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Teaser In this Keynote we consider recent progress with the antibiotic discovery process and make recommendations for further, often collaborative, advances.

Meeting the discovery challenge of drug-resistant infections: progress and focusing resources

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Following multiple warnings from governments and health organisations, there has been renewed investment, led by the public sector, in the discovery of novel antimicrobials to meet the challenge of rising levels of drug-resistant infection, particularly in the case of resistance to antibiotics. Initiatives have also been announced to support and enable the antibiotic discovery process. In January 2018, the Medicines Discovery Catapult, UK, hosted a symposium: Next Generation Antibiotics Discovery, to consider the latest initiatives and any remaining challenges to inform and guide the international research community and better focus resources to yield a novel class of antibiotic.

Introduction

In the face of an impending loss of therapeutic options for the most severe and life-threatening infections, WHO issued a list of important, highly important and critically important antimicrobials for human medicine in 2005. In 2009, WHO issued a statement acknowledging antibiotic resistance as one of the three greatest threats to human health; and, in 2015, the 68th World Health Assembly adopted the WHO Global Action Plan on Antimicrobial Resistance – aimed at mitigating the impact of antimicrobial resistance on our ability to manage infectious disease [1]. In March 2018, WHO announced a list of priority bacteria for the development of antibiotics [2]. Critical-priority bacterial targets include the Gram-negative species *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (both displaying resistance to carbapenem antibiotics) and the carbapenem- and cephalosporin-resistant *Enterobacteriaceae* [2]. The WHO 2018 priority list also highlights the need for effective antibiotic agents against drug-resistant community-acquired infections including those caused by *Salmonella* spp., *Campylobacter* spp., *Neisseria gonorrhoeae* and *Helicobacter pylori* [2]. Calls-to-action have also been issued to the scientific and pharmaceutical communities to make the identification and development of new, effective drugs a priority

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Chris Dowson holds a personal chair at Warwick University and is a member of the Medical Research Council Infections and Immunity Board. His research focuses on the emergence and evolution of antibiotic resistance across a wide range of bacteria. His recent focus has been to better understand how penicillin targets bacteria. This work began during his postdoctoral time at the University of Sussex, in the laboratory of Professor Spratt (1986–1990), and subsequently with his Lister Institute Centenary Fellowship (1991–1996).

John Overington joined the Medicines Discovery Catapult as Chief Informatics Officer in April 2017. In his previous roles, he was involved in development of novel data extraction and integration strategies, integrating deep learning and other artificial intelligence approaches to drug target validation and drug optimisation. He has also led the development of a series of computational and data platforms to improve drug discovery, including the medicinal chemistry database StARLite. He was central to the transfer of StARLite to the EMBL-EBI (now known as the ChEMBL). More recently, the work extended into large-scale patent informatics with the open patent database SureChEMBL.

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by a number of agencies, including the United Nations General Assembly (Resolution A/RES/71/3; http://www.un.org/en/ga/71/resolutions.shtml), US Centers for Disease Control (https://www.cdc.gov/drugresistance/biggest_threats.html) and the European Academies' Science Advisory Council (EASAC; https://www.easac.eu/fileadmin/PDF_s/reports_statements/Easac_statement_AntimicrobialDD_webvs.pdf).

There is a need to assess progress, move forward and focus on identifying and overcoming barriers to new antibiotic drug discovery and development. To this end, a symposium: Next Generation Antibiotic Discovery, was convened in January 2018 by the UK Medicines Discovery Catapult, an independent, not-for-profit organisation funded by a government agency: Innovate UK. The meeting brought together international academics, researchers and clinicians, with representatives of public health, public and private funding organisations, biotech companies and the biotechnology and pharmaceutical industries. The meeting considered the resources currently available, many under new initiatives, and areas in need of further development and advancement. In particular, four key areas for further intervention and priority knowledge gaps were identified to enable the discovery and development of new antibiotics. This Keynote provides a summary report of the discussions that took place during the symposium and is a platform to raise awareness, highlight requirements and promote collaboration and action.

The challenge

Antibiotic agents are an underpinning component of our healthcare system. Surgery, critical care, premature infant care and organ transplantation all depend on the availability of effective antibiotics to prevent or treat bacterial infections [3]. Figure 1 illustrates the existing classes of antibiotic agents and the Pew Trust provides an oversight of the current development pipeline [4]. The rise of drug-resistant infections threatens to undermine many if not all the developments in healthcare over the past century. Yet, in the past decade, we have seen a rapid decline in the investment made by the pharmaceutical industry in the development of antibiotics (Box 1 provides an overview of the antibiotic discovery and development pathway). Only a few major pharmaceutical companies continue to have infectious disease programmes focused on the identification and development of novel antibiotics. Currently, GlaxoSmithKline, Merck, Novartis and Roche have active, dedicated, infectious disease research programmes focused on the discovery and development of new antibiotic agents. Other leading pharmaceutical companies, including Sanofi and Novartis, are seeking to transfer their antibiotic research and development programmes to other companies. For example, Sanofi has concluded negotiations with Evotec to integrate their antibiotic R&D into the internal pipeline of Evotec [5]. The impact on global health of this aggregate under investment cannot be overstated, because integrated pharmaceutical companies possess the wherewithal to bring together fundamental research with state-of-the-art techniques to identify new antibiotic classes, evaluate their clinical utility and distribute products. The limited private sector investment under current market conditions necessitates an alternative approach. A concerted, coordinated and collaborative community approach involving public and private sector funding, with incentives to attract new entrants, academics and smaller biotechnology companies, is underway. The symposium identified new entrants, under-appreciation of the role of surveillance, availability of isolates from biobanks and emerging new sources of finance.

