Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

SECURING NEW DRUGS FOR FUTURE GENERATIONS: THE PIPELINE OF ANTIBIOTICS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

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CONTENTS

FOREWORD:

JIM O'NEILL, CHAIRMAN OF THE REVIEW

Multiple factors drive the development and spread of antimicrobial resistance (AMR). It is a complex issue to which there is no single or simple solution, but for which the costs of inaction are huge.

For these reasons, we decided at the start of our assignment that we would publish a series of papers on what we saw as the key challenges. It would allow us multiple opportunities to raise the broad topic, but in each case focus on a specific part of the challenge.

We also decided to seek bold, simple but decisive solutions for us to influence the world and ensure that AMR does not have a chance of becoming a problem of the scale we identified.

In our first paper, we showed that if we fail to act on AMR then an additional 10 million lives would be lost each year to drug-resistant strains of malaria, HIV, TB, and certain bacterial infections by 2050, at a cost to the world economy of 100 trillion USD.

We have identified the wide variety of things we need to do to get to grips with this problem. These range from the very basic – such as better hand-washing and sanitation to reduce the spread of infections – to far more sophisticated issues such as the development and adoption of new technologies to improve the way that we diagnose infections and prescribe antimicrobial drugs. We need to make changes which reduce our dependence on antimicrobial drugs and drastically cut our misuse and overuse of them in humans and in animals. Our second paper discussed five areas for immediate action where solutions can be found without too complex challenges so long as the interested parties are focused and determined.

Another key dimension of this solution is ensuring that the world has a sustainable supply of antimicrobials. If we are to keep pace with the rise of drug resistance, we need to replace those generations of drugs rendered useless by the emergence of resistance to them. This is the specific focus of this, our third paper.

The problem of the global pharmaceuticals market failing to produce drugs to respond to unmet medical needs is not a new one. We have seen before how the market neglects the needs of the populations of developing countries, where the absence of a commercially valuable market held back the development or the availability of much needed drugs to combat malaria, TB, and the HIV/AIDS epidemic. But the enormously successful initiatives to stimulate the pipelines for these drugs over the past decade, including through ground-breaking public-private partnerships, have demonstrated just what can be achieved with public and political mobilisation to overcome seemingly intractable problems.

In the case of antibiotics, though, the fundamentals of the situation are different, and the unmet need is not confined to the developing world. Despite the existence of a growing unmet clinical demand, and affluent potential markets, the pipeline for new antibiotics has paradoxically experienced a long-term decline. Antibiotics are being developed, but not ones targeting the most urgent needs, and not in the diverse portfolio required to combat the rise of bacterial resistance.

Given this, interventions should be possible to increase commercial investment in antibiotics R&D, without having to rely entirely on upfront funding from public and philanthropic organisations.

In this paper we propose a bold set of interventions which directly address the specific problems of antibiotic development, and find ways to balance issues of profitability with access and conservation, so that commercial investment flows again into the area. We set out here our initial ideas on how we think this can be achieved.

We believe that the proposals we outline are amongst the most specific that have been made so far about both the new drugs needed and their development costs. No doubt specialists in the field will have their own view on aspects of our suggestions. Indeed we hope they do and make those clear to us: we will use this input along with the other ideas we are developing as we build to our final recommendations in summer 2016.

EXECUTIVE SUMMARY

The problems and the causes of antimicrobial resistance (AMR) are diverse. In our two published papers so far, we have made the case that the potential future human and economic costs of AMR are too catastrophic to ignore; and set out five necessary steps that should be taken immediately to tackle this challenge.

In this paper, we focus on one element of the problem: the need to boost the development of new antibiotic drugs.

Our analysis of the antibiotics that have been recently approved and those at various stages of development shows a mismatch between what we know the world needs, given emerging levels of drug resistance, and the size and quality of the pipeline to address this growing challenge.

For example, there is rising resistance to 'carbapenems', a class of antibiotics that constitute doctors' last good line of defence against a range of potentially life-threatening infections such as pneumonia, and bloodstream infections. Yet perhaps only three compounds under development at the moment have the potential to be active against the vast majority of bacteria resistant to carbapenems, despite them having reached worryingly high levels in some countries already.

The main reason for this mismatch is that the commercial return for any given new antibiotic is uncertain until resistance has emerged against a previous generation of drugs. In other medical fields, a new drug is meant to significantly improve on previous ones and so will become the standard first choice for patients quickly once it comes to market. That is often not true for a new antibiotic: except for patients with infections that are resistant to previous generations of drugs, a new antibiotic is most probably no better than any existing and cheap generic product on the market. By the time that new antibiotic becomes the standard first line of care, it might be near or beyond the end of its patent life. This means that the company which developed it will struggle to generate sufficient revenues to recoup its development costs.

We set out proposals to address this problem and bring forward the financial reward to new antibiotics that address drug resistance. We think our proposals can radically overhaul the antibiotics pipeline over the next 20 years: our costs are modelled on achieving 15 new antibiotics a decade, of which at least four should be breakthrough products, with truly novel mechanisms of action or novel therapeutic profiles targeting the bacterial species of greatest concern.

First, we want to make antibiotics R&D commercially sustainable so that the field can attract the best minds from research organisations, small biotech companies, large firms or not-for-profit entities. To do that we propose a system by which a global organisation has the authority and resources to commit lump-sum payments to successful drug developers. Payment would have to be set against selective criteria agreed in advance. Such an approach would 'de-link' the profitability of a drug from its volume of sales, supporting conservation goals by eliminating the commercial imperative for a drug company to sell new antibiotics in large quantities – a key factor in contributing to the development and spread of resistance.

Creating a more stable commercial end market for antibiotics in this way should, over time, encourage investment into the earlier stages of the pipeline. But we think we should also jump-start a new innovation cycle in antibiotics by getting more money into early stage research. A global AMR Innovation Fund of around 2 billion USD over 5 years would help boost funding for blue-sky research into drugs and diagnostics, and get more good ideas off the ground. Big pharma should have a role in paying for this innovation fund: it needs to look beyond short-term assessments of profit and loss, and act with 'enlightened self-interest' in tackling AMR, recognising that it has a long term commercial imperative to having effective antibiotics, as well as a moral one.

Finally, there are ways to further reduce barriers to drug development by lowering costs, improving the efficiency of research, and lowering global regulatory barriers wherever possible without compromising patients' safety. Much has already been done in this space but we should continue to explore ways to bring new drugs to market as quickly and as easily as possible.

These interventions will require political leadership at a global level. To work, it requires giving health authorities the means to deliver the new system, with rules in place to limit unfair free-riding by some countries or some companies. We do not underestimate the difficulty but there are examples of successful coordination in the health sector and we would like to learn the lessons of initiatives such as UNAIDS on HIV/AIDS, GAVI on improving access to vaccines, or the Medicines for Malaria Venture (MMV) to combat malaria.

These interventions will also require financial resources but the cost is modest compared to the problem the world faces if AMR is not tackled. Today in the US antibiotic resistance already costs the healthcare system an additional 20 billion USD a year [1].In comparison, we estimate that a comprehensive package of interventions could cost as little 16 billion USD and no more than 37 billion USD over the course of 10 years and would be sufficient to radically overhaul the antibiotics pipeline. This money would only be paid out when new and useful products are brought to market, not as a taxpayer-funded subsidy upfront. Such sums amount to a one-off increase, over the course of a decade, of less than 10% on what the world today spends on antibiotics (40 billion USD a year). This is hardly a high price to pay given that antibiotics are essential to so many aspects of healthcare, from common infections to surgery and chemotherapy.

We look forward to working with governments, industry and other interested parties around the world over the next 12 months, as we develop these initial ideas further into a more detailed package of action.

1. **US Centers for Disease Control.** *Antibiotic Resistance Threats in the United States, 2013.* Available at http://www.cdc.gov/drugresistance/threat-report-2013/. Accessed May 2015

1.

WHICH NEW DRUGS?

Tackling AMR requires an adequate supply of new medicines to beat drug resistance as it arises. This includes drug resistance in HIV/AIDS, malaria, fungal infections, tuberculosis (TB), as well as a range of bacterial infections.

Why this paper focuses on antibiotics

In this paper we have chosen to focus on resistance to antibacterial drugs or 'antibiotics', for two main reasons.

First, antibiotic resistance has been described by the WHO as the single greatest challenge in infectious diseases today, threatening rich and poor countries alike, and yet so far it has not had nearly sufficient attention in terms of medical research. As a global public health threat, it should arguably receive the same kind of public focus HIV/AIDS received in the 1990s or cancer research receives today – although it may not need the same levels of public funding to find a solution.

Malaria, and in particular the risk that artemisinin-resistant strains of malaria could spread out of South East Asia into India and beyond, is an immense challenge too: but despite all the difficulties, it has been identified and is addressed with admirable focus through the work of groups including the Global Fund to Fight AIDS, Tuberculosis and Malaria. As a result, the pipelines for HIV, TB and malaria can be considered to be on a more stable footing than they were 20, or even 10, years ago: these efforts now need to be sustained rather than fundamentally changed (see box on the following pages). Such a push to promote antibiotic development has barely started, with only relatively small pilot efforts deployed recently by the US government and the European Commission.[2]

The second reason for focusing on antibiotics R&D in this paper is that the market for antibiotics is different to that for other drugs in the field of infectious diseases. It is a large and very profitable market for many companies with in the region of 40 billion USD[3,4] annual sales globally, but despite this it fails to incentivise enough R&D. It also gives rise to a set of problems that economists call 'negative externalities'[5]. When a patient uses an antibiotic, a collateral effect is that it contributes to additional bacterial resistance, which has a negative impact on all of society. But there is also a positive externality of appropriate and proper antibiotic use, from its role in controlling the spread of infection. These effects must be taken into account when policymakers consider the market for antibiotics, to ensure the incentives provided for R&D balance the interests of patients, society as a whole and drug developers.

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2 For example, the European Innovative Medicines Initiative's (IMI) public-private New Drugs For Bad Bugs project, and the US Biomedical Advanced Research and Development Agency (BARDA) broad-spectrum antimicrobials programme have between them spent 650 million USD over five years on antibiotic discovery efforts.

3 *Global Use of Medicines: Outlook Through 2017*. IMS Institute for Healthcare Informatics, 2014.

4 Hamad B. The antibiotics market. *Nature Reviews Drug Discovery* 2010; 9: 675-676.

The state of the current pipelines for HIV, malaria and TB

HIV/AIDS

Since the 1980s, significant sums have been devoted to the cause of HIV/AIDS research. The US National Institutes for Health (NIH) alone spends 3 billion USD annually on HIV/AIDS research, providing a foundation for considerable further spending by private firms developing lucrative treatments for patients living with HIV in the developed world. At least 1.1 billion USD was spent on R&D activities specifically related to treatments for HIV/AIDS sufferers in developing countries in 2013, of which more than 95% came from public and philanthropic sources (including the US NIH.) A significant proportion of this – nearly 60% – was dedicated to research into HIV vaccines.[6]

The pipeline for new HIV treatments is generally regarded as being robust with close to 100 products currently under development at Phases One, Two or Three, or in pre-registration.[7] Although this features a significant number of follow-on products which offer incremental rather than transformational clinical improvements over existing products, many offer benefits in terms of improved antiviral action and greater tolerability. Significant investments in vaccine research have resulted in a number of products entering clinical trials (albeit with sometimes disappointing results), and there is evidence of some diversification within the pipeline towards products tailored to the needs of users in low-income settings. The level of research into HIV has also yielded beneficial spillovers into other areas of antiviral research, including significant new products for the treatment of viral hepatitis.

However, today there are still gaps in investment that addresses the need for products where demand is restricted to patients in developing country settings, such as vaccines, and paediatric diagnostics and treatments.

Malaria

Artemisinin resistance was first identified in Cambodia and Myanmar during the late 2000s, and there are now acute concerns about the possibility of its spread within and beyond South-East Asia. This is one of the most alarming antimicrobial resistance threats if it is allowed to continue to rise.

