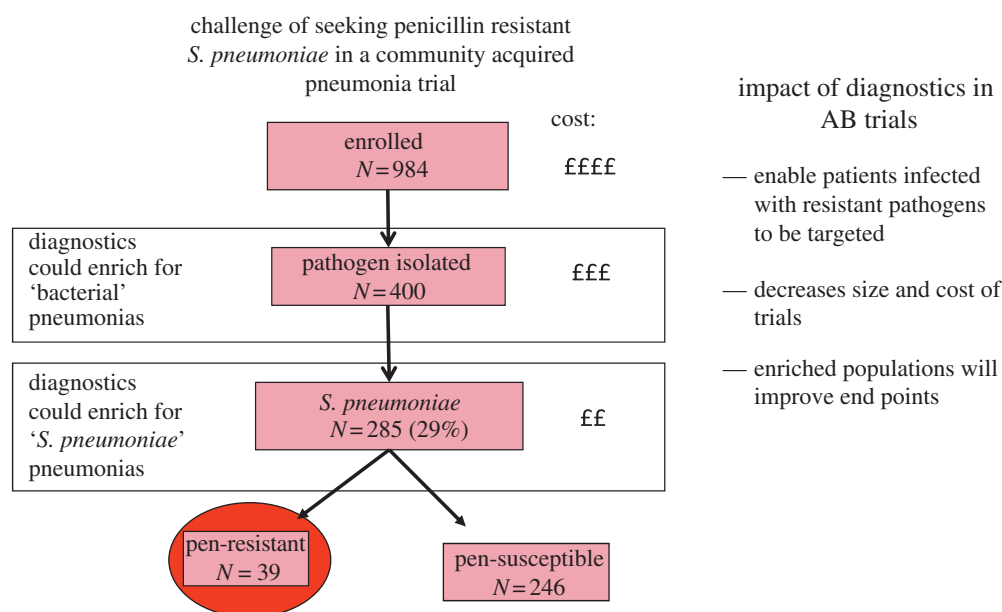
Figure 3. Potential impact of rapid diagnostic on clinical trial costs [27].

(a) Focus on tests with highest hurdles to development and use

One of the greatest areas of need for accurate, rapid, simple, inexpensive point of care diagnostics is in pneumonia, both community and hospital associated. In addition to pneumonia, rapid inexpensive diagnostic tests for urinary tract and intra-abdominal infections are lacking and needed.

We propose that new point of care diagnostics need to achieve the optimal parameters listed below to provide a transformational improvement in the way antibacterials are prescribed and substantially improve the efficiently of antibacterial clinical trials. Low cost, simple or no instrumentation and ease of use are crucial to global utilization of diagnostic tests.

(i) Optimal parameters
— Direct from specimen.
— Reasonable level of pathogen (and/or resistance mechanism) detection sensitivity and specificity (assume at least more than or equal to 95% sensitive and specific).
— Turnaround time for results—optimal less than 20 min; minimal less than or equal to 30 min.
— Distinguishes colonizing from infecting organisms.
— Simple, easy to use test (acceptable as point of care test; Clinical Laboratory Improvement Amendments waived).
— Instrumentation and consumables—acceptable costs (less than or equal to $10).

The above will raise debate among stakeholders in this field and are proposed for the purpose of initiating that debate. However, turnaround times of 20–30 min are stated as a goal by 2020 in the US National Strategy for Combating Antibiotic-Resistant Bacteria [19].

The target pathogens to be considered for these new direct from specimen diagnostic tests are carbapenem-resistant Enterobacteriaceae, including *Klebsiella pneumoniae* carbapenemase, New Delhi metallo-beta lactamase and other metallo-beta lactamase producers; *Acinetobacter* species

(including MDR strains); *Pseudomonas aeruginosa* (including MDR strains); *S. aureus* (MRSA/MSSA) and *S. pneumoniae* (including MDRSP strains).

(b) Factors impeding development of needed diagnostics

There are scientific, regulatory and reimbursement factors that are impeding development of the more challenging diagnostic tests for pneumonia and MDR pathogens described above. Also, it is important to recognize that an accurate test that is not easily incorporated into laboratory and medical practice will be useless. Widespread use of new rapid diagnostics will only occur if they are clinically relevant and impactful, feasible for use in clinical microbiology laboratories and/or point of care settings, are cost effective for the laboratory and are adequately reimbursed to support development by diagnostic companies.