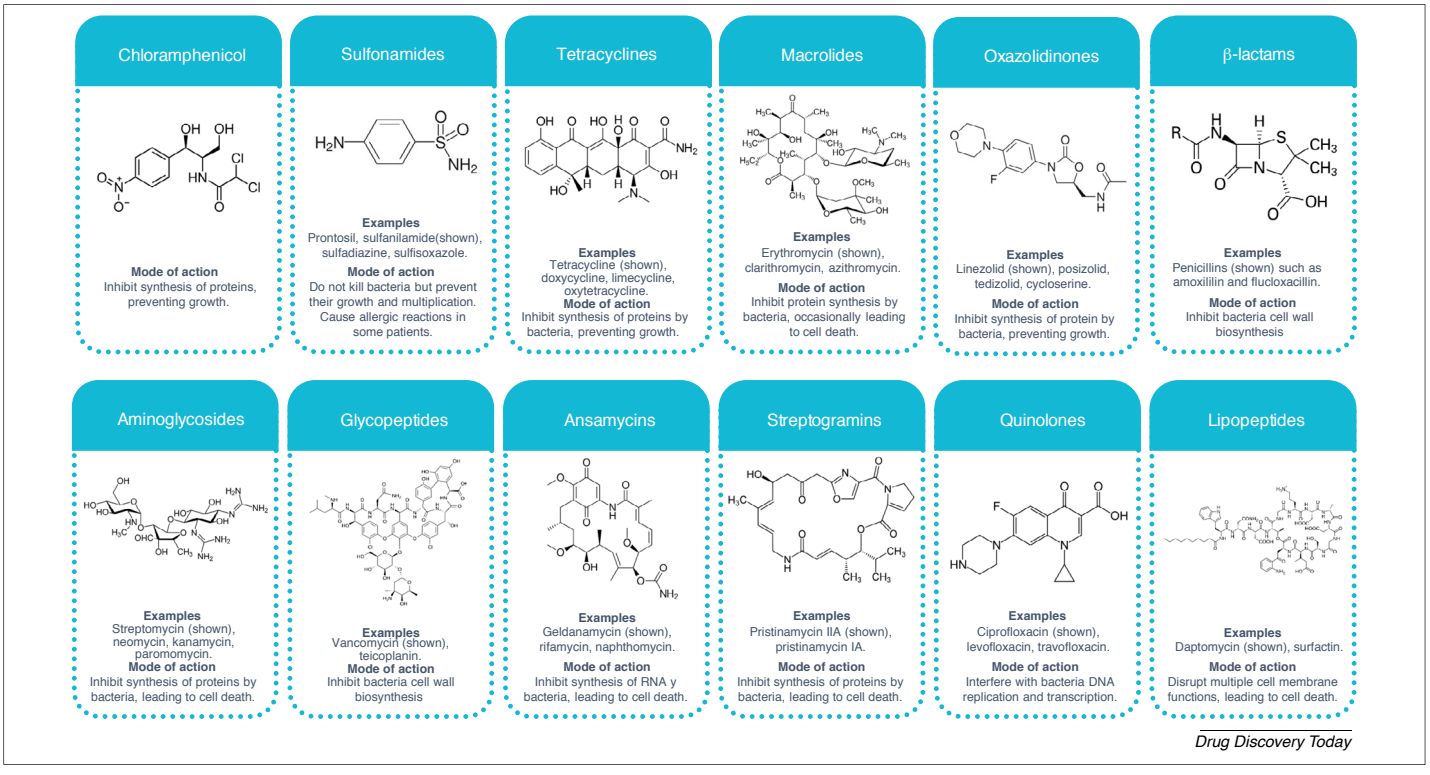

FIGURE 1

Classes of antibiotics and their mode of action.

BOX 1

Antibiotic discovery and development pathway

The process of bringing an antibiotic to market is costly and lengthy. The first phase – discovery – is a process whereby potential chemical entities for preclinical evaluation and testing are identified. This phase can take up to 7 years and, factoring in attrition, cost in the region of US$100 millions [33,34]. Once potential antibiotics have been identified, they enter an exhaustive evaluation pathway, the elements of which are largely mandated by regulatory authorities who ultimately approve and license medicines for use in humans. The whole process, from discovery to licensing of a single antibiotic, can take more than a decade and typically costs several billion dollars (Fig. I).