As an area of research, malaria struggled to attract adequate funding for many years, with private investment constrained by the low incomes of the regions worst-affected by the disease. But by the efforts of innovative public-private partnerships like the Medicines for Malaria Venture (MMV), great advances have been made in managing malaria and in pulling new and improved treatments through the development pipeline. Initiatives such as this, with close coordination of global research efforts, provide a strong basis to support an adequate drug development pipeline.

Thanks to these efforts, global R&D funding for malaria was close to 550 million USD in 2013 – of which more than 80% came from public and philanthropic sources.[8] A major study of the pipeline in 2012 identified 37 antimalarial products in the development pipeline between pre-clinical studies and Phase IV – then a significant increase on two years previously [9].The current pipeline includes research across a number of fronts, including later-stage studies on malaria vaccines, with a focus on developing new treatments to combat the threat of emerging artemisinin resistance.

5 Externalities are the cost or benefit that affect a party who did not choose to incur that cost or benefit. A classic example is pollution: when manufacturing products, a company's factory might pollute a local river, which puts a cost on people who drink the water and fish there. Externalities are often a justification for public policy intervening in a market to regulate it.

6 G-FINDER Report 2014. Policy Cures, Sydney – available at http://www.policycures.org/gfinder.html

7 Wong A. The HIV pipeline. *Nature Reviews Drug Discovery* 2014; 13: 649-650.

TB

Tuberculosis continues to inflict a great disease burden globally. The spread of multi-drug-resistant (MDR) and extensively-drug-resistant (XDR) strains is most acute in poor regions, where the challenges of TB treatment and control are the greatest and are exacerbated by high rates of HIV co-infection.

The vitality of the TB pipeline is in large part intertwined with that of the pipeline of new antibiotics, as these are needed as the basis for new and more potent combination therapies. But just as important is achieving breakthroughs in the delivery of TB treatments, to allow current treatment regimens for MDR and XDR strains of six months or more – where patient adherence is very low – to be reduced considerably in length, and their compatibility with HIV treatments to be improved.

580 million USD was spent on global R&D focussed on TB in 2013, nearly 80% of it from public and philanthropic sources. Much of the basic arsenal of antimycobacterial drugs for treating TB was developed in the 1950s and 1960s, following on from the early breakthrough in the development of streptomycin in the 1940s. The long period of very limited progress in TB treatment since the 1970s had prompted concerns that the pipeline was inadequate in countering the threat of emerging drug resistance. Thanks to concerted global efforts, a stronger pipeline has emerged in the past ten years – with 2013 seeing the approval of the first 'breakthrough' TB treatment, bedaquiline, in four decades. This, and other drugs in the pipeline, offer significant potential for the development of new combination therapies that are effective against MDR and XDR strains, or over shorter courses of treatment. But given we need at least four separate drugs to develop a new combination treatment, and that drug resistance is a growing problem, it is imperative to support these opportunities and improve the pipeline.

The continued efforts of non-profit and philanthropic organisations in this field, such as the Global Alliance for TB Drug Development, the Bill & Melinda Gates Foundation (BMGF) and the Wellcome Trust will remain crucial in driving forward the development of treatments on this front.

Developers of antibiotics may need to be encouraged to explore how their products might be applicable as TB treatments. Such encouragement may need to be in the form of support from major charities and public research grants.

8 G-FINDER Report 2014.

9 Anthony M P et al. The global pipeline of new medicines for the control and elimination of malaria. *Malaria Journal* 2012; 11: 316-341.

What antibiotics do we need and are they in the existing pipeline?

Bacteria are commonly divided into two groups, Gram-positives (such as *Staphylococcus aureus*) and Gram-negatives (such as *Escherichia (E.) coli*).

Resistant strains of Gram-positive bacteria – such as methicillin-resistant *Staphylococcus aureus*, or MRSA – pose a continuing threat, but the range of antibiotics available to combat them remains comparatively robust, having been the focus of the bulk of antibiotic discovery efforts over the past two decades. In particular, a concerted focus since the 1990s on tackling rising MRSA infections within US and European healthcare systems appears to have been instrumental in stimulating the relatively large numbers of products targeting Gram-positives in recent years.

It is the emergence of resistant strains of Gram-negatives, though, that currently presents the greater threat to human life and modern medicine, particularly five Gram-negative bacteria: *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter cloacae* and *E. coli*. These bacteria can be deadly, causing infections ranging from urinary tract infections (UTI) to life-threatening pneumonias and bloodstream infections. It is harder for antibiotics to penetrate 'Gram-negative' bacterial cell walls, and even if the drugs can get in, these bacteria are particularly good at pumping them back out again. Added to this is the problem that there are an increasing number of multi-resistant Gram-negative strains, with very few antibiotics that can currently combat them or that are being developed. This is why they cause the greatest concern.

A more detailed assessment of these emerging patterns of drug resistance, and the clinical need which they create, was prepared by the Review as the basis for expert consultation. A summary of this is included with this paper at Appendix A.

We analysed the current antibiotics pipeline against these areas of urgent need. The Pew Charitable Trusts'[10] published pipeline for December 2014 identified 41 antibiotics currently in development. On the face of it, this number sounds impressive, but experience shows that a sizeable majority of these will never progress to licensing. Furthermore, even where a drug does achieve market approval, it may not prove successful in clinical practice, as a significant number are withdrawn on efficacy grounds.[11]

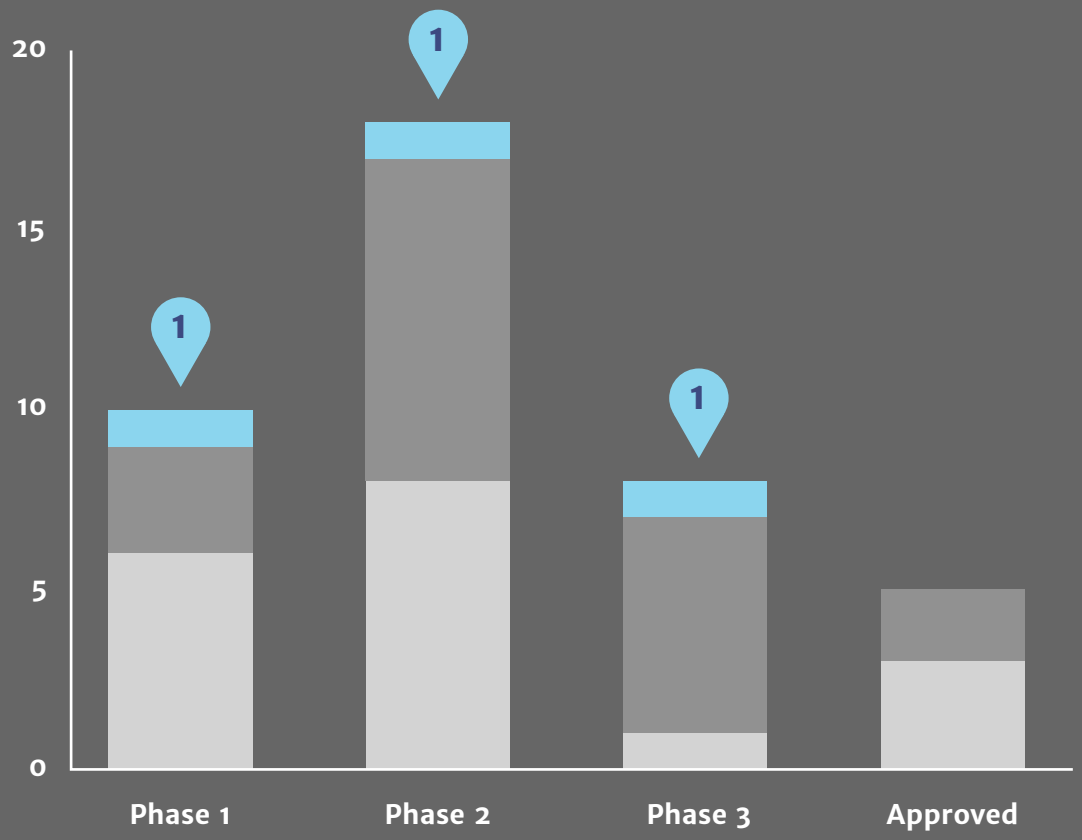
While most of the antibiotic products currently in the pipeline are active against at least some of the list of pathogens identified by the FDA as posing a 'serious threat to public health', barely a third (16 drugs) show significant activity against multi-resistant Gram-negative species. And only perhaps three have the potential to offer activity against the vast majority (>=90%) of the most resistant bacteria that doctors already have to treat today. We refer to these as potential breakthrough antibiotics. This assessment indicates that the antibiotics currently in development – some of which are still 10 to 15 years from market – do not adequately fill the gaps in clinical need that already exist and will in most likelihood increase as resistance spreads. In short, we need more potential breakthrough antibiotics.

Finally, the future health of the pipeline depends to some extent on the state of it today: the most useful follow-on compounds that are currently under development or have come to market recently are often the product of much earlier novel discoveries. By having only a limited number of novel products under development today, we limit the scope for the pipeline to yield useful follow-on compounds in years to come.

10 http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development, accessed April 2015

11 Outterson K, Powers J, Seoane-Vazquez E, Rodriguez-Monguio, Kesselheim A. Approval and withdrawal of new antibiotics and other antiinfectives in the US, 1980-2009. *Journal of Law, Medicine and Ethics 2013*; 41: 688-696.

ANTIBIOTICS IN THE PIPELINE OR RECENTLY LICENSED



High priority

Potential for activity against at least 90% of carbapenemase-producing bacteria in the UK

Low priority

Does not meet the criteria for "clinically useful"

Medium priority

Targets at least one CDC 'Urgent' threat (Clostridium difficile, carbapenem-resistant Enterobacteriaceae or drug-resistant Neisseria gonorrhoea, but is not classed as a potential break through)

Source: Review's own analysis, pipeline data provided by Pew Charitable Trusts

Review on Antimicrobial Resistance

What would a successful pipeline for antibiotics look like?

In considering incentives to stimulate the antibiotic pipeline, we should not be seeking to support the development simply of more new drugs. Nor should we be looking to intervene in those areas where the market already works well. We should instead target incentives at those drugs with the potential to address the greatest unmet medical need.

Inevitably, our future needs are hard to predict precisely, because drug resistance develops in unpredictable ways. An assessment of what we need can only be based on what we know today, and could be altered by an unforeseen scientific breakthrough or step-change in antibiotic resistance. A number of agencies around the world undertake their own analysis of the emerging threats of drug resistance. But the world lacks any single authoritative assessment of AMR which could focus drug development efforts towards the areas that present the biggest global risks. Therefore, we have defined what a 'healthy' antibiotics pipeline might look like, using input from experts to understand where the gaps are that need to be filled.

As explained above, the most urgent need is to develop new medicines that address the threat posed by drug-resistant strains of Gram-negative bacteria. But we should also seek to have an arsenal of antibiotics that is appropriately varied in terms of how they can be used, striking the right balance between broad spectrum drugs that can treat many infections, and narrowly-targeted drugs.

On this basis, we urgently need new narrow-spectrum agents that are active against resistant bacteria of public health importance (such as those which have developed resistance to carbapenems or colistin – our current 'last line' antibiotics.) New 'broad-spectrum' agents are also needed that are active against a range of bacteria with existing resistance. These new drugs would increase the chance that empirically-prescribed therapy would be appropriate, even for infections resistant to our current antibiotics.

However, broad-spectrum agents are a double-edged sword: although an important tool, they are more prone to encouraging resistance to develop in many different bacteria, and cause 'collateral damage' by harming the many good bacteria in our bodies that we need. Over the long term, reducing the length of or need for empiric, broad-spectrum treatment is an important goal. This can only be achieved by embracing new generations of fast and accurate diagnostics to detect bacterial infections, identifying the species causing them, and measuring antibiotic susceptibility – so that prescribers can be confident that they can use a narrow-spectrum drug effectively.

