PIRU POLICY INNOVATION RESEARCH UNIT

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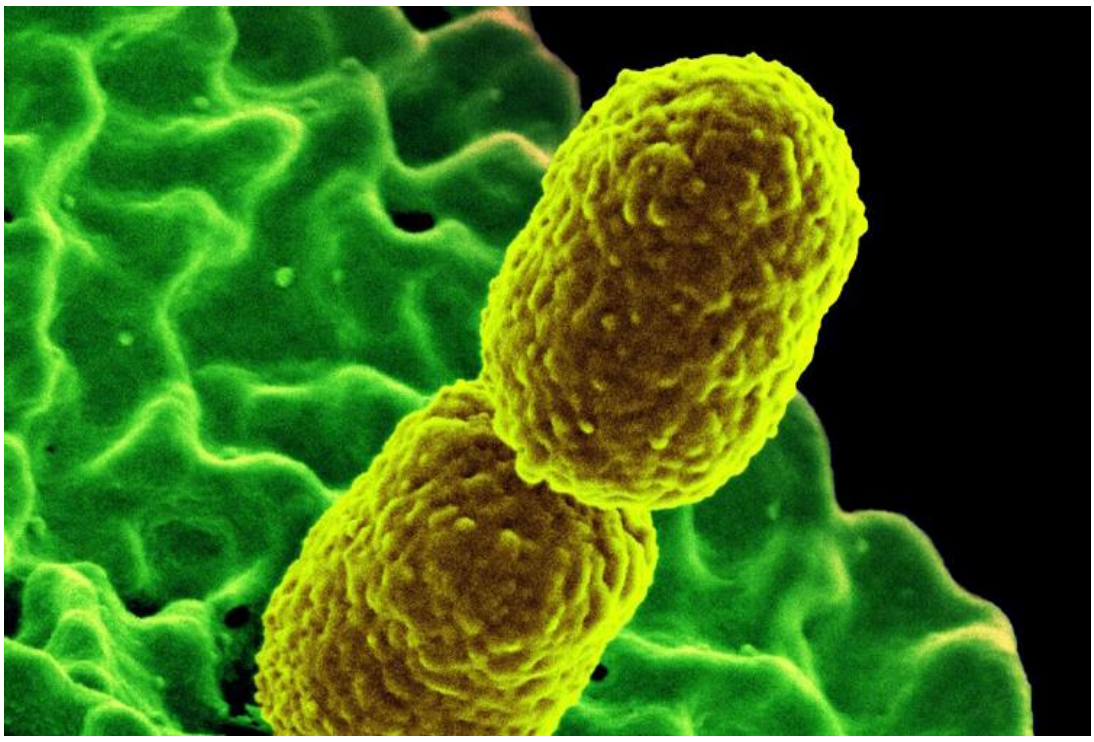

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EXECUTIVE SUMMARY

The UK Five Year Anti-Microbial Resistance Strategy, 2013-2018 was released by the Department of Health (now Department of Health and Social Care, DHSC), with the Department for Environment Food and Rural Affairs (Defra) and Public Health England (PHE), in September 2013. We reviewed progress on the actions in the Strategy requested of the pharmaceutical industry, including the scale and scope of activity underway, the role of various forms of incentives to encourage pharmaceutical innovation, and the scientific, regulatory and commercial challenges experienced by industry and funders. We explored the way government efforts within and beyond the Strategy to address commercial viability issues have been viewed by industry, gaps in the approach taken by the Strategy, and opportunities for government to help improve the contribution of biopharma to AMR reduction.

Informants recognised the efforts of the Government in responding to the challenges of developing new drugs to tackle AMR, especially the O'Neill Report, development and implementation of the Strategy, the framework of working groups, provision of new research funding, and associated actions around antibiotic stewardship and infection prevention.

The availability of 'push funding' (direct support for research) has grown, particularly in the form of multinational public-private partnerships to stimulate research and development for new antibiotics and novel therapies. This type of support was considered more beneficial for small and medium sized companies working on the discovery and pre-clinical stages of drug development than for large pharmaceutical companies. While smaller companies benefit from push incentives, their impact on drug development was seen as limited unless large pharmaceutical companies, which have the capacity and resources to bring products to market, step in and acquire promising new therapies. Industry informants therefore felt that while push incentives were welcome, additional policy approaches were required to overcome the wider business pressures that have driven industry away from investing in developing new antibiotics. Interviewees focused largely on the potential to use 'pull incentives' (e.g. forms of market entry reward, 'transferable market exclusivity' or extended patents) to address market failure in the availability of antibiotics. They were especially concerned that Government and industry address remaining technical issues (e.g. the approach to health technology assessment) and implement the proposed trial of a model that de-links the volume of sales of selected new antibiotics from payment. There was little or no interest from informants in a 'pay or play' model, recommended in the O'Neill Report, and transferable market exclusivity was seen as more feasible in a US rather than UK context.

There was concern from industry and research informants to improve the availability of 'forgotten' antibiotics but repurposing or repositioning of existing drugs for AMR use was not a strategic priority for any of the larger pharmaceutical companies interviewed. Informants highlighted the potential role of drug recombination or combination therapy, which they felt were not being explored due to commercial and legal issues related to IP rights.

All informants felt that there had been a decline in political attention paid to AMR in the UK since the referendum on UK withdrawal from the EU (so-called "Brexit") and that the UK's international leadership in combating AMR had slipped.

BACKGROUND

There are a number of interrelated challenges to the use of pharmaceuticals to tackle anti-microbial resistance (AMR)[1] and enable greater diversity in prescribing and treatment options. The slow pace of discovery and development of antibiotics and other antimicrobials[2], a low rate return on investment, and regulatory costs and uncertainties all inhibit a sustainable pipeline of drugs. There has not been a new class of antibiotics in over twenty-five years (WHO, 2017) and most drugs currently in the pipeline are only short-term solutions because they are modifications of existing classes of antibiotics (Årdal et al., 2018; Pew Charitable Trusts, 2019a). The Antimicrobial Resistance Benchmark 2018 report found that of 28 antibiotics in late stages of development, only two have developed plans designed to ensure they would be accessible and used prudently (AMF, 2018).

New antibiotic discovery and development is not commercially attractive for the pharmaceutical industry since antibiotics are drugs whose use is actively limited and discouraged, and their net present value is significantly below that of other therapeutic categories (Sharma and Towse, 2011; Sertkaya et al., 2014; Di Masi et al., 2004; O'Neill 2016). In recent years there has been an exodus of large pharmaceutical companies from antibiotics' R&D, resulting in a loss of skills and experience as scientists and technical experts are allocated to other areas of research. Development and use of vaccines could help to reduce dependence on antibiotics. However, this might exacerbate commercial challenges in antibiotic development by suppressing the predictable demand for antibiotics (Wellcome Trust and BCG, 2018), and drug companies also face challenges in establishing a commercial case for investment in vaccines (Plotkin et al., 2017; Davis et al., 2011).

The lack of commercial viability presents particular challenges in finding the optimum mix of industry and government action to address the failure of traditional models of drug development (WHO, 2015; Cecchini et al., 2015). Market failure in the development of new antibiotics has been the subject of intense policy attention internationally for many years. The European Commission's Communication to the European Parliament (European Commission (2011) on rising threats from AMR called for 'unprecedented collaborative research and development efforts to bring new antibiotics to patients', leading to the launch of the Innovative Medicines Initiative's (IMI) 'New

[1] It should also be noted that globally there will be bigger gains in the fight against AMR from measures to improve sanitation and access to clean water, and ensure there are well governed and funded health systems (Collignon et al., 2018).

[2] Antimicrobials are all chemicals and drugs that can kill microorganisms (bacteria, fungi, parasites and viruses), while antibiotics are a subset of antimicrobials that kill or inhibit the growth of bacteria.

Drugs for Bad Bugs' programme in May 2012. At the supranational level, there are now several funding and coordinating initiatives in the EU and elsewhere. The need for a wide-ranging approach was recognised by the pharmaceutical industry in 2016, with the release of a joint plan by 13 companies to take action in four areas, including stewardship, improved diagnostics and collaborative R&D (IFPMA, 2016; AMR Industry Alliance, 2016, 2017, 2018). The G20 summits in 2016 and 2017 generated commitments from member governments to examine practical market incentives to encourage industry to develop new antimicrobials and maintain the global supply of existing drugs.