Medical and scientific factors have hindered development of direct from specimen rapid diagnostics in pneumonia and other body sites. These include the following:

— difficulties in obtaining a specimen that reflects clinical situation; and
— sample preparation hurdles for lower respiratory tract and urine specimens.
  (i) Interfering substances in specimen may hinder some molecular tests.
— inability to distinguish colonization versus infection;
— multiple pathogens causing infection; and
— risk of basing antibacterial therapy on test result that can be false negative or positive.

In addition to the medical/scientific factors, clarity and facilitation of global regulatory requirements for development of diagnostics as well as co-development of diagnostics and therapeutics would help facilitate new diagnostic tests for bacterial infections.

A new paradigm of targeting bacteria therapy based on rapid, point of care testing will also require that these tests are reimbursed adequately to incentivize development and that their use makes sense for patients. The challenging question of 'what is the cost benefit to patients of empiric therapy versus targeted therapy?' will need to be answered. We must acknowledge that in many cases, it is faster, cheaper and more clinically effective for an individual patient to be treated with antibacterials empirically. However, for the community and future populations, targeted therapy which reduces the potential of resistance may ultimately cure more infections and save more lives. Guidelines for use of new tests will need to be developed and accepted by the medical community.

(c) Proposals to overcome hurdles to diagnostics development

There is a tsunami of diagnostic tests being developed for infectious diseases. It is crucial, therefore, that stakeholder resource be focused on overcoming hurdles for the diagnostic tests that are the most difficult to develop. These are tests where, without additional assistance, development will not occur.

The hurdles for diagnostics for pneumonia and MDR Gram-negative pathogens are particularly high. One solution could be strong PPPs to: (i) conduct basic research, (ii) improve understanding between key stakeholders, (iii) support changes in regulatory guidance for diagnostic testing and/or therapeutics, and (iv) determine how diagnostic tests can be adequately reimbursed. Perhaps a new business model, as is needed for antibacterial R&D, is also needed for diagnostic test development.

A multi-faceted approach is needed and there is encouraging progress focused on efforts to invest, coordinate and incentivize.

(i) Invest

As the scientific and logistical challenges for transformational diagnostics is daunting, major investment in new science, new biomarkers and new platforms is needed. The IMI in the European Union has a number of exciting projects that include diagnostics test development for bacterial infections. One of these is the IMI RAPP-ID (Rapid Point of Care Platforms for ID; RAPP-ID, http://www.imi.europa.eu/content/home). This 5-year PPP is focused on three point of care tests: Influenza Breath POCT; a Community-Associated Lower Respiratory Tract Infection test and a Nucleic Acid-Based Ventilator-Associated Pneumonia test. Significant new understanding is coming from this program that will push forward the boundaries for the most challenging test needs.

Another example of how investment can make a difference is the collaboration announced by Cepheid, AstraZeneca, Cubist Pharmaceuticals and GlaxoSmithKline on 19 June 2014 (Cepheid, http://ir.cepheid.com/releasedetail.cfm?ReleaseID=855545). The Xpert® Carba-R is a rapid test under development by Cepheid to identify the presence of genes that code for key carbapenemase enzymes in rectal swab samples. Specifically, the consortium is working to extend the number of body sample types from rectal swabs to other body samples such as respiratory samples from patients with pneumonia. The goal is to develop the test for use in enriching clinical trials for patients likely to be infected with a carbapenemase-producing pathogen. However, the data generated on the Xpert® Carba-R test in the clinical trials will be useful in understanding applications for this test in clinical practice.

(ii) Coordinate

There are a number of different initiatives lead by academic, medical, governments, regulatory and commercial stakeholders that are trying to spur the development of rapid diagnostic tests for bacterial infections. Therefore, it is important to try to raise awareness of these multiple efforts to encourage synergy and avoid unnecessary duplication. As a pharmaceutical company with the goal of developing new antibacterial agents for drug development, GlaxoSmithKline facilitated an informal network of stakeholders to share information on initiatives and make connections and is a founding member of a new organization in the US called the Diagnostics Action Team (DAT). The DAT is lead by the Foundation to Combat Antimicrobial Resistance (http://thefcar.org/). It consists of FDA, NIH, diagnostic companies, pharmaceutical companies, as well as payers. The goal of the DAT is to catalyse development of diagnostics that radically change antibacterial prescribing and conduct of clinical trials.