Faced with current patterns of emerging resistance, and given the need for a balanced range of effective antibiotics, we believe that a supply of between two and four licensed 'first in class' compounds or new therapeutic profiles active against key species every ten years would allow us to keep ahead in the race against antibiotic resistance. This will hold true only if these new drugs are treated as a well-guarded resource, accessible to all, but with limited usage only as warranted by resistance to existing drugs, rather than by an opportunity to exploit commercial potential.

For the purposes of the rest of this paper we will model the investment needed to achieve in the region of 15 new licensed antibiotic therapies every 10 years; with incentives specifically focussed at generating two new broad-spectrum classes and two new narrow-spectrum classes per decade.

It is very important that any new incentive system should not incentivise novel patentable drugs at the expense of existing off-patent drugs that could be revived, repurposed or combined to break resistance. Both could be equally effective and the latter are possibly quicker and cheaper to bring to patients. Research to make more out of our existing arsenal of drugs should be a priority, as we have set out in our previous paper.[12]

This 'ideal pipeline' is used as an example and a starting point to allow us to assess the cost of investment. We expect that this would be refined and changed as thinking and policy decisions will progress to stimulate the antibiotics pipeline. Ultimately, as set out in more detail below, what may be needed is a framework to value and compare the benefits of different antibiotic projects in the pipeline, possibly based on a points system. We look forward to engaging with experts doing this work in the future.

Having established the inadequacy of the current antibiotics pipeline and set out our 'ideal' pipeline, we now consider what the obstacles in the market are as it is currently structured and what can be done to overcome these.

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12 *Tackling a Global Health Crisis: First Steps* – published February 2015 and available at www.amr-review.org

2.

IS THERE A PROBLEM WITH THE MARKET FOR ANTIBIOTICS AND HOW SHOULD IT BE CORRECTED?

At first sight, antibiotics sales represent a large and potentially profitable market that should not require more public support than other commercial drug areas. It generates annual sales in the region of 40 billion USD worldwide, in rich and poor nations alike. Patients who use antibiotics are spread across all levels of income, although many patients in the poorest parts of the world still suffer from not having good access to antibiotics.

It is hard to predict when a new antibiotic will need to be used and bring a return to its developer

Companies must make investment decisions years before an antibiotic comes to market. It typically takes about 15 years for a product to go from the start of initial research to marketable product, with significant money needed upfront to fund a project before knowing whether it will fail or succeed. The failure rates of research into new antibiotics are high, with only between 1.5% and 3.5% of drug compounds making it successfully from early exploration to market approval[13]. This means that in the majority of cases a significant amount of money is invested in a product where there is ultimately no financial return.

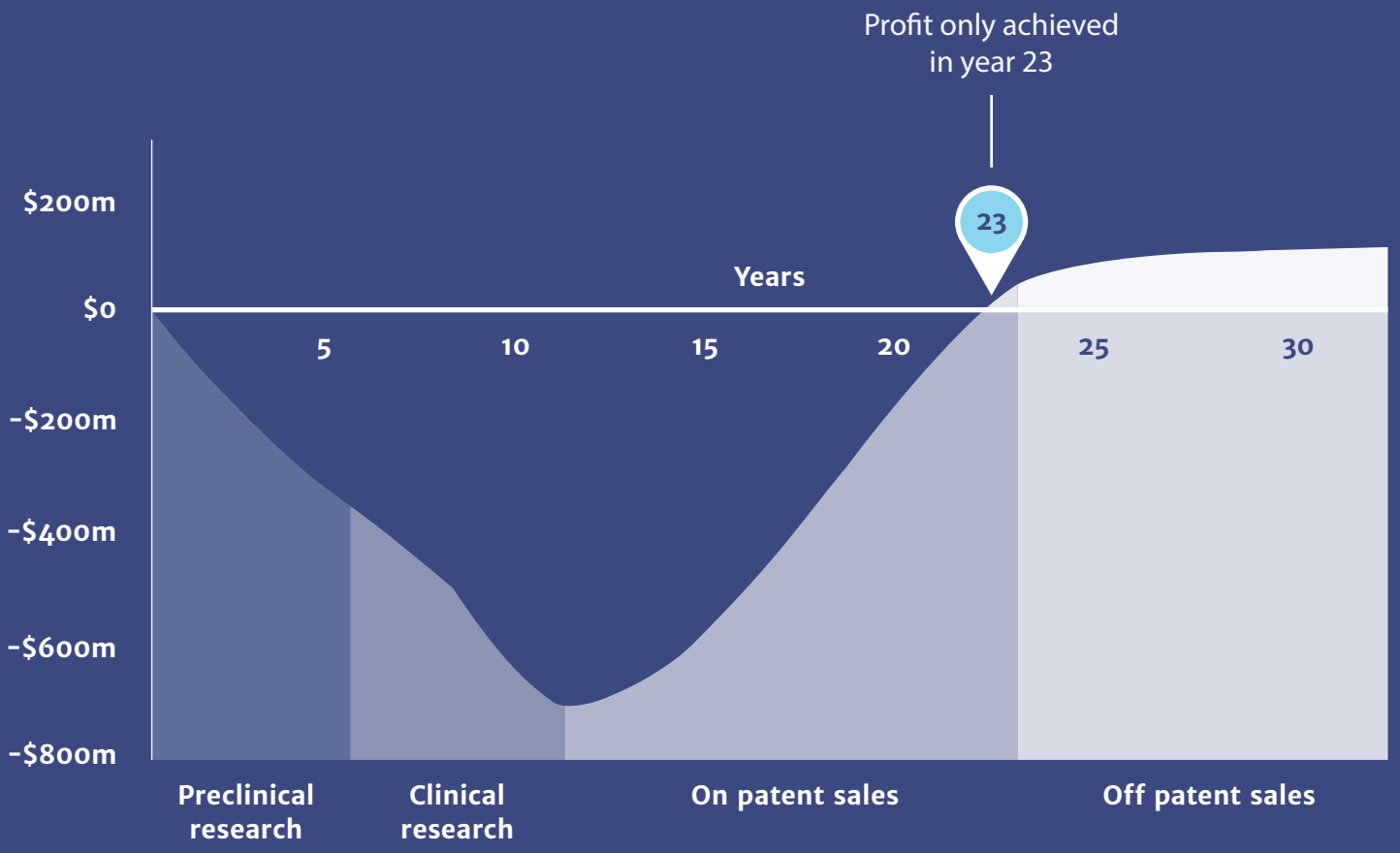
These problems are true of all classes of drugs, but the problem is exacerbated in the case of antibiotics. This is because it is hard to predict how big the health need will be at early stages of investment. For many non-communicable diseases like cancer or diabetes, there is information on demographics and patterns of illness that allows developers to predict with some degree of confidence the size and nature of their future patient populations. But with antibiotics, in the absence of resistance, older products (usually generic) can treat infection just as well as new ones for far less money. So the market for a new antibiotic is normally limited to a subset of patients with resistant infections, which might be very small and spread sporadically across a population. As mechanisms and patterns of resistance and rates of infection can change quickly and unpredictably, it is difficult for a developer to estimate with any certainty the future size of the market for a new antibiotic, when they need to do so many years before it reaches the market.

These features beg the question: why should any special public or charitable provision be made to stimulate antibiotics R&D?

We have considered three reasons why intervention could be justified in this market. We believe the first two characteristics below do justify some carefully conceived action to stimulate drug development.

13 Figures derived from data provided to the Review team by IMS Health UK and selected pharmaceutical companies; see also Sertkaya A *et al. Analytical Framework for Examining the Value of Antibacterial Products*. US Department of Health and Human Services, 2014.

CUMULATIVE PROFITS FROM ANTIBIOTIC RESEARCH



Source: Review's own modelling of the discounted average expenditure and revenue for a sample of antibiotics R&D projects based on historical input dating back to 2002 and forward projections provided by IMS health and selected pharmaceutical companies. More detail on the modelling can be found at amr-review.org

Review on Antimicrobial Resistance

Effective generics, and necessary conservation efforts, mean that sales of new antibiotics will often be limited

Because bacterial resistance almost always emerges in response to new antibiotics, public health authorities will initially want to reserve any new drugs as a last line treatment, used only where existing products have already failed. So these new drugs will likely become first and second line treatments only many years after their introduction, as older treatments will be lost to resistance. This contrasts with many other drug categories, where a new product to market will often immediately become the first-line treatment of choice across the marketplace.

The result is that the drug developers who come up with a new antibiotic create considerable benefits for society but are not guaranteed to benefit financially: the drug only starts being used for the general population of patients many years after it was licensed, by which time it may be off-patent and can be manufactured by any company as a generic product.

This situation creates a tendency for companies to wait until resistance is already rising in an area before deciding to invest. This time lag means that the pipeline is likely to yield drugs for particular problems only once they have become established medical problems – something evidenced by the significant number of products targeted at Gram-positive MRSA infections over the past 15 years. In the case of MRSA, researchers were able to rely on relevant discoveries made during the 1980s and 1990s that were fit for being developed into new products: this is why the void was filled relatively quickly. This is not the case for new antibiotics active against Gram-negative bacteria where research for new molecules often has to start from scratch.

Taken together, these reasons mean we need to look at systems that pay for drugs with a financial reward that reflects better the benefit that the drug is likely to offer society in the long term instead of looking at the narrow period during which they are 'on patent'. Such a system will also be able to reflect the enormous 'insurance value' to society from having an effective supply of antibiotics – something on which so many aspects of modern healthcare depend. Like any form of insurance, we hope that these new generations of antibiotics should not need to be widely used – but we should value highly the protection that they provide. Without an approach that properly reflects this value, we cannot expect commercial investment in antibiotics R&D at a sufficient level.

Some argue that antibiotics provide lower returns than longer course treatments such as diabetes or cholesterol drugs

The case is often made that because courses for antibiotics are short – one to two weeks – companies make less return on their R&D investment than, say, for new breakthroughs in chronic disease areas such as diabetes, where drugs are usually taken over the course of many years. Therefore companies tend to prioritise other areas of research that are more profitable than antibiotics, or so the story goes.

This on its own is not a strong argument for intervening in the market for antibiotics, other than perhaps encouraging the price of new antibiotics to increase enough to provide a sufficient return. Some other classes of drugs have become commercially lucrative despite providing short, curative courses of treatment – but have usually done so via very high prices – a point we return to below.

> *"We need to look at systems that pay for drugs with a financial reward that reflects better the benefit that the drug is likely to offer society in the long term instead of looking at the narrow period during which they are 'on patent'"*

So there is a strong case for some market intervention to ensure enough investment in antibiotics R&D, while conserving the new drugs so they last longer

The profitability of a new drug hinges on the simple fact that revenue increases the higher the price and the higher the volume of sales. Companies are incentivised to increase their sales, even if these extra sales have little or no medical value and come at the cost of adding to drug resistance. This leads to a large amount of over-use for antibiotics and is at odds with the objective to conserve antibiotics to make them last longer before resistance arises.

Put simply, there are two ways to address this problem which are often seen as being on opposite ends of a spectrum of policy interventions. One way is to use regulation: prohibit the overuse and misuse of antibiotics. The other way is to use markets: increase the price of antibiotics until most overuse and misuse becomes unaffordable.

Neither extreme is effective on its own, so we have considered the best possible intervention in between.

Of course a lot can be improved in the way we manage the demand for antibiotics and this is an important focus of our work[14]. But as long as the financial incentive for companies is solely to maximise the volume of antibiotics they sell, it is very difficult for governments and healthcare systems to regulate the sale of antibiotics effectively. This is a problem everywhere, even in the most developed countries and it is an issue that drives inappropriate antibiotic use, particularly in middle income countries.