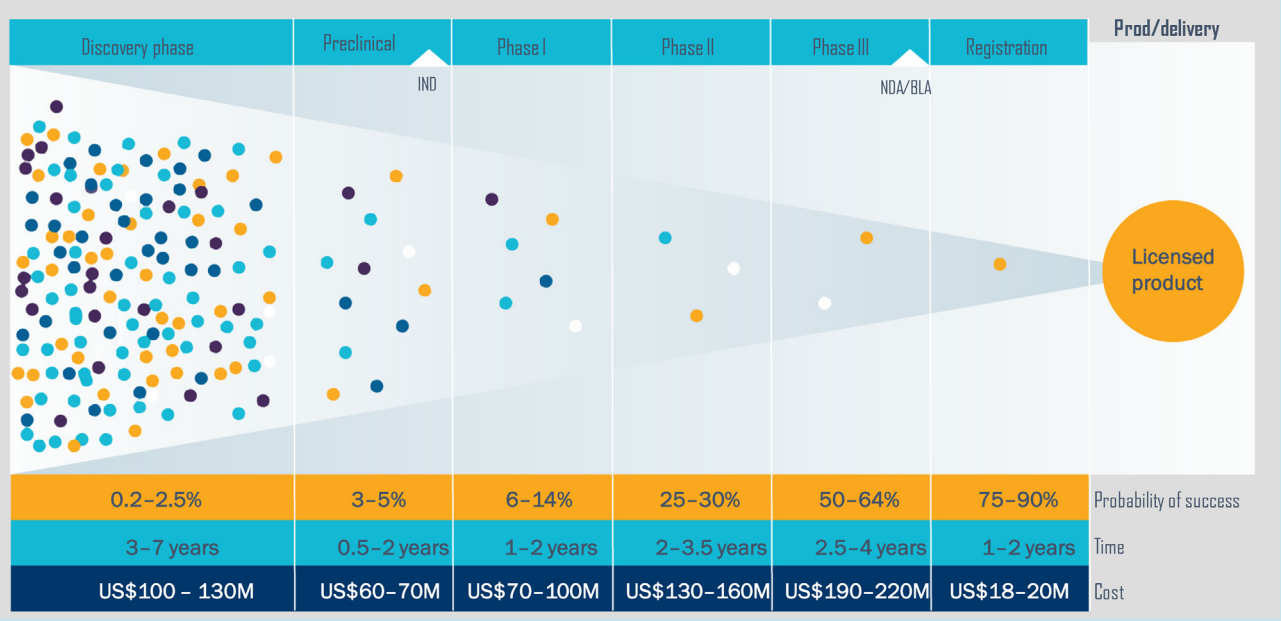

FIGURE I

The antibiotic drug development pathway.

Microbial surveillance and biobanks

Microbial and antibiotic resistance surveillance provides a contemporary understanding of the profile of pathogenic microorganisms in circulation and their resistance profiles, helping to guide areas towards more-intensive R&D efforts. Although surveillance data have long been generated by pharmaceutical companies as part of the required data package for approved antibiotics (e.g., ATLAS involving Pfizer; https://atlas-surveillance.com), there is a greater reliance on surveillance programmes coordinated (to avoid duplication, gaps and enable data sharing) by national governments [e.g., Centers for Disease Control, USA (CDC)] and charitable organisations.

WHO has established the Global Antimicrobial Resistance Surveillance System (GLASS; http://www.who.int/glass/en/) as part of the Global Action Plan on Antimicrobial Resistance. Data collection began in 2016 and the first report on global and regional antimicrobial resistance data in human health was issued in January 2018 [6]. The European Antimicrobial Resistance Surveillance Network (EARS-Net), established in 1998 and operating under the administration of the European Centre for Disease Prevention and Control (ECDC) since 2010, supports and collates national antimicrobial resistance surveillance data across Europe (https://ecdc.europa.eu/en/home). The World Data Center for Microorganisms (WDCM; http://www.wdcm.org) and the ECDC collate and coordinate national surveillance efforts but are not in themselves culture repositories. The WDCM provides a global biobank catalogue of microorganisms spanning 118 culture collections across 46 countries and regions.

In the UK, the British Society for Antimicrobial Chemotherapy (BSAC) has a well-established (17 year) resistance surveillance initiative that collects clinical isolates from community- and hospital-acquired infections. Their Resistance Surveillance Programme [7] collects up to 6000 clinical isolates, plus associated antibiotic susceptibility data, each year in the UK and Ireland. The programme is designed to provide long-term surveillance of antibiotic resistance to understand how patterns of resistance are changing. The database are available to search online, and isolates can be requested for research purposes (http://www.bsacsurv.org). In the USA, the CDC gathers data on antibiotic-resistance infections in healthcare and community settings. These data are shared through a number of networks including the Active Bacterial Core (ABC) Surveillance Programme, the National Antimicrobial Resistance Monitoring System (NARMS) and the National Healthcare Safety Network (NHSN) [8].

A key development is next-generation sequencing, which enables the characterisation of human pathogens at the genetic level. The Wellcome Trust Sanger Institute has sequenced a large number of pathogenic bacterial genomes and has collaborative projects in place with the BSAC and with Public Health England's National Collection of Type Cultures (NCTC) Reference Collection to provide genomic characterisation of their respective isolate collections. The Wellcome Sanger Institute Centre for Genomic Pathogen Surveillance uses whole-genome sequencing and conducts structured, large-scale, pathogen surveys on a global basis.

The aim is to provide data on the emergence and spread of antimicrobial drug resistance [9].

Funding initiatives in action

With the divestment of integrated R&D programmes by larger pharmaceutical companies, the role of smaller companies and academic groups focused on defined elements of the development process has become increasingly important. Although larger pharmaceutical companies might have the financial capacity to fund compound development from hit identification through preclinical and clinical evaluation and, if successful, to market entry, academic groups and smaller companies must often seek investment and external funding for their R&D activities. The development of the candidate antibiotic ridinilazole and antibiotic plazomicin are examples of how this process can work to move a novel antibiotic from discovery through to market. Ridinilazole (Box 2) is an instructive example in contemporary approaches to funding antibiotic discovery and development, for which a hybrid of public and private finance was deployed. Financial input from The Wellcome Trust at crucial steps in the development process enabled the preclinical and early clinical evaluation of this agent. Further clinical development is now ongoing with support from the Biomedical Advanced Research and Development Authority (BARDA). Recently approved Zemdri™ (plazomicin) [10] has shown that a hybrid approach together with 'pull' mechanisms (facilitated by the GAIN Act, 2012, https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM595188.pdf) is effective for gaining regulatory approvals. Under the GAIN Act, the FDA granted fast-track status for plazomicin in 2012, followed by qualified infectious disease product designation in 2015, collectively these provide an expeditious priority review by the agency and an additional 5 years market exclusivity for the product. This agent was recently (June 2018) approved in the USA for the treatment of adults with complicated urinary tract infection caused by multidrug-resistant *Enterobacteriaceae*. The clinical evaluation of plazomicin was supported in part by federal funding.