As well as challenges in the development of new drugs due to a lack of commercial viability, there are problems with manufacturing and supply of existing antibiotics. These arise from a combination of supply side issues, including bottlenecks in capacity to increase production at short notice, and low profit margins which prevent investment in manufacturing capacity.

In 2014, the United Kingdom (UK) House of Commons Science and Technology Committee inquiry into AMR, and the Government's response to its recommendations (House of Commons, 2014), reiterated the need for action on R&D and bringing new antimicrobials to the market. Also, in 2014, Government commissioned an independent review of the global AMR challenge and response, chaired by Lord O'Neill (O'Neill, 2016). The review made ten recommendations, many dovetailing with those of the then national AMR Strategy 2013-18 (DHSC, 2013), and the Government subsequently set out five new ambitions. These include working to develop a global system that rewards the successful development and distribution of new antibiotics (DHSC, 2016).

Key Areas 4 and 6 of the UK AMR Strategy 2013-18 and Interventions 6 and 9 of the O'Neill Report discuss how to stimulate the pipelines for drugs to tackle AMR. There are three main ways in which this can occur:

- development of new therapeutics (e.g. a new class of antibiotics and treatments such as bacteriophages or lysins);
- reviving 'forgotten' antibiotics; and
- seeking new AMR-related uses for other drugs through 'repurposing' (i.e. expanding an existing drug's original indications), identifying a new indication for an existing drug that is already known and in use (i.e. 'repositioning'), and developing new formulations for a drug (i.e. 'reformulation') (Langedijk et al., 2012; Brunel and Guery, 2017).

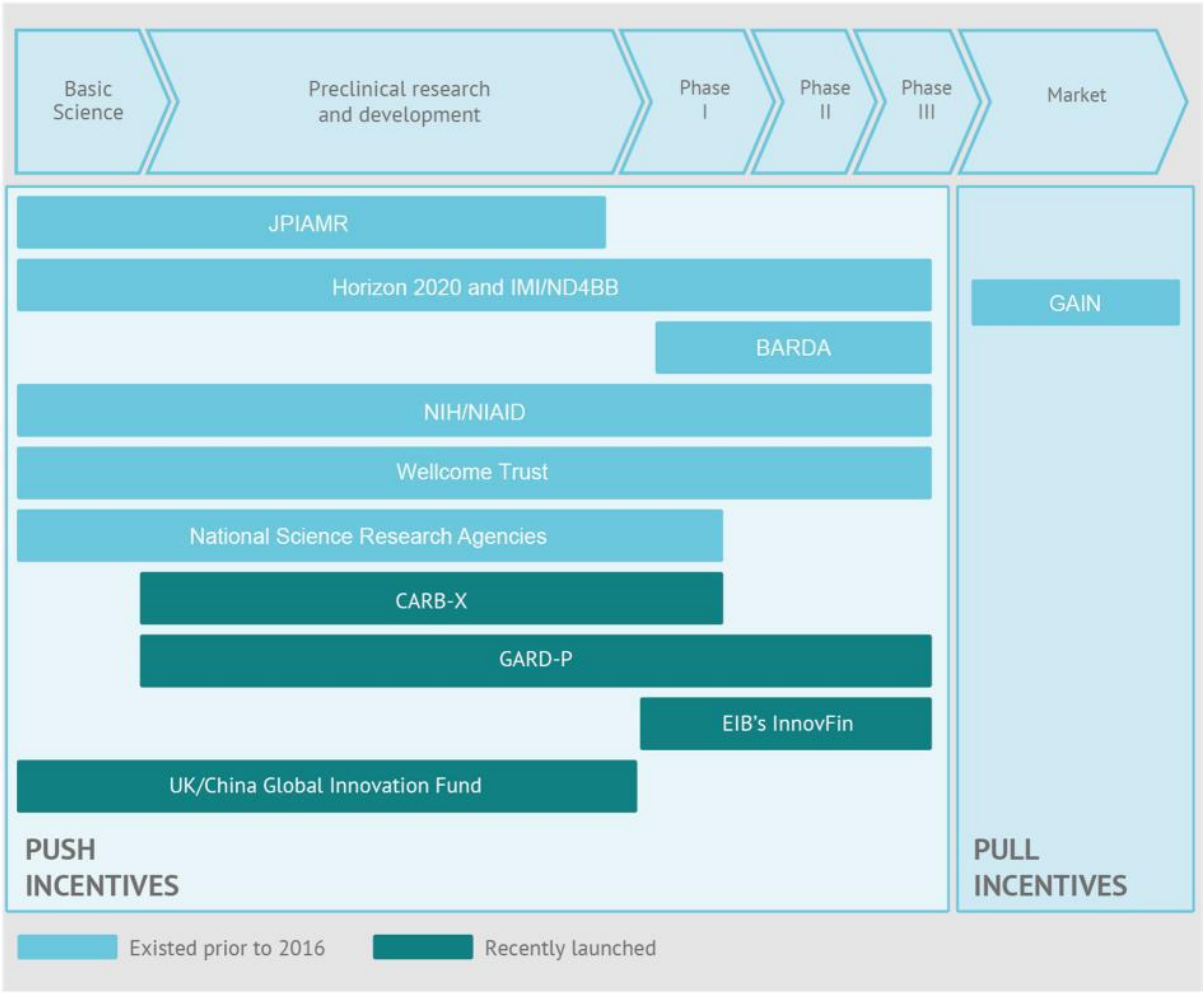
This report presents an overview of the actions taken in response to the calls for action in the Strategy and the O'Neill Report to ameliorate market failure in the development and provision of drugs to tackle AMR, based on research conducted during the period January-October 2018 (see appendix for details).

The next section discusses the range of options put forward for stimulating the pipeline for drug-based solutions. We then discuss the actions carried out by the UK Government under its AMR Strategy to tackle challenges in the drugs pipeline. The final section reports on the views of our interviewees and workshop participants on these actions and the Strategy's implementation, at the time of the research.

OPTIONS FOR STIMULATING THE DRUG DEVELOPMENT PIPELINE

A range of options for stimulating the pipeline for drug-based solutions to the AMR challenge has been put forward. These can either target the development of drugs through financial support for R&D and facilitation of new partnerships between research organizations and drug companies ('push' support), or they can seek to improve the 'pull' of new drugs through the pipeline by putting in place pricing and purchasing models that are designed to reward successful outcomes from R&D, thereby improving the likelihood of successful commercialisation. Figure 1 illustrates the global range of push and pull funding initiatives, discussed below, that are available at different stages of the drug development pipeline. The figure highlights the concentration of push funding available, prior to Phase 1b of drug development, when large pharmaceutical firms tend to become more closely involved in the development pipeline.

Figure 1. Supporting the drug development pipeline



‘Push support’

Push funding, such as grants awarded to universities, institutes and small companies for basic and early-applied research, is important for supporting R&D costs but it does not improve the attractiveness of the overall market for antibiotics and other antimicrobials, or vaccines.

A range of new partnerships and funding schemes has emerged in the recent years to foster greater R&D. Table 1 provides a summary of the landscape of major funders of push support and pledged funding. Notable efforts include the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Global Antibiotic Research & Development Partnership (GARDP), the UK / China Global Antimicrobial Resistance Research Innovation Fund (GAMRIF), and the Innovative Medicines Initiative’s ‘New Drugs for Bad Bugs’ (ND4BB) programme, which includes the European Gram Negative AntiBacterial Engine (ENABLE). In the US, the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA) are the largest public funders of antibiotic research and development. BARDA does not fund basic science and focuses on the development of medical countermeasures to antibiotic resistance.

There are also several supranational efforts which provide funding and coordination of research activities, such as the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) and the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR). In 2018, the German government followed up its commitment at the 2017 G20 meeting to establish the Global AMR Research and Development Hub. This promotes alignment of current public and private funding on AMR by bringing together governments and foundations from across the world, agreeing global R&D priorities, and leveraging investment for AMR R&D initiatives.

The Organisation for Economic Co-operation and Development (OECD) has estimated that US$537 million (€452 million) has been invested, including the funds drawn down from multinational granting bodies such as CARB-X and GARDP (OECD, 2017). It is unclear whether this is the full figure as there is a reported lack of transparency in national figures (Årdal et al., 2018).