Based on experience in other areas (see box on page 14 for an example based on the regulation of morphine as a pain killer, and restrictions on the use of artemisinin), we are concerned that a purely regulatory approach to conserving antibiotics could harm access to them, which is already a major problem for many of the poorest people in the world. Systems of regulation rarely work when there is a large financial incentive for producers or suppliers to break them.

We also think that an approach based solely on increasing the price of antibiotics to stimulate investment and reduce over-use would not be sufficient. The reasons why are set out in more detail below.

This is why we look for solutions that can make antibiotics R&D profitable to pharmaceutical companies by creating more certainty of demand while also supporting prudent use of these new drugs, so they can last longer before resistance arises.

> *"As long as the financial incentive for companies is solely to maximise the volume of antibiotics they sell, it is very difficult for governments and healthcare systems to regulate the sale of antibiotics effectively"*

14 See Section 7 on our next steps for more detail on how we will be covering such issues in future papers.

Better regulation has a role to play in stopping overuse, but it can be a losing battle when financial incentives are not aligned: the case of malaria drugs and morphine.

Artemisinin (a malaria drug) is regulated to stop its use as a mono-therapy (which would breed drug resistance), while morphine (a powerful but highly addictive opioid analgesic) is regulated to stop it being used as a narcotic. Both attempts are examples of how well-intentioned government regulation can fail at preventing misuse and produce damaging unintended consequences. With artemisinin, many governments have failed to stop generic products from being supplied as cheaper mono-therapies, which in the short term are as good at fighting malaria but lead to rising levels of drug resistance in patients. Stopping counterfeits and regulating all companies is hard in any context. It is made harder when health regulators are under-resourced as is often the case and given governments have a simultaneous desire not to reduce access to affordable artemisinin products.

In the case of morphine, governments have tended to place greater emphasis upon limiting use, because of concerns that it will be misused for recreational purposes. This means that its supply is tightly regulated in most countries in the world, severely harming legitimate access to morphine as a painkiller in low and middle income countries. Patients with high incomes are often able to get hold of the drugs despite regulation, whilst poor patients are usually unable to. As a result, in up to 150 countries patients have difficulty in accessing cheap opioid painkillers because of failing government regulation[15].

These examples show the risks associated with both excessively strict regulation, and weak enforcement, and demonstrate the potential pitfalls of relying on government regulation as a means of controlling access to and the use of vital drugs.

Despite all of this we do think that regulation has a hugely important role to play in stopping over-use. Much of the problems outlined above could be mitigated against through better funding of regulatory authorities and stronger international rules (something we will look at perusing for antimicrobials), and there are many cases of great success achieved through regulation. However we think that on its own regulation is not capable of curtailing overselling as long as pharmaceutical companies have a clear incentive to oversell their products.

15 Shetty P. The parlous state of palliative care in the developing world. *The Lancet* 2010; 376 (9751): 1453-4.

To support antibiotic development, three sets of interventions are needed

We considered a range of interventions that could be used to stimulate antibiotics R&D. We think three sets of interventions need to be pursued simultaneously:

1.

First, create a more predictable market for antibiotics to sustain commercial investment in R&D – where it is necessary, change how antibiotic developers are rewarded, to ensure a more predictable financial reward for developers of critically-needed new drugs, support conservation efforts, and ensure good value-for-money for purchasers and equitable access.

2.

Second, new focused funding into early-stage research to tackle AMR – as we described in our second paper, we are concerned that there are gaps in research funding for AMR: early-stage and 'blue sky' scientific research into AMR and new antimicrobials lags behind other clinical areas. We propose the establishment of a global AMR innovation fund to redress this imbalance, by providing a means of directing more money into AMR research in a more targeted and coordinated way.

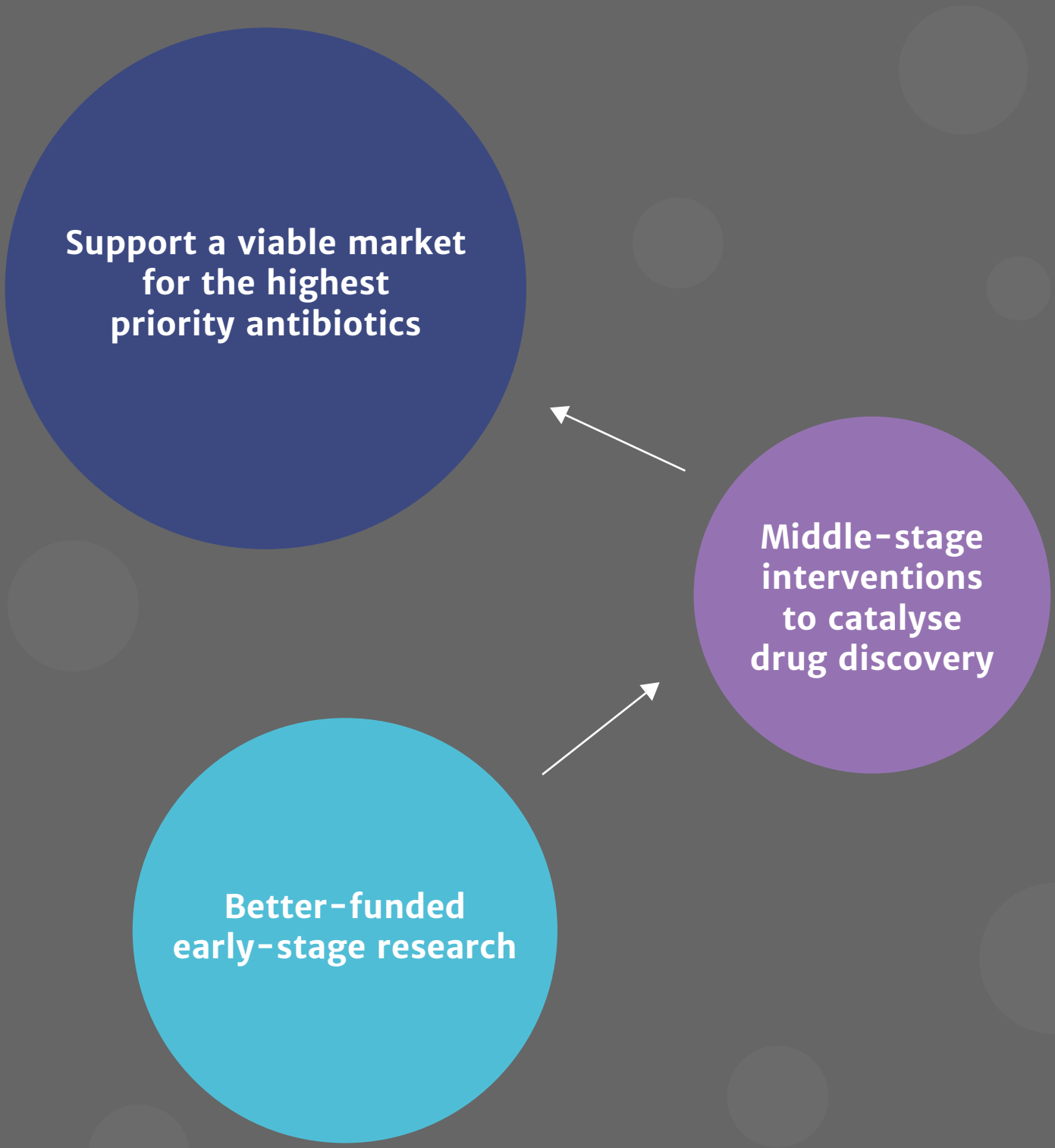
3.

Third, interventions to support efficient drug development through centralised public platforms for clinical trials, better sharing of information at early stages and regulatory harmonisation when they do not endanger patient safety– such interventions have the potential to make the discovery of new antibiotics less costly.

We believe that such a package of interventions at different stages of the pipeline can promote a sustainable pipeline of new antibiotic therapies, at a cost that is affordable and will provide value to taxpayers.

“We believe that such a package of interventions at different stages of the pipeline can promote a sustainable pipeline of new antibiotic therapies, at a cost that is affordable and will provide value to taxpayers”

A PLAN TO OVERHAUL ANTIBIOTIC DISCOVERY



Review on Antimicrobial Resistance

3.

CREATING A MORE PREDICTABLE MARKET FOR ANTIBIOTICS TO SUSTAIN COMMERCIAL INVESTMENT IN R&D

We start with the need for governments to intervene in the market for antibiotics: in our view the first and most important step to fixing the supply problem is to make the market more predictable and therefore more attractive for commercial investment in R&D.

Some of our guiding principles have been as follows.

1.

Focus any public intervention in the market where it is specifically required to develop the most-needed products. The market remains a good way of allocating drug development resources in most cases, but comes up short in this instance when faced with excessive uncertainty. Defining the 'unmet need' over a long time horizon is important, but needs to be done as flexibly as possible to cope with the unpredictability of emerging resistance.

2.

Aim to provide value-for-money in the use of public funds. For instance, interventions should not increase the reward for products that are already adequately supported by the current market mechanisms.

3.

The intervention must address the negative externality created by antibiotics: the fact that individuals using antibiotics inadvertently (and unavoidably) impose a cost on society as a whole by increasing bacterial resistance. This would be less of an issue if rapid diagnostic tests were available and always used before prescribing antibiotics, or if it were cheap and easy to renew the supply of antibiotics – but neither is true at present.

4.

Seek to open the field of antibiotics R&D to new players. Our interventions are aimed at setting a level playing field so that as many actors as possible can enter a competitive field of research into antibiotics – small and large companies, academic research teams, not-for-profit entities and partnerships between private and public sector actors. This could be an opportunity for companies in the BRIC countries and elsewhere to go up the value chain and enter the field of drug development making use of their specific needs and specific know-how.

These principles have led us to recommend a market intervention which involves rewarding the most needed new antibiotic therapies at least partially through the payment of a predictable lump sum. This is to incentivise commercial investment into R&D as well as compliance with rules to conserve future antibiotics. The features of this market intervention are described below.

We have ruled out a number of other potential interventions such as patent life expansions, transferable patent vouchers and relying solely on higher prices to stimulate R&D investment and constrain consumption. The reasons for ruling these interventions out are set out in more detail in Appendix B below.

Profitability should be 'de-linked' from volume of sales

Given the difficulty in significantly curtailing use while there is an incentive for drug companies to sell more drugs, and in the face of weak market incentives for private companies to undertake research into areas that society needs but that are not profitable, we believe that a successful intervention must partially or fully 'de-link' profit from sales. This means that one or several lump sums would be paid to the developer regardless of how many courses of drugs are sold. De-linkage is a widely researched topic and there are many different ways to implement it, which we will go on to discuss.

This approach can guarantee developers an appropriate return on investment where they produce an antibiotic that fills an unmet need, even where sales may not be high enough during the patent life of the product to justify their spending and risk-taking. It also reduces the incentive to oversell antibiotics and can play an important role in conserving future drugs.

An effective de-linkage system has a number of key requirements

Any successful system that introduces de-linkage to the antibiotics market will need to be implemented carefully, to balance certainty for developers with value for payers, while ensuring efficiency and minimising implementation risk.

Scope

The new system needs to be designed such that the best drugs are drawn into it. It should incentivise the new therapies that we need the most, whether they are based on new patents or old molecules. In designing such a system, we would need to guard against the risk of developers not being incentivised to bring forward their most promising products to the new de-linked market, something which would result in significant lost opportunities.

Certainty

Companies need to be sure that they will get a reasonable return for their investment. As already discussed investment decisions are made years – or even decades – before a drug might reach the market. Investors therefore need to have confidence that in 10 or 15 years' time they will be appropriately rewarded if they develop an effective, valuable product. This means limiting the scope for political cycles to influence assurances of future reimbursement. Investors do not like risk, and need greater levels of compensation the greater they perceive the risk to be – requiring, in turn, higher eventual payoffs.