Examples from the symposium of agencies, which offer funding for research into and development of antibiotics, are given in Box 3. These include the Combating Antibiotic Resistant

BOX 2

Ridinilazole: a case study

In recent years, *Clostridium difficile* infection (CDI) has emerged in as a major healthcare concern with a dramatic increase in global prevalence following initial outbreaks, in North America in the late 1990s and early 2000s, caused by hypervirulent BI/NAP1/027 strains. CDI is now the most common hospital-acquired infection in the USA and is one of the three CDC urgent AMR threats. Ridinilazole is a novel, precision antibacterial, being developed by Summit Therapeutics, for the treatment of CDI and reducing the recurrence of CDI with the latter being a key unmet medical need in the management of the disease. Ridinilazole has a highly targeted spectrum of activity designed to treat the offending pathogen while causing minimal collateral damage to the gut microbiota, thereby reducing rates of recurrent CDI as demonstrated in a Phase II clinical trial where ridinilazole was shown to be superior to the current standard of care, vancomycin, on producing sustained cures. Despite the clear unmet need and encouraging profile of ridinilazole, securing the required investment to develop the molecule through traditional investor channels proved challenging. However, Summit were able to capitalise on the 'push' funding mechanisms available for the development of novel antibacterials through two awards from the Wellcome Trust to support discovery and early clinical development and through a contract with BARDA of up to US$62 million to support Phase III development (Fig. I). These funding sources have been fundamental to the development of ridinilazole although the need to use such sources, and time required to secure them, has resulted in periods where the programme stalled, and several development years were lost. Without the funding and support of Wellcome Trust and BARDA and the complementary 'pull' of the USA GAIN Act and nomination as a qualified infectious disease product, this potentially important medicine would not have left the laboratory.

FIGURE I

The ridinidazole development pathway.

BOX 3

Funding organisations

Wellcome Trust

Wellcome, established in 1936, is a charitable organisation that supports scientific projects, from vaccine development to the training of healthcare workers in infection control in >70 countries (https://wellcome.ac.uk/about-us). In 2005, the Wellcome Trust introduced the Seeding Drug Discovery Initiative (SSDI), a programme aimed to facilitate the development of new drugs to address unmet medical needs by providing funding for projects in academic and private organisations. Drug-resistant microbes are a priority area for Wellcome and they are supporting the Global Antimicrobial Resistance Collaboration Hub – a programme announced in 2017 during the German Presidency of the G20 that will seek to coordinate global antimicrobial research and investment (https://wellcome.ac.uk/what-we-do/our-work/drug-resistant-infections).

CARB-X/BARDA

CARB-X provides early-stage Phase I funding for antibiotics, diagnostics and vaccines (https://carb-x.org). The Biomedical Advanced Research and Development Authority (BARDA), which operates under the governance of the US Department of Health and Human Services, supports clinical development programmes from Phase II onwards (https://www.phe.gov/about/barda/Pages/default.aspx). CARB-X funding scope includes small and large molecule therapeutics, diagnostics, vaccines and other prevention approaches, microbiome, phage and related technologies that address the most dangerous drug-resistant bacterial pathogens identified by the CDC and WHO. Funded projects are supported by a network of scientific and business support partners enabling small companies to access funding and expertise that would otherwise be unachievable.

GHIT

The Global Health Innovation Technology (GHIT) Fund has the vision of crushing the burden of WHO priority pathogens for billions of people in developing countries through facilitation of global R&D partnerships for the discovery and development of new health technologies, investment in these global R&D partnerships through a grant-making mechanism and advancement of Japan's contribution to global health (https://www.ghitfund.org).

REPAIR

The Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR) Impact Fund was established by Novo Holdings in February 2018 and is funded by Novo Holdings. US $165 million will provide investment for small companies in Europe and the USA (https://www.repair-impact-fund.com/people/). Potential programmes are reviewed by an international scientific selection board and priority is given to those targeting high-priority pathogens (as defined by the WHO and the US CDC) and first-in-class therapies (small molecules, biologics and new modalities) from early-stage drug development to early-stage clinical development (Phase I).

WHO and GARDP

WHO, in a joint initiative with the Drugs for Neglected Diseases initiative (DNDi), established the Global Antibiotic Research & Development Partnership (GARDP) in 2016 (https://www.gardp.org/). The aim of GARDP is to develop and deliver new treatments for drug-resistant bacterial infections. The GARDP model is to operate as a virtual R&D initiative with collaborative contributions from academic researchers, biotechnology and pharma companies as well as national governments and international organisations. GARDP has raised over €65 million towards its 7-year goal of €270 million.