(iii) Incentivize

A third strategy that is being increasingly pursued to encourage development of rapid diagnostics for bacterial infections is the creation of Inducement Prizes to incentive innovation. The leading example of this was the inclusion, in 2014, of 'Antibiotics'—and specifically development of Rapid Diagnostics for Bacterial Infections, as one of the candidates for the 2014 Longitude Prize (Longitude, http://www.longitudeprize. org/). The Longitude Prize 2014 is a £10 million prize fund intended to help solve one of the greatest issues of our time. In July 2014, the UK public voted 'Antibiotics' for the prize above various other important challenges of our time (e.g. paralysis, environmental challenges and Alzheimer's) and signals that the public now understand the need for action to address AMR. This prize, along with the new EU Horizon 2020 Prize [28] and the $20 million prize recently announced by the US Government [29], will hopefully create momentum and solutions to create the scientific breakthroughs that are needed for transformational diagnostics.

7. Conclusion

The challenges of AMR have been a concern for the past few decades but it has been a challenge to raise awareness about the significance of antibacterial resistance outside of the scientific and antibacterial R&D community. Strong patient advocacy groups do not exist for AMR as they do for cancer and HIV as most bacterial infections are acute and transient. Therefore, it is promising that political leaders in Europe, UK and USA and the public are now beginning to understand what is at stake if we do not take action.

In conclusion, we propose that the following is needed to create a long-term solution to AMR:

— a new commercial model that attracts substantial new investment and removes incentives to sell a high volume of new antibacterials to create commercial value;
— transformational diagnostics to dramatically change the practice of antibacterial prescribing and profoundly transform antibacterial clinical trials;
— a globally harmonized regulatory environment; and

— a thriving research environment across academia and industry (like the 'call to action for HIV').

All key stakeholders have a role in creating solutions to AMR and success will require leadership in academia, industry and governments globally. There are encouraging signs that multi-faceted, multi-stakeholder solutions are being envisioned and those visions need to be turned into a reality of a new generation of life-saving antibacterials. We can solve this problem by working together, sharing information and creating a sustainable economic model built around recognizing the societal value of antibacterials.

References

1. COMBACTE (Combating Bacterial Resistance in Europe). See http://www.combacte.com/About-us/ND4BB.

2. Rex JH. 2014 ND4BB: addressing the antimicrobial resistance crisis. Nat. Rev. Microbiol. 12, 231–232. (doi:10.1038/nrmicro3245)

3. Stavenger RA, Winterhalter M. 2014 TRANSLOCATION PROJECT: how to get good drugs into bad bugs. Sci. Transl. Med. 6, 228ed7. (doi:10.1126/scitranslmed.3008605)

4. DRIVE-AB. Driving reinvestment in R&D for antibiotics and advocating their responsible use. http://drive-ab.eu/ (accessed 12 March 2015).

5. Payne DJ. 2014 GlaxoSmithKline2140944: a novel bacterial topoisomerase inhibitor with activity against both conventional and biothreat pathogens, Abst. 143. Washington, DC: American Society of Microbiology Biodefense and Emerging Diseases.

6. Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. 2007 Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat. Rev. Drug Discov. 6, 29–40. (doi:10.1038/nrd2201)

7. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. 2010 How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat. Rev. Drug Discov. 9, 203–214. (doi:10.1038/nrd3078)

8. White AR, Kaye C, Poupard J, Pypstra R, Woodnutt G, Wynne B. 2004 Augmentin (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent. J. Antimicrob. Chemother. 53(Suppl. Si), i3–i20. (doi:10.1093/jac/dkh050)

9. Lins RL, Matthys KE, Verpooten GA, Peeters PC, Dratwa M, Stolear J-C, Lameire NH. 2003 PK of atorvastatin and metabolites in healthy subjects. Nephrol. Dial. Transplant. 18, 967–976. (doi:10.1093/ndt/gfg048)

10. Bax BD et al. 2010 Type IIA topoisomerase inhibition by a new class of antibacterial agents. Nature 466, 935–940. (doi:10.1038/nature09197)

11. Page MGP. 2013 Siderophore conjugates. Ann. NY Acad. Sci. 1277, 115–126. (doi:10.1111/nyas.12024)

12. President's Council of Advisors on Science and Technology (PCAST). Report to the President on combating antibiotic resistance. http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf.