Table 1. A summary of the major push incentives available for AMR development

Name	Date established	Funders	Aims	Funds available
Global Health Innovative Technology Fund (GHIT)	2012	Government of Japan (Ministry of Foreign Affairs and Ministry of Health, Labour and Welfare), 16 pharmaceutical and diagnostics companies (Astellas, Chugai, Eisai, Daiichi Sankyo, Fujifilm, GlaxoSmithKline, Johnson & Johnson, Kyowa Hakko Kirin, Merck Group, Mitsubishi Tanabe, Nipro, Otsuka, Shionogi, Sumitomo Dainippon, Sysmex and Takeda), the Bill & Melinda Gates Foundation, the Wellcome Trust and United Nations Development Programme	To "facilitate international partnerships that bring Japanese innovation, investment, and leadership to the global fight against infectious diseases and poverty in the developing world." GHIT (2018)	Over US$300 million
New Drugs for Bad Bugs (ND4BB)	2013	The European Union's Innovative Medicines Initiative	A partnership between industry, academia and biotech organisations to combat antimicrobial resistance in Europe through solutions to the scientific, regulatory, and business challenges that hamper drug development.	€650 million
CARB-X	2016	US Department of Health and Human Services (HHS), the Biomedical Advanced Research and Development Authority (BARDA), and the National Institutes of Health (NIH), the Wellcome Trust, the UK Government's Department of Health and Social Care through the Global Antimicrobial Resistance Innovation Fund (GAMRIF) and the Bill & Melinda Gates Foundation	To fund research and development of new antibiotics, vaccines, rapid diagnostics and other products targeted at drug-resistant bacteria (CARB-X, 2016)	US$500 million to be dispersed by 2021

Global Antibiotic Research and Development Partnership (GARDP)	2016	Bill & Melinda Gates Foundation, German Federal Ministry of Health, Leo Model Foundation, Luxembourg Development Cooperation and Humanitarian Aid, Luxembourg Ministry of Health, Médecins Sans Frontières, Netherlands Ministry of Health, Welfare and Sport, South African Medical Research Council, Swiss Federal Office of Public Health, UK Department of Health and Social Care, UK Department for International Development, Wellcome Trust	Partnership between the Drugs for Neglected Diseases initiative and the WHO to fund antibiotic research and development	US$52 million

‘Pull support’

Various financial and other models for incentivising R&D by improving the commercial environment for adoption of drugs have been put forward. This is because private-sector investment is based on anticipated future monetary returns and while push funding addresses R&D costs, it does not improve the attractiveness of the market for the resulting product. Research therefore suggests that the effectiveness of push funding is limited and urges a stronger focus on pull incentives related to antibiotics and antimicrobials (Ferraro et al., 2017; Simpkin et al., 2017; Rex et al., 2016). DRIVE-AB has evaluated 15 different types of pull incentive, concluding that forms of market entry rewards to stimulate innovation are promising, albeit challenging to develop. This view is echoed by others including the UK Government’s independent review (O’Neill, 2016), Chatham House (Clift et al., 2015), Boston Consulting Group (BCG, 2017) and Duke-Margolis Center for Health Policy (Gregory et al., 2017). Striking the right balance between push and pull incentives may also be politically difficult. Governments can more readily divert funds into R&D than develop complex schemes that provide financial and other forms of support to the drug industry in the form of pricing or purchasing guarantees. Nevertheless, a range of potential solutions has been put forward, which are discussed below.

Market entry rewards

Market entry rewards comprise financial payments to antibiotic developers which successfully achieve regulatory approval for an antibiotic that meets specific criteria, accompanied by obligations for sustainable use, and equitable access and supply. The main goal of the reward is to encourage greater R&D risk-taking.

There are many ways to design a market entry reward, depending on (1) the payment schedule (whether it is a single lump-sum or staged payments over time), (2) the degree of ‘de-linkage’ of the reward from the volume of antibiotic sales (to ensure careful stewardship of the new antibiotic), and (3) ownership of intellectual property (whether the payer or another designated entity acquires the developer’s intellectual property (IP) in exchange for the market entry reward.

Several models have been proposed that aim to delink volume from payment, or provide insurance to ensure the availability of new antibiotics (Årdal et al., 2018; Towse and Sharma, 2011). Rewards can be ‘fully’ or ‘partially’ delinked. In a fully delinked market entry reward scheme, all developer

revenues come from payments over the lifetime of the IP and the drug is supplied at a price set to ensure it is not cheaper than existing antibiotics, to avoid overprescribing the newer drugs.

In a partially delinked model, revenues derive from the reward payments and unit sales, with the price negotiated between the developer and the payer, accompanied by conditions on sustainable use and equitable access. This has the benefit of lowering the payer's upfront financial commitment and risk, while preserving the developer's existing business model. There is also the flexibility to adjust the model according to sales of the antibiotic by including a cap on revenues if sales exceed a level in a given year, by reducing the following year's reward.

'Pay or play'

'Pay or play' – an antibiotic investment charge – was suggested in the O'Neill report (O'Neill, 2016) as a way of giving drug companies the option of either paying the charge or demonstrating that they are investing the equivalent amount or more into R&D relevant to AMR. The charge would be imposed widely on the pharmaceutical sector and paid into a designated fund which would be used to improve the commercial market for successful new drugs, vaccines or diagnostics. The report argued that such a model would encourage more companies, especially those dependent on effective antibiotics to sustain oncology and other clinical areas, to invest in R&D.

A 'pay or play' model is politically appealing because pharmaceutical industry profits from other therapeutic areas are diverted into antibiotic R&D, but it has been argued that additional costs would simply be passed on to payers through the price of other drugs. Another concern is that industry is incentivized to invest in R&D up to the required threshold but not necessarily to bring new, high value antibiotics to market (Årdal et al., 2018). The O'Neill report argued that work on the design and viability of 'pay or play' models, and how they could be combined with market entry and other rewards, should be carried out.

Transferable market exclusivity

The use of 'transferable market exclusivity' (also known as transferable exclusivity extensions, or transferable regulatory exclusivity) has been explored as a way of granting a pharmaceutical company the legal right to extend the monopoly period of any of its patented drugs, in exchange for the regulatory approval of a specified antibiotic. This right would take the form of an exclusivity voucher that could be used or sold to another company. The exclusivity extension could be coupled

to access and appropriate use requirements and could be conferred through a regulatory mechanism, a data exclusivity extension or a patent exclusivity extension.

There are a number of pros and cons to transferable market exclusivity models. The approach does not require upfront or continuing public expenditure because the drug company's revenue comes from extending reimbursement for a product to which the extension is transferred. Depending on the duration of exclusivity offered, there could be a predictable and sustainable source of revenue to incentivise R&D (Årdal et al., 2018; IFPMA, 2018). However, there are concerns that these models will always be more expensive than paying directly for an incentive since the developer's profit margin needs to be covered, unless mechanisms are included to limit the term of any transferable exclusivity, and independently assess its value and impact a fixed time after implementation.

In the US, the Generating Antibiotic Incentives Now (GAIN) scheme, introduced in 2012, extends the regulatory exclusivity of new antibiotics for five years, but this is generally felt to be insufficient to stimulate the degree of innovation required because the exclusivity runs concurrent to any existing patent life and does little to improve the business case for investment (Spellberg et al., 2012). Another concern is that the threshold for inclusion on the scheme – in terms of qualifying new drug or target disease - was set too low (Outterson et al., 2015; Outterson and McDonnell. 2016).

THE UK GOVERNMENT'S RESPONSE TO CALLS FOR ACTION, 2013-18

Successive UK governments have been highly visible in drawing attention to the challenges of addressing market failure in the development of new antibiotics through the UK AMR Strategy (DHSC, 2013) and O'Neill Report (O'Neill, 2016). A framework of working groups, strategic partnerships and coalitions between government, industry, academia and philanthropic foundations has emerged to address the challenges and the Strategy's recommendations. This activity addresses antibiotic stewardship, infection prevention and new commercial models for antibiotics, such as trialling a form of delinked reimbursement for selected new antibiotics.

Global leadership

Because the UK alone is too small a market to stimulate the development of new drugs and products targeted at AMR, it has engaged in globally coordinated activities with a wide range of international bodies (Staerk and Knai, 2019). There have been efforts to align UK-funded research with national

and international research programmes, and influence research strategies on AMR-related issues through bodies such as the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), the WHO's Inter-Agency Coordination Group on Antimicrobial Resistance (IACG), and the Global AMR Research and Development Hub. The UK plays a leadership role through board membership or by co-convening several of these initiatives. The UK also co-funded the Antimicrobial Resistance Benchmark, with the Netherlands Ministry of Health, Welfare and Sport, to track the progress in developing new antibiotics (AMF, 2018).