IMI-ENABLE

The Innovative Medicines Initiative (IMI) European Gram-negative Antibacterial Engine (ENABLE) Programme provides funding for programmes working to advance the development of antibiotics against Gram-negative bacteria (https://www.imi.europa.eu/projects-results/project-factsheets/enable). The programme began in 2014 and is anticipated to end in 2020 and provides funding for programmes undertaken in academic and public research organisations and small and medium-sized private organisations.

AMR Centre

The AMR Centre was established in May 2016 and is a joint public–private initiative established to support and accelerate the development of new antibiotics and diagnostics (https://www.amrcentre.com/). Through a unique partnering model, the AMR Centre works with companies and research institutions around the world to support the development of their products. This approach enables companies and research institutions to access a fully integrated development capability, capable of providing support from translational R&D through preclinical evaluation and clinical proof-of-concept studies.

Bacteria Biopharmaceutical Accelerator (CARB-X; https://carb-x.org) which has emerged as a pioneering, non-dilutive, funding initiative that considers for-profit and not-for-profit organisations as applicants. It is complementary to its founder BARDA which provided US$455 million of funding together with the National Institute of Allergy and Infectious Diseases (NIAID), and Wellcome has provided further support. The CARB-X focus is on innovative hit and lead finding to Phase I clinical development, whereas BARDA will directly fund from Phase II onwards (Box 3). An added benefit for companies operating at the very early stages of the development pipeline is that access to non-dilutive public funding is allowing them to raise additional private funding. Currently, CARB-X is providing funding for >30 projects in seven countries around the world including eight new classes of antibiotics, ten antibiotics, ten new molecular targets and three rapid diagnostics (https://carb-x.org/). Another important source of funding for companies seeking to develop novel antibiotics is the Antimicrobial Resistance Centre (AMR Centre: http://www.amrcentre.com). The AMR Centre is a public–private initiative for providing funding, capacity and support for drug and diagnostic developers focused on WHO critical-priority pathogens, from preclinical research to clinical proof-of-concept. The AMR Centre provides preclinical and clinical development support from its own facilities as well as via public and private partner organisations across the UK, including access to the UK's National Health Service (NHS) clinical trial networks.

An example of a funding initiative aimed at the discovery of novel antibiotics is that announced by Innovate UK on behalf of the UK Department of Health in February 2018. The initiative will allocate up to £10 million of grants to UK organisations working with a Chinese partner, for projects within the antimicrobial resistance sphere that will benefit Chinese and less developed countries (https://www.gov.uk/government/news/improving-the-manufacture-of-new-medicines-apply-for-funding). The projects will focus on the evaluation of Chinese herbal medicine with the aim of discovering new agents (small molecules, vaccines, antibodies and other biologics) and to develop diagnostic tools to aid treatment selection and surveillance of antimicrobial resistance.

A variety of public and private funding initiatives are now available to support academic groups and private companies operating in the field of antibiotic discovery and development. These initiatives take several different forms from purely financial support, providing finance and infrastructure that would otherwise be unavailable to academic groups and smaller companies. The benefits of such initiatives are clear. Funding is targeted towards supporting the identification and development of new antibiotics and research groups can access skills and resources that would otherwise be unavailable to them. Key areas for intervention to support the discovery of new antibiotic interventions in four key areas that could dramatically improve the process of discovery for new antibiotics and their development to clinically viable medicines were identified at the symposium.

- Integration of discovery efforts and enabling resources is progressing through collaborative networks of academic, public and large and small private organisations to share expertise and avoid duplication [this has been particularly successful in other areas such as oncology and dementia with the International Cancer Genome Consortium (http://icgc.org) and Global Biomarker Standardisation Consortium (https://www.alz.org/research/for_researchers/partnerships/biomarker_consortium)]. However, these initiatives need greater visibility especially to help new entrants. In addition, the sustainability of many of these resources requires new funding models to ensure that collaborations between public and private organisations are initiated and maintained over time, rather than relying on short-term grant funding of the type used for projects.
- New approaches to early-stage hit and lead generation, including *in silico* and focused compound libraries, pathogen and tool-like organisms, to support identification of robust starting points for optimisation and mechanism of action studies.
- Availability of translation from hits to clinical trials – expanding capacity in preclinical development expertise.
- Continued improvement of regulatory approval and health technology assessment pathways and initiatives to ensure a robust market for approved antibiotics to incentivise investment and innovation by private organisations.

Integration across networks of organisations

The need for, and benefits of, greater collaboration and coordination of efforts has been a central feature of the progress by various organisations focused on meeting the challenge of drug-resistant infections. Initiatives such as CARB-X and Global Antibiotic Resistance and Development Partnership (GARDP), and funding from agencies such as Wellcome with a wide network of collaborators, are ideally placed to bring together the knowledge and innovative capabilities of the various sectors: academia, service providers, biotechnology companies and the pharmaceutical industry. Such collaborative efforts also need to include organisations operating surveillance programmes as well as those holding isolate collections and offering services for screening of potential new agents against reference and clinical isolates.

One notable effort to establish cooperative networks to facilitate drug discovery is the Community for Open Antimicrobial Drug Discovery (CO-ADD; http://www.co-add.org/). This not-for-profit initiative to enhance the identification of antibacterials and antifungals offers a screening service free to chemists worldwide by which submitted novel synthetic compounds are evaluated against a panel of key pathogens. Intellectual property rights are retained by the provider of the compound submitting the chemical entity with the agreement that all data are made public within 18 months to 2 years after initial results, this timing allows for patent filing for promising molecules. So far, >500 researchers have submitted >200 000 molecules for evaluation, with 70% of molecules being completely novel structures. However, the CO-ADD is anticipated to end in 2018 if additional funding is not identified.