13. Mugabe C, Halwani M, Azghani AO, Lafrenie RM, Omri A. 2006 Mechanism of enhanced activity of liposome-entrapped aminoglycosides against resistant strains of Pseudomonas aeruginosa. Antimicrob. Agents Chemother. 50, 2016–2022. (doi:10.1128/AAC.01547-05)

14. Shapiro AB, Jewman J, Goteti K, Beaudoin M, Harrison R, Hopkins S, Agrawal N, Rivin O. 2013 Improvement of the pharmacokinetics and in vivo antibacterial efficacy of a novel type IIa topoisomerase inhibitor by formulation in liposomes. Antimicrob. Agents Chemother. 57, 4816–4824. (doi:10.1128/AAC.00163-13)

15. McEnaney PJ, Parker CG, Zhang AX, Spiegel DA. 2012 Antibody-recruiting molecules: an emerging paradigm for engaging immune function in treating human disease. ACS Chem. Biol 7, 1139–1151. (doi:10.1021/cb300119g)

16. Ghose C. 2013 Clostridium difficile infection in the twenty-first century. Emerg. Microb. Infect. 2, e62. (doi:10.1038/emi.2013.62)

17. Smith SB, Magid-Slav M, Brown JR. 2013 Host response to respiratory bacterial pathogens as identified by integrated analysis of human gene expression data. PLoS ONE 8, e75607. (doi:10.1371/journal.pone.0075607)

18. Mellman I, Coukos G, Dranoff G. 2011 Cancer Immunotherapy comes of age. Nature 480, 480–489. (doi:10.1038/nature10673)

19. The White House. National Strategy for Combating Antibiotic Resistance, 2014. http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf.

20. European Medicines Agency. Telavancin (Vitabiv) EMEA/H/C/001240. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001240/human_med_001467.jsp&mid=WC0b01ac058001d124.

21. US Department of Health and Human Services, Food and Drug Administrations, Center for Drug Evaluation and Research. Guidance for industry: antibacterial therapies for patients with unmet medical need for the treatment of serious bacterial diseases. Draft guidance. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf.

22. European Medicines Agency. Addendum to the note for guidance on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95/ REV 2) to address indication-specific clinical data. Draft, 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129443.pdf.

23. Infectious Diseases Society of America (IDSA). Limited Population Antibacterial Drug (LPAD) approval mechanism. http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/LPAD%20one%20pager.pdf.

24. H.R.3742 - Antibiotic Development to Advance Patient Treatment Act of 2013. 113th Congress (2013–2014). https://beta.congress.gov/bill/113th-congress/house-bill/3742.

25. Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, Outterson K. 2014 Analytical framework for examining the value of antibacterial products. Washington, DC: US Department of Health and Human Services/ASPE.

26. Caliendo AM et al. 2013 Better tests, better care: improved diagnostics for infectious diseases. Clin. Infect. Dis. 57(Suppl. 3), S139–S170. (doi:10.1093/cid/cit578)

27. Bhatt K, Kalia V, Berkowitz E, Twynholm M, Abraham-van Parijs B, Hodge R. 2005 Efficacy and safety of pharmacokinetically enhanced amoxicillin/clavulanate 2000/125mg (PKE AMX/CA) in patients with community-acquired pneumonia, including cases caused by penicillin-resistant S. pneumonia. 15th Eur. Congr. Clinical Microbiology and Infectious Diseases, Copenhagen, 2–5 April. Abstract 1134_02_88.

28. European Commission. First Horizon 2020 Work Programme update – launch of FTI and innovation prizes. http://europa.eu/rapid/press-release_MEMO-14-492_en.htm.

29. Monaco L, Holdren JP (The White House). New Executive actions to combat antibiotic resistance and protect public health: launch of a $20 million prize. http://www.whitehouse.gov/blog/2014/09/18/new-executive-actions-combat-antibiotic-resistance-and-protect-public-health.