In the absence of a predictably lucrative market, mechanisms are needed which allow payers to make commitments to an alternative, de-linked means of reimbursement many years in advance of products reaching market, which drug developers will trust. But while offsetting the economic risk of antibiotic development, such interventions should not seek to indemnify developers entirely against the scientific risk inherent in antibiotic development – that is, the risk that a product fails during development or proves to be ineffective in practice once it does reach the market. Pharmaceutical companies are adept at managing this type of risk across their R&D portfolios: we do not see antibiotic development as necessarily being an exception to this, and it is not a burden which can efficiently or justly be transferred to public bodies.

Efficiency

Any system needs to be good value for money for society. We need to make sure we pay enough to get the drugs that we need, whilst not wasting public money.

What to pay, and when?

Under many models of de-linkage, the absence of an efficiently-functioning market leaves a question mark hanging over how to set the right 'price' for new antibiotics, and how best to phase reimbursement. Where antibiotic producers are reimbursed directly via public funds, achieving value for money will depend on defining a particular drug's 'worthiness' in combatting AMR, and structuring payments in a way which optimises outcomes both for the payer and the product developer.

Defining value

This would need to be judged against a clear set of criteria and independently adjudicated. Such assessment would need to look at the level of unmet need fulfilled by the product, as well as its likely efficacy – factors which would determine its 'score' against defined criteria, which are linked to payments afterwards.

Such an approach would need to be considered both for 'first in class' products, and also subsequent follow-ons. Many follow-on drugs offer only minor improvements upon existing antibiotics – so should not qualify for the same levels of reimbursement as genuinely ground-breaking products. However, where a follow-on drug manages, for instance, to significantly reduce toxicity compared to their predecessors, or circumvent established patterns of resistance, they should be rewarded appropriately.

If some areas of research, such as combination therapies, prove able to provide effective products but at a markedly lower development cost than conventional antibiotics, there would be a case for considering whether their lump sum payment is lower to ensure that their level of expected profit is broadly similar. However as a general principle, we believe that the payment level should be based on a product's value, and that developers who achieve the same results at lower cost should be allowed to make a greater profit.

Timing of payment and what it means for sharing risk between private and public sectors

There is a trade-off in paying for drugs early versus late in development. The earlier that companies are paid, the cheaper it is for the payer, as pharmaceutical companies' discount rates are so much higher than those of governments. However, delaying payment ensures that the payer has more knowledge about the product and does not risk buying a product that is ultimately unsuccessful.

To give an example of the effect of this discounting, paying 2 billion USD as a lump sum the year a product is launched has about the same effect on its profitability as 6.5 billion USD worth of sales over the following 20 years. 2 billion USD at the time of launch is also worth the same as 2.8 billion USD in year three. The payer gets much better value for money paying for a drug early.

On this basis, the bulk of a payment should come at the earliest point that a drug's effectiveness and quality can be confidently and meaningfully assessed – in practical terms no less than about two to three years after it reaches the market. Some funding may need to be provided in the interim to allow the company to sell the drug in this period.

In some cases, it may be efficient for Governments to provide money prospectively during drug development process, for instance as milestone payments at given points in the development process. Alternatively, this could be a full product development partnership. These interventions can help lower the cost of development and can offer good value for money depending on the probability of success of the project because they require the public sector payer to take on the scientific risk. In other words, when the public sector makes a payment into a project early on, a smaller amount can have a big impact but because the project may fail the government has to pick and pay for many different projects upfront. The later the public sector makes a payment, the more expensive it will be, but it only needs to buy projects that have succeeded already, leaving the private sector to make the upfront investment.

We see two broad approaches for implementing de-linkage, requiring different levels of market intervention

There are broadly two ways in which a de-linkage model could work, each requiring different levels of global coordination to implement. These represent the basic structures which we believe are the most promising – and which we want to use as the basis for much more detailed discussion over the course of the next 12 months.

A new global buyer

The most radical means of implementing de-linkage would be for a designated global body, with a broad base of buy-in from nation states, to establish a mechanism to purchase the global sales rights to new antibiotics, and to subsequently manage their supply internationally. The development and manufacture of drugs would still take place within the pharmaceutical industry, drawn through the pipeline by the incentive of a full 'buyout' of their product once it is ready to market. Although the developer would surrender the right to market their new drug, they would be reimbursed by an amount sufficient to ensure an adequate return on their development costs, and the investment risk incurred.

Eligibility for such a buyout, and the price at which this would be done, would be set transparently against well-defined criteria, providing developers with as much certainty as possible, and ensuring that new antibiotics are reimbursed according to their value (or potential value) to society.

With full control over the marketing and supply of a new antibiotic, the global body would in principle be able to ensure that the drug is used internationally according to unmet need and patterns of emerging resistance, subject to strict conservation measures but still accessible to countries at all income levels.

To function effectively, such a body would require the buy-in from a suitable number of countries who together have sufficient buying power to be global 'market makers'. This could beneficially be a group such as the G20, or even broader; but, equally, the current size distribution of pharmaceutical markets means that it would be viable with the backing of a much smaller grouping of affluent nations.

Creating an initial 'critical mass' of willing countries signed up to a global scheme is essential if so-called 'free-rider' problems (i.e. a situation where countries are able to benefit from the drugs generated without contributing directly) are to be avoided. Such an issue cannot be eliminated entirely, but a global body with the ability to control the terms upon which countries access the antibiotics would be able to go some way towards mitigating its effects.

The principal advantage of this system is that a single global body operates in the public interest and controls the rights to the drug, so is able to insist on high standards of conservation from nations and prescribers as a condition of supply. This allows usage to be managed according to clinical need and emerging patterns of resistance, rather than being subject to commercial forces and irresponsible or sub-optimal prescribing.

On the other hand, setting the prices for this type of buyout would be difficult: it needs to be sufficient to repay the developer's investment and reward their risk-taking, without 'over-paying'. As an approximate figure based on our modelling, we estimate that a reasonable global buyout price for a new

"To function effectively, such a body would require the buy-in from a suitable number of countries who together have sufficient buying power to be global 'market makers'"

antibiotic would be between 2-3 billion USD. These figures should be higher for areas where there is acute clinical need, and should vary based on the general quality of the product. They also might need to be higher in some areas, for example pneumonia, where clinical trials are inherently more expensive to conduct. This is less than the price that health systems might pay for a new antibiotic during its patented life currently, but nonetheless represents a very significant commitment of public funds to a single drug.

The implementation of such a model would be complex. One question is whether for this model to work, the new global payer needs to become the only route to market for any new antibiotic globally. If this cannot be agreed internationally, there are difficult questions as to how parallel systems of antibiotic development and sales could co-exist successfully. Great consideration needs to be given to issues such as how eligibility criteria and reimbursement prices could be set; whether the role could be filled by an existing organisation or would need to be some new body; and on what terms the products involved would be supplied internationally so as to incentivise rational usage. We will continue to consider and discuss these questions – and the overall viability of this type of intervention – over the coming months.

A hybrid model

This approach would represent a hybrid between the orthodox price by volume model and the global payer approach above. Again, this would rely on coordination by a single global body, and would work by giving a lump sum payment to companies who come up with new antibiotics, according to their value to society, but also allowing them freedom to sell their drugs for a profit.

The lump sum payment should either be worth about the same amount as the cost of investment for areas where there is potentially a social need but not currently a market, or be high enough to offer a small profit with the payer taking back some of their money from the company if the product sells well. This means that companies could invest in drugs, and know that when they come up with something useful they are guaranteed not to lose money as a result of an inadequate market, and any sales they make would then leave them to profit.

We estimate that a lump sum of between 1 and 1.3 billion USD to cover development costs of a new drug on average, including costs of projects which fail along the way. The advantages of this system are that it offers drug companies protection against the risk of investing in this area, whilst also rewarding those who come up with more useful drugs. The level of risk borne by the public funders of such a system is also lower than under the buyout system described above, as a greater proportion of developers' overall reimbursement is linked to the product's performance on the market.

Under this system we would expect the lump sum payment to come with a variety of conditions linked to stewardship and global access goals. For instance, the global body awarding the payment could impose conditions on the provision of drugs at an affordable price in low and middle income countries; and limits on how the drug is marketed, avoiding situations – for example – where doctors or hospitals are directly incentivised to increase prescriptions. This approach could potentially make it easier to implement rules around conservation, as it would not require multiple agreements with individual countries committing to regulation, and instead rely on a straight contractual agreement between the payer and the producer to ensure proper stewardship.

As with the other de-linkage option, implementation questions remain about how and who to set up the global player entity. Questions about stewardship conditions and how the drugs should be priced also need considering. Our views on these questions are not yet formed, and much will probably depend on the quality of each drug, and the arrangements by which sales and distribution are managed in different health systems around the world.

This system allows market-based rewards to play a central role, while ensuring that high-quality products which meet a defined need will not lose their investors' money. It is also likely to be the easier to implement than a system based around a single

> *"This system allows market-based rewards to play a central role, while ensuring that high-quality products which meet a defined need will not lose their investors' money"*

global buyer, as it requires less public funding and co-ordination. For these reasons this is provisionally our favoured approach, but we are still very much considering a range of options.

Why not rely on higher prices to encourage antibiotics development?

Some of the most vibrant areas of drug discovery – such as oncologics – are notable for being sectors where the end products command extremely high prices, in stark contrast to the market for antibiotics. This is driven to a large extent by the high proportion of generic products within the antibiotics marketplace, but even where products are on-patent and offer life-saving potential they attract far lower prices (on a per-patient-per-day basis) than other classes.

It is therefore reasonable to question whether a paradigm of higher prices for patented antibiotics might improve their commercial attractiveness and revitalise R&D in the field. Based on the examples set by other, vibrant areas of drug development – such as research into breakthrough antivirals to treat hepatitis C infections, or highly segmented markets for ultra-specialised cancer therapies – it is clear that an assurance of premium prices for antibiotics would almost certainly be a very significant stimulus to antibiotic development. This would draw greater private capital into the field, markedly reducing the level of public support necessary to sustain a healthy pipeline.

Although there is no single policy tool that could increase prices (and in practical terms they could not simply be legislated), it should be feasible to encourage price rises in a way that does not fundamentally alter the drugs market (see Appendix B).

Notionally, higher prices should also deter usage, supporting conservation efforts. However, in practice, patients and prescribers in many health systems are often insulated from the cost of the drugs which they consume, making price an imperfect tool for limiting demand. In order to better understand this relationship between higher prices and antibiotic usage we commissioned IMS, a consultancy specialised in providing data about the pharmaceutical industry, to examine what happens in a typical high-income healthcare system when a patent ends and the price of an antibiotic falls substantially. Their research – based on sales data for two types of antibiotic across six high-income countries – suggests that there are not substantial increases in antibiotic use when prices fall as a result of patent protection ending.

Paradoxically, though, in some health systems (particularly in low and middle-income settings) higher prices may actually incentivise drugs companies – and even doctors themselves – to encourage greater consumption and oversupply, with major negative implications for the development of resistance.

A model of high prices also creates inevitable access issues for patients in lower-income countries. There have been examples in recent years of initiatives to establish mechanisms to make medicines that command very high prices in western health systems available at lower cost in low and middle-income settings. But such approaches are complex and often imperfect, and the access barriers associated with high-cost essential medicines remain an issue of fundamental concern for emerging and less-developed economies.

These factors together mean that an objective of higher prices is on balance inappropriate in the market for antibiotics. It would also fail to address directly what we identify elsewhere in this paper as being the core problem of antibiotic development – that it is impossible to predict when resistance will spread in the future and therefore what size of market the product will have.

A possible exception to this, though, would be targeted narrow-spectrum antibiotics for which use is guided by a rapid diagnostic confirmation. Such products would be largely immune to the problems of overuse and 'supplier-induced demand' described above, and – access issues aside – premium pricing might play a valuable role in making them commercially viable.

4.