Another important resource is the European Lead Factory (https://www.europeanleadfactory.eu/). This public–private partnership offers access to 500 000 novel compounds that can be screened for activity against potential biologic targets amenable to HTS assays and relevant for drug discovery. Informatics knowledge-sharing collaborations include Antibiotic DB hosted by British Society for Antimicrobial Chemotherapy (http://www.antibioticdb.com); inspired by Laura Piddock, it includes details of targets and agents that have been examined and not progressed by the larger pharmaceutical companies. At present there are >1000 agents within this database and the aim is to provide access to the antibiotic development community as a free service. The Pew Charitable Trust (http://www.pewtrusts.org) is establishing the Shared Platform for Antibiotic Research and Knowledge (SPARK, announced August 2017), which will bring together published and unpublished data relevant to Gram-negative entry and efflux to enable the exchange of data and ideas and to identify and design new antibiotics that can then be tested in the laboratory. SPARK is now publicly available on the Collaborative Drug Discovery (CDD) portal (https://www.collaborativedrug.com). GARDP has created REVIVE (https://revive.gardp.org) as a platform to capture and retain knowhow from the 'golden age' of antibiotic development.

Early-stage hit and lead generation

Historically, antibacterial discovery started with empirical phenotypic screening of chemicals and natural products to find agents that inhibited growth of bacteria. As the specific molecular targets of these initial agents were elucidated, more-rational approaches to screening for inhibitors of specific functions or biosynthetic pathways were undertaken; although this proved less fruitful, discoveries were made. With the advent of genomics, discovery efforts turned to finding inhibitors of specific gene products, generally with *in vitro* screens but also with whole-cell directed phenotypic screening. For the past 20 years, target-based discovery was the dominant approach, notwithstanding the rational and creative efforts, the poor success was one of the reasons pharmaceutical companies de-emphasized antibacterial discovery. One of the key learnings for target choice is greater emphasis of the propensity for arising resistance; for example, the inhibition of single enzyme targets is highly likely to lead to rapid resistance, whereas multiple targets or the products of multiple genes will be better than single targets for resistance avoidance.

The symposium considered early chemical hit identification and validation as the major rate-limiting step in the identification of new developable antibiotics. However, the preferred physiochemical properties of compounds for entry into and accumulation

in bacteria lacked a consensus at the symposium, the assertion these physicochemical requirements are different from those embodied in most Lipinski-type chemical collections [11] had confounders where Lipinski's and permeation chemical space were shown to be similar in certain cases [12,13]. Clearly, a greater understanding of compound properties for permeation and accumulation is necessary and will enable focused libraries to be designed and made available for screening.

Emerging high-performance computing and modern machine learning techniques synergize to support new artificial-intelligence-driven approaches with the potential to yield novel chemical scaffolds as *in silico* hits for subsequent testing (Box 4 provides an example of a research programme integrating computational approaches to antibiotic discovery). *In silico* approaches could be of particular value for either biological targets currently intractable to screening assays or, alternatively, well-known targets that have failed to yield effective new chemical entities. One such computational approach involves the mapping of the physicochemical properties of a compound against the properties of compounds with known antibiotic activity to identify key structure–activity features [14]. These features can then be used to identify or build new chemical libraries for a focused hit-generation programme.

Tool organisms, such as genetically engineered and indicator organisms for susceptibility and mechanism of action studies, tend to be laboratory *Escherichia coli* derivatives. The symposium identified the need to generate tool organisms in more-relevant and -diverse isolates, especially different types of bacterial pathogens such as *Staphylococcus sp., Haemophilus sp., Moraxella sp.,* and *Pseudomonas sp*. This lends itself to a community-wide approach to identify and create a repertoire of tool organisms to support drug discovery efforts and a need to improve the visibility and access to what is available. Combined approaches have been effective in other fields; for example, mouse geneticists have created the International Mouse Phenotyping Consortium with 20 000 knock-out lines (http://www.mousephenotype.org). Many valuable contemporary clinical collections exist and, although they are not freely accessible, they can be accessed through contract research agreements (e.g., BSAC, International Health Management Associates, Public Health England). Other collections have limitations owing to inadequate data collected alongside the isolates, poor availability of isolates to the wider community or collection bias. There is a need to create a central hub where information about isolate collections can be accessed. There is also a need to ensure that isolate collections span the genetic diversity within a given species.

BOX 4

The IBM 'science for social good' imperative

As part of IBM's commitment to science for social good, IBM-Research is seeking to blend cognitive computing concepts, including novel simulation strategies, to generate new insights and new discovery paradigms (http://research.ibm.com/healthcare-and-life-sciences/#research-areas). The initial focus is on peptide-based therapeutics aimed at overcoming the challenge of the bacterial membrane. Through simulation of molecular models of action, molecular drug discovery can be accelerated by identifying potentially useful molecules and excluding those unlikely to have any useful antibacterial activity.

Preclinical evaluation

Robust pharmacokinetic/pharmacodynamic (PK/PD) laboratories and expertise are essential to ensure the progress, or not, of potential new antibiotics from the discovery phase through to clinical evaluation in humans. PK/PD packages are key for regulators and these studies are important for the transition from *in vitro* profiling to first-in-human testing and determining a dosing regimen for later stages. Insight into the PK/PD profile of new antibiotics also contributes to understanding the potential for the development of antibiotic resistance and to design dosing regimens to minimize the emergence of resistance [15]. Relatively few PD laboratories focusing on antibiotics currently exist outside of the larger pharmaceutical companies and, in the UK at least, there is a shortage of investigators with the necessary pharmacological, clinical and quantitative expertise. It will therefore be crucial to steadily build this field as a viable career choice for science graduates.