The G20 summit in 2017 made a commitment to explore practical market incentive options and the UK has sought to ensure this remains a priority. Both the Global AMR Research and Development Hub and the IACG have a mandate to consider the use of 'pull' incentives, and the UK is playing a leading role in investigating how it is possible to change the way antimicrobials are purchased (see below).

UK Government working groups

The Department of Health and Social Care (DHSC) high-level joint government-industry AMR working group comprises industry representatives and government bodies (including NHS England, Public Health England, and the National Institute for Health and Care Excellence, NICE). The working group was established partly in response to the recommendations from the House of Commons Science and Technology Committee to include more voices from industry in policy making (House of Commons, 2018). The group's work has focused on the potential implications of alternative funding arrangements for NICE appraisals of new antibiotics. The working group commissioned the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) to develop a framework for the value assessment of new antimicrobials (Rothery et al., 2018).

The reimbursement and evaluation subgroup of the joint government-industry AMR working group was formed in 2015 and oversees two strands of work: appropriate use of antibiotics by the pharmaceutical industry; and new therapeutics. The five industry representatives in this group are part of the Association of the British Pharmaceutical Industry (ABPI) network group: Glaxo-Smith Kline (GSK), MSD (known as Merck in the US), Janssen (known as Johnson & Johnson outside the UK), Shionogi and Pfizer. Its work has focused on the development of a new reimbursement model for new antibiotics that does not link volume of sales to payment.

Push support – funding for R&D

The UK has invested significant sums of public funding in research and development on AMR. This has been coordinated through the Antimicrobial Resistance Funders' Forum (AMRFF), which shares information on AMR research by the various member organisations. This brings together the UK's Research Councils, Health Departments and other Government bodies, as well as charities and other funders with an interest in AMR. A number of the organizations comprising AMRFF support research on novel therapies, new targets and translational proof of concept studies. Several interdisciplinary funds have been made available through the Global AMR Innovation Fund (GAMRIF), which includes research to support innovation in drugs and related product development. Innovate UK's Small Business Research Initiative (SBRI) is funding research on a range of antimicrobials, other new therapies, and use of machine learning and artificial intelligence (AI) to identify new drugs and new drug targets. There are also significant bilateral funding schemes, such as the UK Research and Innovation/Newton Fund collaborative programme with the National Natural Science Foundation of China.

Pull support – new reimbursement model

At the time of this research, there had been substantial efforts by pharmaceutical companies, industry representative bodies, the UK Government and healthcare bodies to develop and pilot a delinked payment model for new antibiotics. This emerged as the key theme in our interviews and workshop with industry and technical experts (see appendix for details). The primary concern was to test a payment model and develop a valuation approach that reimburses value rather than volume (OHE, 2017).

"… the UK is potentially a very, very neat crucible to undertake the … trials or to implement some sort of thing because obviously the NHS being such a unitary purchaser of antibiotics, it gives you a very neat testbed. But I think actually the problems that you face in progressing … that sort of thing, they're fairly universal problems in health systems across the world."

Research funder

The broad principles of the model were developed and agreed by the joint government-industry AMR working group and endorsed by all members of the ABPI network group. Initially, five new antibiotics designed to address the priority resistant pathogens were proposed for use in a trial of the reimbursement model. Subsequently, it was agreed that two candidate antibiotics would initially be selected. The proposed approach involves the NHS being given access to a new antibiotic which targets a priority resistant pathogen for a defined period, with the developer receiving a payment based on the value of the drug, even it is reserved and not used. Each antibiotic will have an appropriate use and stewardship plan, with built-in data collection and monitoring. Agreement to trial this model was reached in June 2018. The project board comprises the Department of Health and Social Care, NHS England, National Institute for Health and Care Excellence (NICE) and Public Health England.

At the time of this research, discussions were continuing over the details of the trial. These have now been finalised. A valuation framework using an adapted health technology assessment model is being developed by NICE, designed to forecast the value of the health benefits provided by a new antimicrobial which will be used to inform payments to the developer. It is unlikely that a single 'one size fits all' model is feasible, and the framework may need to be tailored to the specific conditions of a candidate drug. A commercial model to agree payment levels for candidate antimicrobials is being developed through negotiations between NHS England, NHS Improvement and drug companies. It is expected that evaluation of the initial two products will be conducted during 2020.

FINDINGS FROM INTERVIEWS AND WORKSHOP

From stakeholder interviews and a workshop convened for this research, we found that the pharmaceutical sector informants believed that the activities of the UK Government had been instrumental in facilitating greater collaboration and engagement between stakeholders and in ensuring that there was a high level of commitment to tackling the challenges of AMR. Some informants judged that there still needed to be more effort to engage the UK biopharma sector with policymakers. There was, however, concern from all informants that there had been a decline in the political attention paid to AMR since the referendum on the UK withdrawal from the EU (so-called "Brexit").

The consensus amongst all informants at the time of this research was that the role of push incentives for large companies was marginal in supporting the scale and scope of research needed to

address the challenges of the underlying science of new antibiotic development. The incentives provided by push funding were not large enough to overcome the wider business pressures driving exits of large pharmaceutical firms from antibiotic development. While there have been substantial improvements in the availability of financial support for increased R&D, industry and research funding informants felt that push incentives have limited success without substantial changes on the demand side through pull incentives, and the overall emphasis of government should be on the latter.

Government leadership

> *"… the UK is certainly more than carrying its weight, not only for the country itself, but the role that it's playing as an international participant in this global problem, so keep doing this with the international focus. I think that is very, very, very important. And, you know, having it lapse down to a national only prioritisation would be a disaster. So, it's very good now. [It] can't go backwards into a national perspective."*
>
> *Research funder*

Informants from all sectors felt that the O'Neill report had been crucial in raising the profile of AMR as a global and domestic policy issue, and in facilitating a higher level of collaboration and engagement between key stakeholders from industry, research support and funding, and Government. These actions were attributed to the Coalition (2010-2015) and Conservative (2015-2016) Governments led by the former Prime Minister, David Cameron. While there was unanimous support for the UK Government's leading role in the global policy arena following the 2014 G7 meeting, informants from industry and research funders also said that the UK Government's leadership role in combating AMR at both the national and international level had slipped, a view noted by the House of Commons Health and Social Care Select Committee (House of Commons, 2018). At the time of this research, there was hope it would be renewed though the future development and implementation of the Strategy. The decline in political attention paid to AMR was said to have largely occurred since the referendum on the UK withdrawal from the EU in June 2016, although the work of the Chief Medical Officer, Dame Sally Davies, was praised for maintaining attention and resources on AMR and keeping the issue high on the national risk register. While collaborations with the Department of Health and Social Care, NHS England, and NICE were described as still proceeding well, informants from industry and research funders believed that

renewed attention was needed from the Secretary of State for Health and Social Care and other senior political figures at the national level.

> *"We are aligned on wanting to tackle the AMR challenge, but the organisations who have it within their gift to give, to make it happen now are the NHS who ultimately will be the payers for the products that come through the pipeline, and the Department of Health … who need to be visible and vocal about the political will to see this change happen."*
>
> *Large pharmaceutical company*

Working groups

Informants from industry were supportive of the role of the Government working groups in engaging industry in the policy making process. The biotech sector's interests are represented by the UK Bio-industry Association (BIA) but informants from this sector said they were not involved in any Government working groups and were vocal about the need to include small and medium sized enterprises (SMEs) in the future (cf. Bionow, 2018). Greater engagement with this sector was felt to be especially beneficial to the UK because its R&D activity is largely based domestically, unlike that of large pharmaceutical companies whose antibiotics research programmes occur in other countries.

> *"…there's no big pharma antibiotic R&D going on the ground in the UK. The only people trying to address this are SMEs… [W]e desperately need a mechanism in place to be able to represent the voice of SMEs in some of the decision making, in particular, the development of the next five-year AMR Strategy."*
>
> *Research funder*

Push funding

There was strong support among informants from both small biotech and large pharmaceutical companies that government should play a leading role in supporting R&D to identify potential new antibiotics, vaccines or antimicrobials. However, there were mixed views on the degree to which push incentives could ameliorate the commercial viability issues associated with bringing new products to market. At the time of this research, it was felt that push incentives for R&D and partnerships with CARB-X, the IMI and GARDP had been useful. Informants identified CARB-X as one

of the more important funding sources. The programme was seen as particularly helpful due to the range of technical and commercial assistance available alongside funding. BARDA received praise for providing financial support through Phase 3 of the product development pipeline.