THE AMR INNOVATION FUND: MORE MONEY FOR EARLY-STAGE RESEARCH

Pump-priming funds for early-stage scientific research relating to AMR needs to happen urgently. It is required even if the market incentives are corrected in the ways we propose above: we should not wait until the market 'pulls' are all in place to push R&D for antibiotics with a global targeted fund[16].

Research is needed in a range of areas including efforts to develop new antimicrobial drugs, the next generation of diagnostic technology, an improved understanding of the development and spread of resistance, and the opportunities to use alternative approaches based on vaccinations or our immune system. At stake is the early-stage, often 'blue sky' science that underpins later stages of development. It is inherently high-risk and unattractive to commercial investors and is usually the preserve of academic researchers and public or philanthropic funders.

Governments around the world have already begun to reflect the potential severity of the AMR crisis in how they prioritise national research funds. Initiatives like the Joint Programming Initiative on AMR (JPIAMR) in the EU, the UK joint research council initiative in the UK and the recent US Government proposals to significantly extend NIH spending in the area are all the right steps towards ensuring that early-stage research is better-funded.

We need to create a dedicated fund for AMR innovation

We have therefore called for a new and separate initiative that we have named so far a 'Global Innovation Fund for AMR'. It should have the right leadership, focus and accountability to fill in the gaps that have been left open by traditional research funding.

Examples of such gaps are:

- **A programme to revisit old libraries of antibiotics and find ways to combine antibiotics** with other agents that can act as 'resistance breakers'. This area is neither sufficiently commercial to attract companies nor sufficiently innovative to attract scientists supported by research grants. But it could be the key to make our existing drugs last longer, until new ones are found. A global AMR innovation fund could look specifically to support such an important programme of research in an effective and pragmatic manner.

- **A bold approach to AMR that looks across and beyond established avenues of research.** The peer review system that underpins most public funding is critical to the long term, rigorous funding of academic research done by research councils. But in some specific cases like AMR it can leave some blind spots. For instance it rarely funds research that is not perceived to be cutting edge or novel, which scientists are not naturally attracted to, however useful the research might be in practice. For AMR, dosing and pharmacology studies would likely fall within this 'blind spot' in funding. Studies which look beyond established avenues of AMR research may be similarly under-explored areas. Interesting thinking is already surfacing around, for instance, ways of harnessing the body's immune system to fight infection itself. Again, a global AMR Innovation Fund has the potential to go further by more actively commissioning and guiding research where it identifies neglected opportunities.

- **Support to improve and promote scientific understanding of drug resistance.** The mechanisms by which drug resistance develops – and the ways in which it can be beaten by new drugs – is an area where understanding may sometimes be patchy, and which develops as quickly as resistance itself. Research to improve understanding of this, and the pharmacokinetics and pharmacodynamics of products which can overcome resistance, will be invaluable in supporting drug discovery efforts.

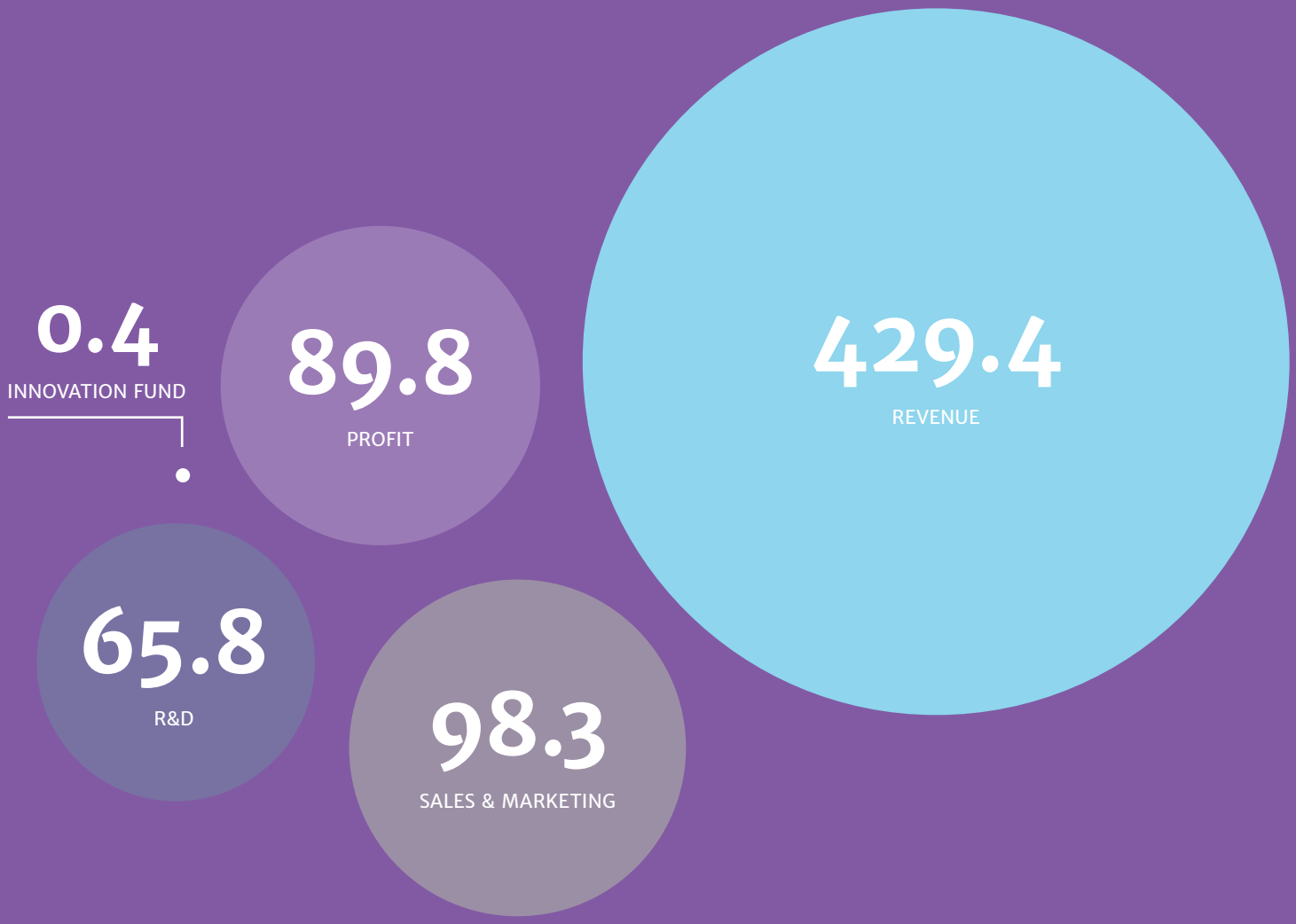
- **A focus on practical diagnostic tools for AMR.** It is widely agreed that affordable and rapid diagnostics have an important role in combatting AMR, by giving clinicians more data with which to make their prescription – meaning less unnecessary antibiotic use to exacerbate resistance. There have been welcome international prizes announced for successful diagnostic devices in recent months, but there is also a case for more early stage investment in this area to kick-start promising ideas.

> *"At stake is the early-stage, often 'blue sky' science that underpins later stages of development"*

16 *Tackling a Global Health Crisis: First Steps* – published February 2015 and available at www.amr-review.org

THE AMR INNOVATION FUND IS AFFORDABLE

Annual pharmaceutical revenue and expenditure on key areas for the ten largest pharmaceutical companies, billion US dollars



Source: GlobalData, via BBC News (http://www.bbc.co.uk/news/business-28212223)

Review on Antimicrobial Resistance

A well-resourced Innovation Fund can complement the long term research being funded by established science funding bodies. Their track record in commissioning high quality research has often been outstanding, with barriers between industry and academic researchers increasingly being broken down to support collaborative innovation. But a new fund has the potential to go even further, faster, by more actively commissioning and guiding research where it identifies neglected opportunities. A new type of body, agile and proactive in its approach and borrowing from the best examples of major philanthropic organisations such as BMGF and the Wellcome Trust, has the greatest potential to fill the critical gaps.

The sums involved are comparatively small and should be committed for a time-limited five-year fund to begin with

Research of this type is high risk compared with other stages of drug discovery, but also has the advantage of being much lower cost. Projects at this level may require funding in the order of as little as tens or hundreds of thousands (and no more than the low millions) of dollars – amounts which are minimal in the grand scheme of pharmaceutical R&D, but for the lack of which many valuable projects fail to get off the ground.

This means that relatively limited sums of money, if made readily accessible to researchers, have the potential to go a long way. Two of the most significant sources of public research funding internationally, the US NIH and European Commission, currently between them spend approximately 425 million USD annually on AMR-related research, funding which is the lifeblood of early-stage activities in the field. Set against this, we believe that the same sum again – approximately 2 billion USD of new money over five years – has the power to support a transformation of the global AMR research landscape.

And as long as the market incentives for antibiotics R&D are fixed and private capital flows back into the area (see below), this innovation fund should not need to exist in perpetuity. Five years of extra, targeted multi-year funding of this type could be sufficient to re-invigorate the research space over a total of 10 to 15 years, to such an extent that it is no longer required over the longer term.

Global pharmaceutical companies should play a part in contributing to this new fund

We recommend that the global pharmaceutical industry should pay for this new AMR innovation fund and to contribute its technical expertise to it. This is in the industry's own interest and it is a balanced way of funding AMR research, given the significant interventions proposed previously to prop up the market for new antibiotic therapies.

Antibiotics underpin many areas of modern medicine: cancer chemotherapy, organ transplants and many surgical procedures all depend to some extent on the availability of effective antibiotics to provide protection from infection to vulnerable or immunosuppressed patients. So the pharmaceutical industry as a whole has a stake in ensuring that the world has a sustainable supply of new and effective antibiotics: the long-term profitability of other therapies is compromised by the rise of antibiotic resistance.

So it is reasonable to look to major pharmaceutical companies to look beyond their immediate commercial interests and contribute to the creation of an AMR Innovation Fund. Over five years, a Fund of 2 billion USD would amount to 0.6% of the top ten pharmaceutical companies' global R&D spending; and less than one tenth of a percent of their total revenues. The level of share buy-backs in the industry over recent years is indicative of its remarkable success in generating high levels of return, and suggest that there is scope to adopt an approach which allocates greater funds to R&D activity which may not be immediately lucrative but which is of long-term strategic value[17]. The AMR Innovation Fund will close a critical gap by supporting critical R&D which the world needs, while creating new commercial opportunities in the medium term: companies providing funding are themselves then ideally placed to benefit directly by taking on and advancing the discoveries and breakthroughs that the Fund has the potential to generate.

> *"A new fund has the potential to go even further, faster, by more actively commissioning and guiding research where it identifies neglected opportunities"*

17 *See Buy Back or Pay Forward?*, by Jim O'Neill for Project Syndicate, May 6 2015 - http://www.project-syndicate.org/commentary/pharmaceutical-buybacks-research-by-jim-o-neill-2015-05

5.

MID-STAGE INTERVENTIONS: OILING THE GEARS OF ANTIBIOTIC DEVELOPMENT

The two large-scale interventions proposed above are critical: without them the supply of new antibiotics will not be sufficient.

But there are further things that can be done that do not require direct subsidies to drug development but which have the potential to significantly lower the cost and risk of developing new antibiotics.

There are many small ways that the cost of researching and developing new antibiotics could be reduced. Although such measures are often individually not substantial, collectively they have potential to make it easier for developers of all types to bring new antibiotics onto the market. This list is not exhaustive, and we will continue to explore innovative ways to reduce costs that do not harm patients or society at large.

Harmonising and simplifying the drug approval process globally

With the exception of EU member nations, almost every country in the world requires new antimicrobials to be registered individually with them. This means that a company developing a new product would need to file registrations and pay fees in up to 170 different jurisdictions if they wanted to achieve global market access. This is an expensive and slow procedure that costs money and requires considerable expertise and manpower, while hindering access in many countries and reducing the accessible market size for companies.