Regulatory approval and health technology assessment

As new classes and modes of action emerge, such as drugs directed at antivirulence or host response targets, the clinical and health technology assessment tools might need to evolve. Fundamentally, the questions to be answered are always the same: what is the benefit and who benefits? But, novel products such as bacteriophages or virulence inhibitors might require innovative approaches to features such as clinical endpoints, assessment of payor value and assessment of broader societal value.

Substantial alignment between the EMA and FDA has been achieved and, along with this, the community has clearly defined examples of approaches for general development. In addition, modified pathways are increasingly well understood for situations when only limited clinical data are possible (e.g., development of a product focused on a single, less-common species). Of particular relevance is the need to standardise approval processes between countries and regions to encourage a global approach to antibiotic drug development. In this regard, the recent tripartite announcements by the EMA, FDA and the Pharmaceuticals and Medical Devices Agency (PMDA) are noteworthy and encouraging [16,17]. These three agencies recognised the need for flexibility regarding clinical development programmes for antibiotics and the appropriateness of conducting trials in smaller numbers of patients than would normally be required. They also recognised the value of developing clinical trial networks for the evaluation of new antibiotics.

Knowledge gaps and unmet needs

Getting compounds to the site of action

There are considerable gaps in our knowledge of how molecules cross the bacterial cell membrane and which compounds are effluxed back out again or reach the site of action, particularly with regard to the more-complex Gram-negative bacterial cell envelope [18,19]. Dependence on protein transporter molecules for access to the bacterial cell is associated with the development of resistance because genetic mutations alter crucial binding sites and preclude uptake of the antibacterial agent [20,21]. Consequently, there is a need to understand how other uptake mechanisms could be targeted to ensure access to the bacterial cell such as self-promoted uptake, 'Trojan horse' uptake and the use of membrane

'permeableisers' or potentiator adjunctive agents [22–25]. This research would benefit from new biophysical detection technologies and the creation and use of tool organisms in more-relevant and -diverse isolates, especially different types of bacterial pathogens, as mentioned previously.

Understanding and leveraging the host response

Research is underway to explore host responses to infection that could ultimately lead to ways to modulate such responses to overcome the pathogenic consequences of drug-resistant infections [26–28]. Such research could potentially reveal a paradigm change in antimicrobial therapy with increased understanding of the microbe–host interaction and the impact this has on drug efficacy and resistance. Indeed, it could be that new drug development should take account of patient physiology with efforts to explore how host immune or other biological processes might be optimised to fight infection.

Important lessons around the need to understand host responses to disease can be learned by looking at other therapeutic areas, particularly oncology. New chemotherapy drug development stalled in the 1990s and there was considerable concern that the fight against cancer would be lost [29]. This parallels with the concern that antimicrobial resistance could result in a global loss of control of the most serious bacterial infections. In the field of oncology, a refocusing of research efforts onto the patient and to the specific biology of cancer cells opened up the immunotherapy and targeted therapeutics fields. Looking beyond tradition in the field of antimicrobials can also be expected to open up new and effective opportunities for new drug discovery. For example, machine learning techniques were applied to identify diverse new inhibitors of double-stranded (ds)RNA-dependent protein kinase (protein kinase R) – a component of the host innate immune response that appears to support persistence of *Mycobacterium tuberculosis* within macrophages [30,31].

Genomic profiling of human pathogenic organisms

Genomic profiling of clinically relevant isolates will enable mapping of drug targets to species and phylogeny and the mapping of existing and emerging resistance mechanisms. This will improve the preclinical candidate selection process.

Utilization of novel models for preclinical and human evaluation

In vitro or *ex vivo* models of greater biological relevance allowing preclinical candidates to be evaluated in, for example, a polymicrobial competitive growth environment with different phylogeny or species has the potential to reduce risk of failure in the subsequent human study. Developing human challenge models analogous to those used in discovery of antivirals for certain bacterial infections could provide an early efficacy evaluation gate (after first-in-human safety) for a drug candidate and be a more reliable predictor for the risk of emerging drug resistance than conventional functional assays (Box 5). This approach should bring the benefit of avoiding elimination of drug candidates based on *in vitro* frequency of resistance, which has poor relevance to the human in which host response selection pressures will exploit the *in vivo* 'fitness' cost to the organism from evolving an often energy-consuming resistance mechanism. Studies can also be expanded to include treatment arms with standards of care and provide a comparative indicator of efficacy for the new candidate drug.

BOX 5

Potential for adaptation of human challenge models

The development of effective vaccines against the organism associated with typhoid, *Salmonella enterica* serovar Typhi (*S.* Typhi), illustrates the use of human vaccine challenge models as an early efficacy signal. The adaptation of such models to antibacterials will give developers a similar early signal and a more relevant assessment of the potential for arising resistance, and comparator arms can be added to the study.