Push funding was regarded by informants as unimportant for larger pharmaceutical companies since they do not invest in early stage research in the AMR field. The general view was that push funding is more beneficial to small and medium sized biotech companies working on the discovery and pre-clinical stages of drug development; it was suggested that some of these companies may only continue to operate due to the presence of research grants. Such support was regarded as important for SMEs because they are often stalled at key points in the product development pipeline and would benefit from assistance with the following:

- Assistance is needed to support basic science and engage with university research teams in discovery, preclinical and Phase 1a stages. This helps to generate data necessary to bid for funding from CARB-X or similar.

- Obstacles at Phases 1b and 2 are due to resource limitations (financial and technical skills). Small and medium companies need to partner with larger companies with the capacity, infrastructure and resources to fund human trials, but this has become increasingly hard as large pharmaceutical firms have exited the antibiotics market because the commercial potential and return on investment are significantly lower than for drugs targeted at chronic conditions.

- For companies that are successful in attracting funds from BARDA to conduct Phase 2 and 3 trials, there is a funding gap in bringing a product to market. More targeted push funding (and pull incentives) could help to support the health technology assessment and marketing required to launch a new drug.

Most informants from the biotech sector expected that their products would be acquired by large pharmaceutical companies for further development, but the exodus of these companies from antibiotics' R&D meant there were fewer opportunities for this to happen. This trend is accompanied by a loss of technical skills and experience within the larger pharmaceutical companies, as scientists and technical experts are allocated to other areas of research, and specialist knowledge and skills are not transferred to antibiotics development programmes in other pharmaceutical companies. However, it was recognised that there had been efforts to fill the gap in skills through the UK's AMR

Centre, founded in 2016. This uses a public-private partnering model to provide companies and research institutes with technical support and specialist expertise.

The consensus amongst all informants was that the contribution of push incentives alone is insufficient to counter the business pressures which has led to the withdrawal of large pharmaceutical firms from antibiotic development. Push incentives are only likely to be helpful if there exist biotech or specialist pharmaceutical companies with antibiotics R&D programmes and large pharmaceutical companies willing to take-up promising new drugs emanating from these players for further development. While early stage push funding for R&D helps generate potential products for antibiotic development programmes, it is insufficient to rely on push incentives as a lever for tackling the shortage of new antibiotics. Moreover, this detracts from the need for pull incentives to address challenges of market failure and commercial non-viability.

"Push funding on its own is not going to solve [market failure] because … companies are looking for ways to simplify their R&D operations. To focus on push funding alone doesn't give a financial return. It helps keep you there but doesn't give a financial return."

Technical expert - public sector

"… as the world exists today, it's unlikely that most of the successful CARB-X projects have a home to go to because that overall environment is weak. So, the fact is, we've moved forward on the assumption that more will be done across the entirety of this ecosystem, so that we can have strong private sector participation to carry forward the development to get the products approved."

Research funder

" [push incentives] are very important but they're just not enough …, it's sort of a diversion for governments to think that putting defined pots of money aside is going to solve the problem."

Technical expert - public sector

"The challenge for many companies is they complete their phase three trials. They go to the FDA or EMA, they get approval for the drug. They've then got to launch and market the drug. That's the big gap that they have. That's not a small amount of money. You're looking at $200 to 300 million investment required to get the drug launched and start marketing it, and put the sales force in place."

Small biotech company

Product development partnerships

The UK AMR Strategy 2013-18 recommended that pharmaceutical, biopharma and diagnostics' manufacturers and trade associations should stimulate the development of new products by developing a European product development partnership scheme for antimicrobial drugs (DHSC, 2013).

We found little interest among industry informants in ways of increasing collaboration through risk-sharing agreements with governments and funders. Informants were unable to describe any tangible actions taken in response to the proposals for a European product development partnership scheme. Informants from the biopharma sector said there were obstacles to accessing EU funding because it tended to be awarded to multi-partner and multi-country consortia which tend to be led by large pharmaceutical companies. One funder said SMEs were wary of joining such consortia for EU funding due to concerns about IP and ownership of future commercial rights to any products developed.

Pull incentives

Transferable market exclusivity and patent extensions

Transferable market exclusivity was not regarded by informants as viable for companies operating in the UK. This is because of the Pharmaceutical Price Regulation Scheme (PPRS), a voluntary agreement between the DHSC and the pharmaceutical industry, to control the prices of branded drugs sold to the NHS (DHSC, 2017). One informant warned that there was a risk of new antibiotics being available in the US market, where transferable market exclusivity was felt to be more viable, but not in the UK.

Informants from biotech and pharmaceutical sectors discussed the potential benefits of extended exclusivity. Extending the patent term was felt to be of limited benefit because new antibiotics are not intended to reach high volumes of sales since they are drugs of last resort. Most industry informants said that the current policy focus in the UK should remain on developing a delinked reimbursement model.

> *"… in effect … you give them a piece of paper they can sell which allows someone else with a best-selling drug to hang on to their patent for another year, or two years, or whatever is appropriate. And that, in a sense, falls on the health budget but it doesn't require a minister to write a new cheque, it's just already in the system [but] there's a lot of pushback, particularly in Europe, but also in the US as*

well, against that sort of policy but it does seem to me it's, that one's worth thinking about."

Technical expert

"In Europe, in the UK in particular, I think [Transferable market exclusivity] is a nonstarter … Companies love it because it means that they can create a … a significant revenue stream for themselves but it's completely transparent. But it shifts costs into another area of the health service, which makes it a nonstarter in the Europe and in the UK, but means it does have some attraction in the US … That said, I think in the US politically the tide has turned a bit. I think the idea of pushing the cost of antibiotic development onto other areas of patented pharmaceuticals has some attraction, but the wider political push [in the US] is around saying let's bring prescription drug prices down … So our reading is that it doesn't have much political mileage even in the US now."

Research funder

"… in terms of the level of stimulus it provides, it's a fairly inefficient tool … on a menu of preferred options it's a long way down in terms of an objective assessment of is this is a good policy tool?"

Research funder

Pricing and reimbursement approaches for new or forgotten antibiotics

Industry informants were clear in emphasising that the current landscape for new antimicrobials is limited by the lack of commercial viability and that financial incentives are necessary to sustain R&D work in this field. Informants from large pharmaceutical companies tended to steer the conversation back to the delinked payment model as the most promising and politically feasible market entry reward.

Non-industry informants suggested that this might reflect a concern on the part of large pharmaceutical companies that their existing products might become less profitable if antibiotic resistance rises, and routine surgery and oncology treatments become too risky. However, one industry informant felt that the time horizon over which this might appear was beyond that of shareholders and companies were more concerned with the immediate problems of commercial viability of antibiotic development and production.

Industry interviewees all emphasised the importance of developing appropriate pull incentives, such as a payment model that delinks revenues from volumes used, in order to safeguard new antibiotics from overuse while ensuring a commercial rate of return on companies' investments. A delinked

payment model was seen as a more viable approach for the UK than transferable patents or market entry rewards. Market entry rewards, such as advanced market commitments, were dismissed as a good idea that was likely to be very hard to implement due to short political time horizons of elected governments and public concerns over the use of public funds to subsidise the pharmaceutical industry.

"… in a sense [we are] saying to finance ministers around the world, well, all you have to do is find the 40 billion or whatever was the number that O'Neill came up with … I think the bit that's missing is the value part … the real issue for … a health economist or for a finance minister or a health minister or certainly for their advisors is … I'm not going to … eliminate all of the disease, … how much of that problem do I solve by spending this money?"

Technical expert

"… the numbers [for market entry rewards cited in the O'Neill report] were massaged downwards between the interim report and the final report … I don't think it's a big deal, although obviously … people who scrutinised those numbers the most will be industry, so it sends the wrong signals to industry about how serious, you know, the report is. But … I'm sure that policy people in the industry recognise that … you have to start off with a realistic proposition, a potentially sellable proposition … If the G7 finance ministers had been interested in market-entry rewards, I'm sure a lot more work would have been commissioned on exactly how much they needed to be and how many drugs needed to be in there."