The European Medicines Agency (EMA) and the FDA have already done much to align and streamline their approval procedures for antimicrobials to make it easier for drug companies; we applaud this and hope to see it go further. But we believe that more could be done to provide mechanisms to allow developers to register their antimicrobials in multiple regions at the same time, comparable to the 'rapporteur' approach led by the EMA in Europe. As with the EMA this would require strong engagement from individual countries, who would need to retain their own responsibilities for domestic pharmacovigilance, as well as the capability to register drugs individually if they wish.

We believe that such a system would mean that pharmaceutical companies could look at a wider range of markets – not just a handful of the most affluent – when making investment decisions about antibiotic development, increasing their predicted profits and improving a project's viability. Furthermore, such an approach has the potential to save the governments involved money, by avoiding costly duplication of approval processes and directly supporting market access in poorer regions.

Maintaining a robust and safe approval process is obviously crucial: regulatory harmonisation should mean convergence to the standards of the best processes globally, not simply those with the lightest touch. But benefits could be realised by strengthening existing mechanisms within, for instance, the WHO, to get countries to co-operate more closely on the approval of new antimicrobials, and allowing others to sign up to the system.

A greater role for public bodies in facilitating clinical trials

Clinical trials are by far the most expensive part of the research and development process. Reducing the cost of trials would make it much easier for smaller firms in particular to take drugs to market. However clinical trials play a vitally important role in making sure that drugs are safe and effective. A lot of work to streamline the design of clinical trials for antibiotics so that they are not unnecessarily burdensome has already been done by the FDA, EMA and other regulators, addressing significant problems (many particular to trial design for anti-infectives) which once undermined the development process.

However, one area where we see room to further reduce the cost of clinical trials without reducing their safety or efficacy is by having governments and health systems more actively and intelligently facilitate clinical trials. The National Institute for Health Research (NIHR) already does much to support this in the English NHS, and the Indian Open Source Drug Discovery has tapped into their public healthcare system there in similar ways. We think there should be more of these kind of schemes where drug companies can take advantage of the infrastructure and knowledge of healthcare providers to run trials more efficiently. Even if these two groups just work more closely to identify and enrol trial patients, this could be significant in reducing research costs. Active engagement in clinical research by healthcare providers is in turn often associated with higher quality care for their patients – meaning that health systems,

and not just industry, stand to benefit from establishing, and strengthening relationships of this type.

From what we have seen is there is some appetite within both the private and public sectors to work more closely with one another, but this is sometimes hampered by cultural and practical barriers to inter-organisational working.

Breaking down barriers to share ideas and research

Commercial research is often undertaken amidst great secrecy, as companies seek to prevent their rivals from gaining potentially valuable information about the work it is doing. This can lead to wasteful and avoidable duplication of effort, for instance where two companies research very similar areas unsuccessfully, with neither company aware of the other's activities and failures. There is scope for early-stage research to become more efficient, by embracing opportunities to reduce wasteful overlap and duplication, and guide companies on the best practice for research.

The Medicines for Malaria Venture (MMV), for example, has successfully helped to streamline malaria research by having organisations register the research projects they want to do. If something has already been done, without success, then the researchers will be told and can direct their efforts and resources elsewhere. Something similar to MMV's system could work well for antibiotics, whereby companies have an incentive to share as much detail as possible about their research efforts in order to see if it has been or is being done elsewhere.

6.

THE COSTS OF TAKING ACTION

We have estimated the cost of our proposals on the basis of a pipeline achieving 15 new antibiotics a decade: this would radically overhaul the current situation and allow us to keep pace with the development of antibiotic resistance. To be effective and properly balanced, this pipeline would ideally comprise:

- Two novel and two follow-on broad spectrum products which meet a societal need;
- Two novel and two follow-on narrow spectrum products which meet a societal need;
- Approximately seven further drugs that provide an incremental but nonetheless clinically useful improvement on existing antibiotics.

Using the estimated development costs outlined in Section 3, we calculate that a buyout model which adequately rewards and incentivises the developers of these 15 products would cost as little as 16 billion USD or no more than 37 billion USD over a decade. The higher figure is based on the full 'global payer buy out model' of having a single global body buy out the sales rights for all new useful antibiotic therapies. We expect that considerations about the implementation and risks around such a system will steer a future incentive package towards something more akin to the hybrid model set out above. On this basis, the upfront investment required is more likely to be nearer the hybrid model buyout price of about 15 billion USD.

On an annual basis, this amounts to paying between 1.6 billion USD and 3.7 billion USD a year globally to provide the required 'pull incentives' for new antibiotic therapies, which is between 0.002% and 0.005% of global GDP. The work we did to estimate the global cost of antimicrobial resistance in December, showed that drug-resistant bacterial infections alone could reduce the world's GDP by 2.24% by 2050[18]. Resistant infections are already estimated to impose direct excess costs on the US healthcare system of 20 billion USD a year, a figure that we expect to rise substantially if necessary action is not taken.

It is also worth noting that paying more money earlier on will reduce the amount of money health systems spend on buying antibiotics, thus even in the global payer system the total 'net' cost would be lower than 37 billion USD (see box on 'What to pay, and when'.)

Currently the global market for antibiotics stands in the region of 40 billion USD. Despite having the potential to transform the global supply of effective antibiotics, the packages of intervention which we propose here would amount to a one-off increase in this global spending of between 4% and 9% per annum, over the course of 10-15 years. We do not believe that this is excessive when compared to historical growth trends in health care more generally, or to the 6-8% annual growth rate that the market for cancer drugs (already worth 100 billion USD globally) is projected to achieve over the next three years[19].

The costs of supporting antibiotic development are nominally significant; but they are in fact modest when set against either the costs of failing to act on AMR, or the amounts already spent on antibiotics and pharmaceuticals globally.

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18 *Antimicrobial resistance: Tackling a crisis for the health and wealth of nations*, published December 2014 and available at www.amr-review.org

19 *Global spending on cancer drugs surges to $100bn*. Financial Times, May 5, 2015.

7.

OUR NEXT STEPS: MOVING FROM IDEAS TO ACTION

We believe that the case for intervention to stimulate the development of new antibiotics is clear. Although the development pipeline of new drugs is by no means entirely empty, there is a concerning gap between what the market currently provides, and the areas of the most critical medical need. Would-be developers of new antibiotics are deterred from investing not because of the absence of unmet need but because of the extreme uncertainty associated with the peculiar dynamics of the antibiotics marketplace.

With a carefully-chosen set of interventions, though, this uncertainty can be overcome, in a way that delivers the new generations of antibiotics that we so badly need whilst balancing the commercial interests of drug developers and the conservation needs of society as a whole. Doing so is a complex task, requiring international cooperation between governments and industry, but the lessons learned in stimulating the development pipelines for HIV/AIDS, TB and malaria treatments over the past two decades prove that it can be done.

This is a starting point, rather than an end point

We would like this document to stimulate a discussion around the models that could be used to successfully reinvigorate the antibiotics pipeline. We would welcome feedback and discussions with interested parties who can help us build on this work, ahead of our final recommendations by the summer of 2016. Most importantly, though, we want to use this and future papers to begin building global support for concrete action on this issue as well as a wider package of action to tackle AMR.

Action to stimulate the drugs pipeline may be crucial – but is far from the whole solution

The supply of new drugs is an important part of the problem, but there are equally important problems on the demand side which we will seek to address in our forthcoming work. It would be nonsensical to take bold steps to stimulate the development of new generations of drugs without matching this with action to ensure that they are not misused and squandered in the way that preceding generations have been. Inappropriate and unnecessary use of antimicrobials increases the speed at which resistance develops, exacerbating the human and economic costs of AMR. This serves only to place more pressure on the supply side, as we need a higher flow of new drugs through the development pipeline to replace those existing ones as they become ineffective.

We will provide analysis and recommendations on how to improve this including looking at the following areas:

- **Ways to improve antibiotic use in humans.**
  - Rapid diagnostics are often discussed but we think more can be done to accelerate the progress of these tools and put them into the hands of clinicians. This would give them more data with which to make their prescribing decisions and help cut unnecessary use.
  - Surveillance of drug-resistant infections needs to be improved. The 195 million GBP announcement in March by the UK Government of the establishment of a 'Fleming Fund'[20] to improve surveillance in developing countries was a significant step in achieving progress on this front. However, we also need to consider how diagnostics can play a role in improving surveillance by getting the best use out of the data which they collect – embracing the full potential of the 'digital revolution' in doing so.
  - Global public awareness of AMR is not good enough. Everyone can play a role in tackling AMR by not demanding and using antibiotics when they are not needed.
- **Agriculture and the environment.** A large proportion of the global consumption of antibiotics is from the agricultural sector. We will be producing a paper looking at the economic impact of antibiotics on the agricultural sector, and also considering the wider impacts of antibiotic use and wastage in the environment.
- **Alternatives to antibiotics**. Although antibiotics have become the dominant treatment for infections and will continue to play a key role, there are other opportunities to tackle infection that we will explore. This will include the economic case for examining the use of vaccines, phage therapy, ways to use the body's own immune response, amongst other areas.
- **Preventing and limiting the spread of infections.** Prevention removes the need for therapeutic treatment, whether it is antibiotics or an alternative therapy. There are simple ways we can improve this, such as by washing our hands better, but there are also bigger challenges to address, including improving sanitation and health infrastructure – including systems to ensure safe food and drinking water supplies – in many countries across the world.

Moving the battle against AMR forwards

AMR is one of the biggest health threats the world faces but with coordinated international action we are confident that it can and will be solved. Addressing this problem will cost the world less than 0.1% of global GDP. A major part of this cost will be the package of spending – estimated at between 16-37 billion USD – that we have discussed in this paper to provide a stable end market for new antibiotics, and incentivise the development of the new drugs we desperately need. This is a tiny fraction of the potential 100 trillion USD cost of inaction, not to mention the additional ten million lives that could be lost every year.

The moral case for action has been stark for a long time but we can confirm that the economic case for action is just as stark. We hope that this work will be considered by world leaders and health experts at the World Health Assembly and elsewhere, and that it will provide a solid basis for a continued push for practical, global action on AMR.

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20 See http://www.wellcome.ac.uk/News/Media-office/Press-releases/2015/WTP058933.htm

APPENDIX A:

COSTING A PACKAGE OF PULL INCENTIVES FOR NEW ANTIBIOTICS: WHAT AND HOW MANY DRUGS ARE NEEDED?

Overview

This summary has been prepared by the microbiology adviser to the Review, and used as the basis of consultation with clinical experts about the extent of the unmet clinical need for new antibiotics. On this basis, it is proposed that the Review on Antimicrobial Resistance should model the investment needed to achieve about 15 licensed antibiotics per decade, comprising at least two new broad-spectrum classes of antibiotic (appropriate for empirical prescription) and two new targeted therapeutic classes of antibiotic (appropriate for diagnostic based prescription) every ten years, that address unmet medical needs.

The cost of ensuring that the medical equipment market will develop the rapid diagnostic tools that are needed will be considered and costed separately. Consideration will also be given to whether the combination of existing drugs, revival of abandoned compounds or the discovery of 'resistance breakers' should be considered separately or as part of the same package.

1.

Background

To estimate the cost of action to stimulate the antibiotics pipeline, it is necessary to estimate what and how many drugs are required as a priority to start tackling the problem of antibiotic resistance.

This is what this note aims to do, focusing solely on antibiotics (i.e. it does not consider antivirals, malaria drugs or TB drugs). Needless to say, the estimate in this note is based on what we know today – obviously a breakthrough in science or a step change in resistance would make a big difference. Finally, new drugs, or even new drugs and rapid diagnostics, aren't the final answer to AMR: the Review will publish further work on recommendations and implementation costs in areas such as alternative therapies to antibiotics including vaccines, the use of antibiotics in agriculture, and investment in infection control and better sanitation. When we reach our final recommendations, we may find that the value for money of spending more money

on drugs is lower than spending the same amount on other areas such as infection control or vaccines or finding novel therapies. In this case we will adjust our recommendation on spending based on an overall package aiming to deal with AMR as an ecosystem.