As an example, for the evaluation of vaccine effectiveness, the Oxford Vaccine Group undertook a human infection evaluation of a candidate *Salmonella* vaccine in 112 healthy adult volunteers [35]. Participants were assigned to receive a Vi-conjugate vaccine, a Vi-polysaccharide vaccine or a control meningococcal vaccine. One month after vaccination they received *S.* Typhi orally and were followed for signs of typhoid infection defined as a persistent fever of 38 °C or higher for at least 12 h accompanied by *S.* Typhi bacteraemia. All participants received a course of antibiotics and those diagnosed with typhoid infection were followed up to ensure disease resolution. The proportion of participants diagnosed with typhoid infection was the primary endpoint and defined the efficacy rate for each vaccine. Using this human challenge model, it was possible to rapidly demonstrate the comparative efficacy of different typhoid vaccines and a control non-typhoid vaccination [36].

The human challenge model embodies unique difficulties in terms of regulatory approval because trials involve the deliberate exposure of human volunteers to infectious agents. Subjects are intentionally challenged with, in the example above, an infectious organism following vaccination against the target organism or a 'placebo vaccination' (vaccination against an organism other than the target organism). Later, all subjects then received standard-of-care treatment for the infection. An additional step could be the need to titrate the dose of the 'challenge organism' before testing the vaccine to characterise the symptoms, kinetics, shedding and transmissibility [35]. The benefit of such an approach is reduced reliance on testing in animal models, which is imprecise with regards to reflecting human disease and host response. Indeed, certain infectious organisms for which a vaccine or an antimicrobial agent might be required are species-specific for humans [35]. The human challenge model therefore has the potential to accelerate the evaluation of novel vaccines and antibiotics against suitable pathogens – not all human pathogens would be considered suitable for such an approach because they would be considered too virulent to warrant deliberate human exposure and others might have too long an incubation period before onset of disease or symptoms.

Development of biomarkers

The identification of biomarkers to evaluate the host response to antibiotic drug therapy is also likely to be a valuable area of research. As with oncology, novel diagnostics are likely to be an increasingly important component of new drug development and appropriate use. Such diagnostic tests would help to ensure that only patients who are most likely to benefit from therapy with a given antibiotic receive treatment – an approach that would ensure personalised medicine and the limitation of unnecessary treatment thought to be a key driver of the rise in drug

resistance in recent decades. However, diagnostic testing in the context of antibiotic prescribing represents a behavioural challenge for health professionals because the diagnostic test might be more expensive than empirical treatment with a generic antibiotic. Furthermore, for adaptation in the clinic, such diagnostics must be affordable, extremely rapid and provide information as to drug resistance as well as to species. Biomarkers could also support clinical decision making by rapidly identifying patients not responding to a given antibiotic so that their treatment can be changed without the need to wait for clinical worsening of their condition as a trigger. These latter two approaches, diagnostic tests and biomarkers of response, will be essential to enable the more precise and appropriate use of antibiotics moving forward; a key element of the guidance outlined in the 2016 O'Neill report on tackling antimicrobial resistance [32].

Access to clinical isolates

Access to clinical isolates and biobank strain collections as well as 'indicator' tool strains is challenging and can be time-consuming and costly. This represents a significant challenge to the development of new antibiotics for small or academic enterprises and can delay progress significantly. Biobanks need to be reliably funded, visible, available, have clear terms of access and have the capacity to supply testing facilities or isolate sharing in a timely manner. New and rapid screening techniques are needed to facilitate evaluation of new hits against clinically relevant isolates. These could include *inter alia* HTS assays for more-complex, multitarget pathways, advanced fluorescent probes, improved *in silico* computational drug discovery and 'single-cell' technologies to address variability within bacterial populations.

Collaborative efforts and a global community approach

As discussed above, a number of initiatives and organisations have been established in the past 2–3 years that will facilitate and encourage collaboration and the formation of virtual R&D networks. Multiple educational activities are also underway with, for example, basic training for developers being offered via workshops and symposia, such as those co-sponsored by CARB-X and GARDP or programmes operated by BSAC. Efforts are also underway to coordinate a global community approach to antibiotic discovery. Such an approach would provide researchers and private organisations with a central repository of global data and a directory of global resources. The idea of a pipeline coordination activity was proposed as one of four recommended incentives by the recently concluded DRIVE-AB project [33]. However, there are still gaps in coordination and communication about activities and resources across the whole of the antibiotic development pathway. The establishment of clinical trial networks, such as those established in the field of oncology, might be helpful to coordinate clinical evaluation of antibiotics regionally and to support the clinical trials that could be beyond the scope or capabilities of the smaller biotechnology companies.

Concluding remarks and future perspectives

Global initiatives, especially those providing funding from public and private sources, appear to be rejuvenating antibiotic discovery for established entities and attracting new entrants in the form of academics, not-for-profit organisations and small companies. Entrants, new and old, will benefit from greater international coordination to avoid duplication and costly avoidable failures. To this end, informational or material resources that enable or support the primary drug discovery efforts need greater visibility, coordination and simpler access to physical materials such as clinical isolates. Funding mechanisms need to recognise the medium-to-long-term value of enabling resources that are not best sustained by short-term grant funding of the type used for projects. This symposium recognised the progress being made but identified areas for intervention such as hit-to-lead generation, development of more-relevant preclinical models, PK/PD career development and continued improvement in clinical trial and heath technology assessment. There are priority knowledge gaps to be addressed, such as compound properties for access to and accumulation at the site of action, understanding how to leverage the host response and the need to create a diverse and relevant collection of tool pathogens instead of the over-reliance on laboratory *E. coli*. There are unmet opportunities to use human challenge models, greater use of genomic profiling and identification of host infection biomarkers for patient stratification. We believe adoption of these recommendations will greatly enhance the antibiotic discovery process and increase probability of success.

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