Technical expert

Delinked reimbursement model

At the time of this research, though there was considerable support for a delinked reimbursement model, informants highlighted two significant challenges facing the development and introduction of any such model. Valuing a new antibiotic was regarded as challenging methodologically because of the difficulties in predicting the development of resistance to antibiotics. While the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) provides a good understanding of resistance trends for some pathogens, the ranges of uncertainty were felt to be wider for others, meaning that caveats regarding uncertainty (Rothery et al., 2018) would have to be incorporated into a fixed term payment agreement. Nevertheless, informants recognised that NICE had the ability to be flexible when faced with new technologies that are not amenable to

conventional methods for health technology appraisal (e.g. in the case of orphan drugs and cystic fibrosis treatments), and the view was that valuation challenges were not insurmountable.

"Inevitably the biggest sticking point is what's the right price to pay. O'Neill talked about a range of 0.8 to 1.3 billion, and everyone's kind of centred in on the idea that a billion dollars seems about right, but it's very difficult to produce an evidence base to say objectively that that is the right amount. Obviously, industry would like to start from a value-based approach and say the value of an antibiotic to society is X and therefore we should be paid X. Whereas I think governments and others want to more take the approach of, and this is the approach that the O'Neill modelling took, albeit in a rudimentary way, is to take cost plus approach of trying to work out what does it take to bring an antibiotic to market and then adding a little bit for a reasonable return on investment … So trying to bridge that gap and trying to find a way through that is tricky. We take the view that you do need to look at techniques for valuation of antibiotics that does embody some sort of element of the societal value."

Technical expert

The second challenge highlighted by informants related to the level of payment for new antimicrobials – that is, whether it would be possible to identify a persuasive pull incentive which would also be affordable to the NHS or the Government. There were concerns about the practicality of building in safeguards ex ante within an agreement so that the Government is not committed over an extended period of time to paying for what might later prove to be an ineffective product. Any review period would need to be sufficiently long to encourage the pharmaceutical industry to invest in R&D, and for data collection to begin to indicate the impact of the antimicrobial, but not so long that it would expose the Government or the NHS to undue financial risk. Informants suggested that these considerations could be balanced by adjusting the price according to the reimbursement period.

Appropriate stewardship was seen as an important aspect of the success of any delinked reimbursement model, but concerns were expressed about how the use of new antibiotics could be accurately monitored because it was felt that existing mechanisms for doing this in the NHS were not sufficiently robust.

"if the volume is delinked from the price, or the reward, can there be a place to make sure the use is only limited to the appropriate use? … [G]etting payment is ideally important, but it only makes sense if it's coupled with the stewardship mechanism to ensure use will be only limited for the appropriate patients."

Large pharmaceutical company

"… one of the first principles we need to be adopting is that this isn't about the immediate extant demand, it's about saying that okay, we would value having a product to treat a particular pathogen of concern and we will pay for that and provide an income stream for the person that has taken a risk to develop it and to bring it to market, regardless of whether it goes into 5 patients a year or 5,000 patients a year. It's the value of having it there because we will value it in the future as much as we will value it today."

Research funder

Another risk highlighted by informants was that, in addition to a delinked reimbursement model, industry might later call for additional pull incentives such as market exclusivity and patent extensions, in the long run potentially increasing costs to the Government and payers, and exacerbating imbalances in power between the Government and industry.

Despite concerns over the challenges of a delinking approach to antibiotic reimbursement, informants were optimistic that if a successful UK model could be established, this could provide a template for similar schemes in other countries, especially where there was a similar central pharmaceutical decision maker. Informants agreed that the successful pilot of a new reimbursement scheme would help to further demonstrate that the UK was still providing leadership in the global AMR policy arena, but there would need to be global agreement around the type of model adopted and extent of support to avoid 'free rider' problems if the approach were ever to be adopted across the globe.

"… the questions [are] around how you integrate a country-level approach into a global picture without free rider problems. That's a problem that governments around the world are going to grapple with. The way that I would characterise the global picture … is of having some sort of global layer, some sort of possibility of not necessarily global but certainly supranational action to support antibiotic development, whether that's in the US or in European markets or either G7 or G20 … [but] regardless of whether you end up with some sort of supranational stimulus … the question of how you implement novel reimbursement systems at

a health system level, whether that be in a unitary system like the NHS, or in more fragmented systems where you have individual insurers or centres or CMS in the US [is] how do you implement some sort of delinked system …?"

Research funder

"[I]t's a political challenge as much as the ethical one … [T]here's a real opportunity for the UK to lead here because you have high level political commitment to AMR, real awareness of this issue in the parliament, … a single payer system which simplifies in many ways the payment flows and … it could work relative to countries like the US. I think you have really high-level engagement from [company] and large companies in the UK, so I think there are a lot of facilitating factors, so we're hopeful that … [the] UK can move forward with some kind of incentive and that we can then use that in other markets around the world."

Large pharmaceutical company

Using pull incentives for old antibiotics

The O'Neill report highlighted some potential low cost, high impact measures, notably the rejuvenation of 'forgotten' antibiotics. For example, there has been a revival in the use of two old antibiotics: colistin and fosfomycine, that has helped to slow the rate of further resistance to last-resort antibiotics (Brunel and Guery, 2017).

While the narrative about AMR is heavily focused on R&D and removing barriers to market entry, we also found concern to improve the availability of older antibiotics. Informants from industry and research funders said that market failures in the manufacturing and distribution of existing antibiotics had narrowed the pool of available drugs and discouraged diversity in prescribing, potentially accelerating rates of antibiotic resistance. Limited diversity in prescribing was attributed to existing protocols and formularies that are overly focused on a few drugs, especially in primary care. Industry informants said only six to twelve out of 100 possible antibiotics are used regularly at scale.

Informants suggested that the WHO could take a leading role in establishing a list of ten to fifteen 'forgotten antibiotics' that are not currently used in high volumes, in parallel to its essential medicines list, or national governments could work together to ensure the availability of these antibiotics by forging contracts with suppliers in low- to middle-income countries to maintain manufacturing capacity and ensure availability of underused antibiotics. However, informants felt

that the feasibility of such a model was unclear due to the small number of underused antibiotics that could potentially be mobilised for future use.

We also found concerns over manufacturing and supply. These result from the interplay between a lack of diversity in prescribing practices and supply-side constraints. These constraints are due to companies withdrawing low profit margin antibiotics when manufacturing plants require significant investment, and manufacturing capacity bottlenecks arising when there is a need to increase production of an alternative antibiotic when resistance emerges. Informants indicated that incentives to tackle manufacturing and supply problems had been insufficiently discussed compared to the attention placed on incentivising R&D. Possible solutions included national governments forging contracts with suppliers to maintain existing manufacturing capacity, demand-aggregation for less used drugs, and support for new production capacity that could be hired when there is a need to produce small-batch antibiotics.

Regulation

The UK AMR Strategy 2013-18 called for actions to make clinical trials as effective as possible and support companies through the regulatory procedure, as well as fast-track priority review arrangements for new antimicrobials. Interviewees were concerned that while the UK is very strong at the basic science, it does not play a major role in large-scale trials of new drugs and that departure from the European Medicines Agency after the UK leaves the EU would further reduce the UK's attractiveness as a market for testing drugs. Nevertheless, informants did not raise any concerns over the regulatory process for new products or the role of the Medicines and Healthcare Products Regulatory Agency (MHRA) – the focus of issues discussed in the interviews and workshop exclusively related to pricing and market access.

Innovation trends

Repurposing, reformulation and repositioning existing drugs

Reviving forgotten antibiotics and seeking new AMR-related uses for other drugs through repurposing, repositioning and reformulation were all recommended by the O'Neill report as ways of reinvigorating the pipeline for new antimicrobials. However, there was little indication by informants that the industry was responding to this call.

Repurposing was not seen as strategic and informants were sceptical that there would be many instances of repurposing relevant to AMR. The strategy was therefore dismissed as a limited solution, and one which should not divert attention from the development of new antibiotics. One problem identified with repurposed drugs is their commercial viability (Brown, 2015; AMRC, 2017). New indications for existing drugs tend to be off-patent, so they are likely to be produced by generic drug companies, rather than the company that conducted and funded the original R&D. Some informants suggested that repurposing could be an area of focus for GARDP as it is a not-for-profit research initiative and not subject to the same profit-seeking constraints as the pharmaceutical industry.

In contrast to repurposing, informants were eager to emphasise the importance of drug recombination, or the use of combination therapy as an R&D strategy. They felt that this was not being explored due to commercial and legal issues related to intellectual property rights. It was suggested that if the UK were to introduce multiple indication pricing, where a different price is set for each indication that a drug is approved for (a method used in Italy), then this might stimulate interest from the pharmaceutical industry to pursue repurposing or recombination therapies (Mestre-Ferrandiz et al., 2015).

"The examples where [repurposing] has been proven to be useful, and I'm not talking about commercially successful useful, are very, very rare. You can count on one hand. So, this idea that [with] just a little bit of effort … you're going to get a plethora of things that are needed to address the paucity of the pipeline is unrealistic. It's not to say that when the opportunity presents itself, it shouldn't be pursued, … but to make that a primary focus would be entirely misleading and foolish."

Research funder

"Our strategy is to look for novel products and this is where our focus is … [T]his particular product that we have in phase 3, really it's an existing antibiotic with a novel ß-lactamase inhibitor which basically restores susceptibility of resistant bacteria to this antibiotic. So I think that could be classified as repurposing ..."

Large pharmaceutical company

Other areas for innovation

In June 2019, the Pew Charitable Trusts (2019b) estimated that 29 new non-traditional AMR-related products were in clinical development – vaccines, antibodies, lysins, probiotics and peptide immunomodulators. There has also been research on promising approaches that minimize the emergence and impact of resistance to antibiotics by the use of an 'antibiotic adjuvant' in combination with an antibiotic (Concepción, 2017).

Vaccines

Areas for vaccine development identified by informants included new pneumococcal vaccines, vaccines for high-risk groups used before surgery in place of prophylactic antibiotics and vaccines to address tropical infectious diseases. However, informants emphasised the lack of commercial viability of new vaccines because they are unlikely to be widely distributed, aside from those targeting 'flu or pneumococcal infection prevention. However, it was suggested that there might be a 'tipping point' in the future when resistance to antibiotics rises to the extent that a large proportion of the population could benefit from new vaccines.

Informants from all sectors agreed that the problems of commercial viability could be addressed by a combination of push and pull incentives (Wellcome Trust and BCG, 2018). For the pharmaceutical industry to invest in low volume vaccines, there would need to be clear signals that governments are willing to pursue reimbursement schemes that take the value of the vaccine into account. Vaccine development could benefit from increased funding for the initial R&D costs, and where there is the potential for mass vaccination programmes (e.g. for pneumococcal disease), for governments to agree to bulk purchasing agreements such as that relating to Tamiflu. Informants from industry and research funders expressed a view that the use of existing 'flu vaccines should be expanded more of the UK population than those currently targeted by existing NHS campaigns.

"We are a very significant vaccine company. I think there is a lot of opportunity there and actually it's a relatively low hanging fruit. But really, it's about using more widely the vaccines that we have today, and that's about reducing infections, both bacterial and non-bacterial, but those that are often treated with antibiotics, including the flu vaccine … The pneumococcal vaccine of course is the other absolute no brainer."

Large pharma

"In terms of future vaccine development, there is definitely potential there as well and a number of companies are actively working on that. It seems to me again, there are various of roles for government to say we really want these vaccines and we will make it, again, financially attractive for companies that come up with them."

Large pharma

Antitoxins

Informants were asked whether the development and use of antitoxins was an active area of research, but this was largely dismissed. It was felt that R&D on antitoxins might detract from a focus on developing new antibiotics, which should be considered as the main priority. Informants suggested that the development of antitoxins could be considered alongside other alternative approaches to tackle infections, such as probiotics, lysins or bacteriophages, although there were challenges relating to the intellectual property related to their use (House of Commons, 2014) and there remain concerns about safety and specificity (Lin et al., 2017).

Medical devices and diagnostics

It was not in the scope of this research to investigate innovations in diagnostic tests but we asked informants from the pharmaceutical industry whether they were involved in the development of such tests. Informants emphasised the importance of developing rapid diagnostic tests to combat AMR because of their role in identifying appropriate drugs for particular pathogens. They believed that although rapid diagnostic tests could improve the prescribing of appropriate antibiotics, this would not contribute to solving commercial viability issues for the development of new drugs, especially since better targeted prescribing is likely to drive down overall drug volumes (Årdal et al., 2018).

CONCLUSIONS

At the time of the research, we found that the pharmaceutical and biotech sectors were concerned to play a part in implementing the UK AMR Strategy 2013-18, but there was frustration over the pace at which practical actions were proceeding and a perception that the UK Government had grown less engaged since the referendum on withdrawal of the UK from the EU. Industry informants were highly

focused on the need for pull incentives to address the problems of commercial viability, both in relation to antibiotics and vaccines. Push incentives were seen as helpful for SMEs, but informants noted that the real attention had to be on market entry support, in whatever form. The UK was seen as a potentially valuable testbed for trialling different models, but informants were under no illusion that it would be easy to replicate a successful trial in other health systems. Global engagement and leadership to reach agreement on the best methods was seen as essential.

The UK regulatory review arrangements for new drugs were not seen as a significant hindrance on drug development, but there were concerns over the impact of UK withdrawal from the EU on the attractiveness of conducting drug trials in the UK. The principal concern at the time of this research was to implement the 'delinked' pilot project.

APPENDIX - RESEARCH APPROACH

The research questions for this study were:

- How has industry responded to and implemented the actions asked of it in the Strategy?
- Which aspects of the Strategy, its processes and the wider environment have constrained or facilitated the development of new or repurposing of old drugs?
    - How have Government efforts within and beyond the Strategy to address commercial viability issues been viewed by industry?
    - What is the potential impact of changing the regulatory review arrangements for new drugs on the development of novel agents?
    - How important is the development of new partnerships and coalitions (including with academics and new international partnerships) to the development of new drugs?
    - Are there gaps in the approach taken by the Strategy and are there new opportunities for the Government to help improve the contribution of the pharmaceutical industry to AMR reduction?

The research involved a review of published material on AMR, focusing on issues related to the drugs pipeline, semi-structured qualitative interviews with informants (n=19) from the pharmaceutical and biotechnology sectors, representatives from public and private research funders, industry representative bodies (UK, EU and international associations), and arm's length bodies of DHSC and research community. Initial interviewees were identified through the Association of the British Pharmaceutical Industry (ABPI), and subsequent interviewees were identified using the 'snowball' method.

Informants

Informant type	N=	Attended stakeholder validation workshop
Large pharmaceutical companies	6	4
Biotech SMEs	3	0
Industry representative bodies	3	3
Funders	4	1
Arm's length bodies of DHSC or research community	3	1

Interviews were transcribed and data were analysed using NVivo 11. Interview data were analysed thematically. The researchers designed an initial coding framework. First level coding was based on themes from the evaluation's research questions, interview topic guide and the key issues drawn from the literature on AMR. The research team discussed initial themes before agreeing main themes and sub-themes for further analysis in this report.

The emerging findings were presented at a stakeholder workshop for feedback and validation. The workshop provided several important insights from a stakeholder perspective that the research team drew upon in identifying the key findings and policy recommendations in this report.

Ethical approval to undertake the study was granted by the research ethics committee of the London School of Hygiene and Tropical Medicine (Ref 14396).

Strengths and limitations

While efforts were made to draw on a diversity of informants, a limitation of this study is that the research reports findings from a pool of informants with an active interest in combating antimicrobial resistance. Informants were drawn from actors involved in active R&D, steering groups and networks with an interest in AMR in the UK and in transatlantic partnerships. It was not possible to speak with any staff from the IFPMA or EFPIA because they declined to participate in this research. However, we did capture international perspectives as many industry informants were also responsible for overseeing their organisations' work in Europe, the Middle East, Asia or the Americas. Some also had involvement with IFPMA and EFPIA. Further work should include representatives from these international or EU bodies for their perspectives on the UK's role and influence in combating AMR in the context of Brexit.

Interview and workshop topic guide

About the (national) AMR strategy and your role

1. Can you give me an overview of your role and how you are involved in the response to the National AMR Strategy?
    - Time involved?
2. What other bodies do you work in partnership with?
    - What steering groups or committees are you involved with?
    - What other industry bodies?
    - Are there other pharmaceutical firms with an interest in this?
    - How strong are the links between these bodies?
    - Are there any incentives to develop further partnerships?

Pricing and market access

3. What are the current challenges for the biopharma industry in developing or bringing new AMR products to the market?
4. Can you describe the main issues related to pricing/market entry for new products?
5. What models for reimbursement have been developed?
    - How has uptake of new products been modelled?
    - How can these models be improved?
    - Will these models be tested?
6. What issues might arise in the potential implementation or rollout of a new reimbursement model for new or repurposed AMR products?
7. How can these issues be mitigated?
8. What, if anything, would you change about the way this reimbursement model was developed?

Development of new products

9. What is the current state of development for new AMR products?
    - At what phase in development are these products?
    - Which therapeutic areas will these products be targeted at?
    - Role of vaccines?
10. What partnerships or funding sources have been important for the development of new products?
11. What efforts are being made to repurpose existing products?
    - What indications?
    - Where repurposing has occurred, where did it happen in the life cycle?
    - Which companies or organisations are repurposing existing products?
12. Can you describe any efforts to develop new diagnostic tools?
    - Any incentives to develop new rapid point-of care tests?
13. Can you describe any other actions to facilitate appropriate use?
    - Education/training or smaller pack sizes

Regulatory concerns

14. Describe the regulatory review processes for potential new products?
15. Are these regulatory review arrangements suited for the development of new products?
    - Novel agents?
16. How and in what ways can these regulatory review arrangements be improved?

Key suggestions and closing questions

17. If you could share 2-3 key suggestions from your work for those working on the next stage of the national AMR strategy, what would these lessons be?
18. If you could change one thing about the direction of the current national AMR strategy, what would it be?
19. Is there anything else you would like to comment on that we have not discussed today?

REFERENCES

AMF (2018) *Antimicrobial Resistance Benchmark 2018*. Access to Medicine Foundation.

AMR Industry Alliance (2016) *Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance, Davos Declaration*.

AMR Industry Alliance (2017) *Statement. Global call for action on drug-resistant infections*, 12-13 October 2017, Berlin.

AMR Industry Alliance (2018) *Tracking Progress To Address AMR*.

AMRC (2017) *Facilitating adoption of off-patent, repurposed medicines into NHS clinical practice*. Association of Medical Research Charities.

Årdal, C. et al. (2018) *Revitalizing the antibiotic pipeline. Stimulating innovation while driving sustainable use and global access*. DRIVE-AB.

BCG (2017) *Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development*. Boston Consulting Group.

Bionow (2018) *New Drugs for Anti-Microbial Resistance: Maximising the AMR Opportunity for the UK*. The AMR Centre.

Brown, D. (2015). Antibiotic resistance breakers: can repurposed drugs fill the antibiotic discovery void? *Nature Reviews. Drug Discovery*, 14, 821.

Brunel, A-S and Guery, B. (2017) Multidrug resistant (or antimicrobial-resistant) pathogens - alternatives to new antibiotics? *Swiss Med Wkly*. 147, w14553.

CARB-X (2016) *About CARB-X*.

Cecchini, M., Langer, J., Slawomirski, L. (2015) *Antimicrobial Resistance in G7 Countries and Beyond. Economic Issues, Policies and Options for Action*. OECD.

Clift, C., Gopinathan, U., Morel, C., Outterson, K., Røttingen, J-A., So, A. (2015) *Towards a New Global Business Model for Antibiotics*. London: The Royal Institute of International Affairs.

Collignon, P., Beggs, J., Walsh, T., Gandra, S., Laxminarayan, R. (2018) Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *The Lancet. Planetary Health*

Concepción, G-B. (2017) Antibiotic adjuvants – A strategy to unlock bacterial resistance to antibiotics. Bioorganic & Medicinal Chemistry Letters, 27 (18), 4221-4228.

Davis, M. M. et al. (2011) Failure-to-success ratios, transition probabilities and phase lengths for prophylactic vaccines versus other pharmaceuticals in the development pipeline. *Vaccine,* 29, 9414-9416.

DHSC (2013) *UK Five Year Antimicrobial Resistance Strategy 2013 to 2018.* Department of Health and Social Care & Department for Environment and Rural Affairs.

DHSC (2014) Government response to the House of Commons Science and Technology Committee report Ensuring access to working antimicrobials. Department of Health. Cmd. 8919.

DHSC (2016) *Government response to the review on antimicrobial resistance*. Department of Health and Social Care

DHSC (2017) *Pharmaceutical Price Regulation Scheme (PPRS) 2014. Payment percentage for 2018.* Department of Health and Social Care.

Di Masi, J. et al. (2004) R&D costs and returns by therapeutic category. *Drug Informatics Journal*, 38, 211-223.

European Commission (2011) Communication to the European Parliament and Council. COM (2011) 748.

Ferraro, J., Towse, A., Mestre-Ferrandiz, J. (2017) *Incentives for New Drugs to Tackle Anti-Microbial Resistance*. Office of Health Economics.

GHIT (2018) *GHIT: vision and mission*. *2018.*

Daniel, G., Schneider, M., McClellan, M. (2017) Addressing Antimicrobial Resistance and Stewardship. The Priority Antimicrobial Value and Entry (PAVE) Award. *JAMA*, 318(12), 1103-1104.

House of Commons (2014) *First Report. Ensuring access to working antimicrobials, and Government response*. Science and Technology Committee.

House of Commons (2018) *Antimicrobial resistance. Eleventh Report of Session 2017-19.* Health and Social Care Committee. HC962.

IFPMA (2018) *Policy Position. The need for AMR R&D pull incentives*. International Federation of Pharmaceutical Manufacturers & Associations.

IFPMA (2016) *Industry Roadmap for Progress on Combating Antimicrobial Resistance.* International Federation of Pharmaceutical Manufacturers & Associations.

Langedijk, J. et al. (2015) Drug repositioning and repurposing: terminology and definitions in literature. *Drug Discovery Today*, 20(8), 1027-1034.

Lin, D., Koskella, B., Lin, H. (2017) Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World Journal of Gastrointestinal Pharmacology and Therapeutics*, 8(3), 162-173.

Mestre-Ferrandiz, J., et al. (2015) *Multi-indication pricing: pros, cons and applicability to the UK*. in *Seminar Briefings*. Office of Health Economics.

OECD (2017) *Tackling antimicrobial resistance ensuring sustainable R&D*.

OHE (2017) *Valuing new antibiotics in the context of AMR: challenges and action*. Office of Health Economics.

O'Neill, J. (2016) *Tackling drug-resistant infections globally: Final report and recommendations*. HM Government and Welcome Trust.

Outterson, K., Powers, J., Daniel, G., McClellan, M. (2015) Repairing the broken market for antibiotic innovation. *Health Affairs*, 34(2), 277–85.

Outterson, K., McDonnell, A. (2016) Funding antibiotic innovation with vouchers: recommendations on how to strengthen a flawed incentive policy. *Health Affairs*, 35 (5), 784–790.

Pew Charitable Trusts (2019a) *Antibiotics Currently in Global Clinical Development*.

Pew Charitable Trusts (2019b) *Nontraditional Products for Bacterial Infections in Clinical Development*.

Plotkin, S., Robinson, J., Cunningham, G., Iqbal, R., Larsen, S. (2017) The complexity and cost of vaccine manufacturing. An overview. *Vaccine* 35**,** 4064– 4071.

Rex, J., Outterson, K. (2016) Antibiotic reimbursement in a model delinked from sales: a benchmark based worldwide approach. *The Lancet Infectious Diseases*, 16(4), 500-505.

Rothery, C., et al. (2018) *Framework for value assessment of new antimicrobials: Implications of alternative funding arrangements for NICE appraisal*. Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU).

Sertkaya, A. et al. (2014), Analytical framework for examining the value of anti-bacterial products. DHHS, Washington.

Sharma, P., Towse, A. (2011) *New drugs to tackle antimicrobial resistance*. Office of Health Economics.

Simpkin, V. et al. (2017) Incentivising innovation in antibiotic drug discovery and development: Progress, challenges and next steps. *The Journal of Antibiotics*, 70(12), 1087.

Spellberg, B., Sharma, P., Rex, J. (2012) The critical impact of time discounting on economic incentives to overcome the antibiotic market failure. *Nature Reviews Drug Discovery*, 11(2), 168-71.

Staerk, K., Knai, C. (2019) Implementation of the UK Five Year Antimicrobial Resistance Strategy – strengthening international collaboration. *Policy Innovation Research Unit.*

Towse, A., Sharma, P. (2011) Incentives for R&D for New Antimicrobial Drugs. *International Journal of the Economics of Business*, 18(2), 331-350.

Wellcome Trust and BCG (2018) *Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities*, Wellcome Trust and Boston Consulting Group.

WHO (2015) *Resolution: Global action plan on antimicrobial resistance*.

WHO (2017) *Antibacterial agents in clinical development – an analysis of the antibacterial clinical development pipeline, including tuberculosis*. WHO/EMP/IAU/2017.11