2.

Defining the key unmet needs at the moment

Bacteria can be divided very broadly into just two categories, called Gram-positive and Gram-negative. The distinction is based on their ability to retain a stain that is used to make bacteria more visible under the microscope. Gram-positive and Gram-negative bacteria have different types of cell wall, which is the barrier that most antibiotics must cross before they can reach their critical targets in bacterial cells.

Gram-negative bacteria have an extra layer to their cell wall (an 'outer membrane'), which is not present in Gram-positive bacteria. This additional barrier makes it harder for antibiotics to penetrate Gram-negative bacteria. Gram-negative bacteria also have another line of defense called efflux pumps, which help remove antibiotics before they can reach toxic levels inside bacterial cells.

So some of our existing antibiotics work only against Gram-positive bacteria either because they cannot get into Gram-negative bacteria (the antibiotic molecules are just too big to get through the outer membrane) or because they are pumped out very effectively.

In the 1980s and 1990s, there was significant industry focus on discovering new anti-Gram-positive agents, prompted by rising concerns about methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) in hospitals. As a result, a number of 'new' antibiotics have been launched in the last 15 years or so to fight 'Gram-positive infections'.

However, in the 2000s we started to witness the emergence and spread of AMR in Gram-negative bacteria, and this has become a worsening global problem. There is international consensus that Gram-negative bacteria are the key group for which we desperately need new antibiotics.

Gram-negative bacteria make up 5 of the 7 so-called 'ESKAPEE' pathogens, which collectively cause a majority of healthcare associated infections; bacteria like ***K**lebsiella pneumoniae*, ***A**cinetobacter baumannii*, ***P**seudomonas aeruginosa and **E**nterobacter cloacae*, which can cause infections ranging from urinary tract infections (UTI) to potentially life-threatening pneumonias and bloodstream infections. AMR is not just a threat in hospitals, but is also a growing concern in Gram-negative species that cause community infections, including the commonest cause of UTI (***E**scherichia coli, a.k.a. E. coli)* and the species that causes the sexually transmitted infection, gonorrhoea (*Neisseria gonorrhoeae*).

The unpredictability of discovering new antibiotics, coupled with long development times and high attrition rates means that science and the biotech / pharma industry cannot react rapidly to new or emerging resistance threats. Furthermore, it is generally accepted to be harder to develop new antibiotics that are active against Gram-negative bacteria than to develop anti-Gram-positive agents.

So although AMR has been increasing in Gram-negative bacteria for the last decade or more, the antibiotic development lag means that we are still waiting for an arsenal of new anti-Gram-negative agents to combat infections caused by these latest resistant bacteria. This is why there is so much current concern about untreatable infections. The most multi-resistant Gram-negatives are so resistant that it is almost impossible to prescribe an appropriate empiric therapy in some cases (e.g. carbapenem-resistant bacteria in blood).

New broad-spectrum agents are urgently needed and must be active against a range of bacterial species and overcome a wide variety of existing resistance mechanisms. These new drugs would increase the chance that empirically prescribed therapy would be appropriate even when an infection is caused by bacteria resistant to our current antibiotics.

However, broad-spectrum agents are not a panacea; they are more prone to encourage resistance to develop in many different bacteria. Reducing the need for or length of empiric treatment is a goal we must aim for. To act on this strategy we need a new generation of fast and accurate diagnostics to detect a bacterial infection, to identify the species causing it, and unquestionably to predict or measure susceptibility so that the prescriber can be confident that they can use a narrow-spectrum agent effectively.

This means that **we also need new narrow-spectrum agents** that are active against particular bacterial species or against bacteria with established and emerging resistance mechanisms of public health importance (e.g. resistance to carbapenems or colistin)[21].

3.

What is currently in the pipeline ?

There is no single list of new agents in development that is complete, but the Pew Charity Trust list is updated regularly and gives a good indication of breadth.

Between May and August 2014, two new glycopeptides and one new oxazolidinone were licensed, but these are all anti-Gram-positive antibiotics.

More recently (since December 2014), two new cephalosporin/beta-lactamase inhibitor combinations have been licensed by FDA, with European licensing likely later this year. Importantly, these have activity against selected Gram-negatives.

Of eight agents listed in Phase 3 development (December 2014 list) two are specifically for *Clostridium difficile* infections (a Gram-positive), but five have activity against Gram-negative species.

Nevertheless, resistance problems exist already even for some of these unlicensed late-development agents. Plazomicin, for example, is a new aminoglycoside antibiotic that overcomes most aminoglycoside resistance, though not when it's caused by enzymes called 16S methyltransferases. These modify the targeted ribosome and make bacteria resistant to plazomicin. Unfortunately these enzymes are found regularly in bacteria that have NDM carbapenemases and in some prevalent types of carbapenem-resistant *Acinetobacter baumannii.*

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21 For some infections (e.g. gonorrhoea), over-treatment is widespread standard practice to avoid undertreating the minority of patients with infections caused by resistant bacteria. **New antibiotics are needed to treat resistant gonorrhoea**, but we need to be more targeted in our therapeutic approach. Universal switching to another new agent is a time-limited strategy that is doomed to be beaten by resistance and will demand yet more new antibiotics. Better and faster diagnostics would allow tailored treatment to be prescribed at the time of presentation, based on what the infecting bacteria are susceptible to. And this might be abandoned drugs (at least for treatment of gonorrhoea) like penicillin or ciprofloxacin.

This illustrates the fact that resistance to any new antibiotic is inevitable.

The take home message is that there are no new classes of antibiotic on the horizon that will solve our current AMR problem entirely; some novel compounds are not active against all relevant bacterial species, while others cannot overcome all of the resistance mechanisms that exist.

We will continue to need new agents. The key questions will remain: will resistance emerge in the targeted bacterial species?; how quickly will resistance emerge?; and will resistance be transferable between different bacteria with potential to accelerate spread greatly?

4.

What drugs should be on the priority wish list?

(i)

New antibiotic classes

We need a regular and sustainable stream of genuinely new classes of antibiotics with novel mechanisms of action (MOA) and activity against multi- and pan-resistant strains, which are faced already e.g. Gram-negatives that have metallo-carbapenemases, aminoglycoside resistance due to 16S methyltransferases, tigecycline resistance through efflux and colistin resistance through membrane alterations.

Beta-lactamase inhibitors currently in development do not affect class B enzymes such as the NDM, VIM and IMP carbapenemases. A 'work around' treatment for infections caused by bacteria with these enzymes may be offered eventually by the combination of avibactam-aztreonam (phase 1), but a direct inhibitor of class B carbapenemases would be needed to restore susceptibility to carbapenems reliably.

A broad-spectrum beta-lactamase inhibitor active against any class A, B, C and D beta-lactamase would be the 'holy grail', but is unlikely to be achievable due to the biochemical diversity of the enzymes.

Alternatives are needed for other antibiotic classes threatened by resistance in key or multiple bacterial species.

(ii)

Changes to attitudes and behaviours

Ultimately, new antibiotics do not need to be used widely if older agents remain active against the infecting bacteria and offer reliable alternatives. Future antibiotics therefore should be better targeted to encourage use only when needed to overcome resistance. Better diagnostics are essential to tell us when this is the case.

Therefore there needs to be wide acceptance that rapid diagnostics are a key component of improved antibiotic stewardship, by preserving the antibiotics that we have and by allowing rational prescribing of new antibiotics.

5.

What numbers are needed?

The 2014 English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR)[22] report shows that just 19 antibiotics (belonging to fewer antibiotic classes) currently account for >88% of all prescribing in hospitals and community, and none of these is a recent discovery.

If each new future drug is viewed as a well-guarded resource accessible to all but used only when dictated by resistance, rather than as a potential market blockbuster then a regular supply of two to four licensed 'first in class' compounds per decade would give opportunity to stay ahead of resistance to preceding classes if it arises.

On this basis, we propose that the paper should model the investment needed to achieve about 15 licensed antibiotics per decade, with a funded package of incentives that can cover the cost of at least:

- **two new broad spectrum** classes of antibiotic every **ten** years (appropriate for empirical prescription) that address an important and unmet medical need; and

22 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/362374/ESPAUR_Report_2014___3_.pdf

- **two new targeted therapeutic classe**s every **ten** years (appropriate for diagnostic based prescription) that address an important and unmet medical need.

The remainder of the new drugs over the decade would be 'follow on' compounds offering some, perhaps substantial, improvements. They would not necessarily need to be funded in the same way via the new market incentive offered for new classes as there may be sufficient return on investment as it is. However their use would need to be regulated to minimize the rise of resistance.

The cost of ensuring the medical equipment sector would develop the needed rapid diagnostic tools will be considered and costed separately. Consideration should also be given to whether the combination of existing drugs, revival of abandoned compounds or the discovery or repositioning of 'resistance breakers' should be considered separately or as part of the same package. The answer will likely depend on whether the resulting antibiotic–inhibitor combination is considered novel or not.

A pipeline of successfully licensed antibacterials of this magnitude would be better than we have had in the last 20 or more years. In that sense it can be considered to err on the ambitious side and could be fairly described as a higher end cost figure.

APPENDIX B:

FURTHER INTERVENTIONS WE HAVE CONSIDERED BUT CHOSEN NOT TO RECOMMEND IN THIS PAPER

To support our research into antibiotic development and market interventions to promote it, we commissioned two academic studies to undertake a full evidence review of the field. An analysis of the factors constraining antibiotic development was undertaken on the Review's behalf by the Innogen Institute at the University of Edinburgh, while a critical assessment of incentivisation strategies to support antibiotic development was undertaken by the Department of Social Policy at the London School of Economics. Both papers have been published to coincide with the release of this paper, and are available via our website, www.amr-review.org.

Between them, these two studies took a comprehensive view of the problems associated with antibiotic development, and the myriad possible solutions to this discussed in academic and non-academic literature. Not all of the issues identified by these studies can be covered in this paper, but a number of key areas of intervention – including adjustments to intellectual property legislation – feature prominently in the discourse around this topic. There are three such proposals which we believe do not represent effective solutions to the problems of the antibiotics pipeline, but which warrant further discussion here.

Changes to the patent system

In many sectors of the economy, patents are an important statutory means of stimulating innovation, protecting the exclusivity – and thus profitability – of a new product for its inventor for a defined period. The pharmaceutical sector is no exception, with patents on 'blockbuster' drugs ensuring enormous profits for the companies which bring them to market. As such, changes to the patent system are frequently held up as being a potentially powerful means of stimulating antibiotic development.

Simple extensions to patent life are sometimes proposed as a means of encouraging pharmaceutical innovation, on the basis

> *"Patent life extensions do little to improve cash flow projections in the face of uncertainty, and represent poor value for money"*

that they improve the expected profitability of a drug for its developer. However, while such an intervention would be simple, it would most likely be ineffective in the case of antibiotics.

Firstly, it will do little to stimulate investment in antibiotics, where the most significant factor impeding development is the limited and highly uncertain size of the market for end products. Secondly, the way in which companies developing drugs discount their future projected cash flow means that a future increase in profitability provided by a patent extension is far smaller in value than the actual costs incurred by society through higher drug prices.

Using data provided to us by pharmaceutical companies and by IMS, we calculate that under current market conditions a two year patent extension for a typical antibiotic would protect on-patent sales worth 450 million USD[23]. However, the higher discount rate used by private companies means that these additional societal costs translate to an increase in their estimated net present value of just over 70 million USD at the point at which they make an initial investment decision. This means that every dollar 'spent' by society on providing a patent extension translates to less than 16 cents of additional anticipated future profit for the drug developer when making a long-range investment decision.

23 Review's own calculations; data provided courtesy of IMS HEALTH UK, and selected companies' antibiotics sales data and projections. Assumes typical government discount rate of 3.5%

Transferable patent vouchers – potentially a powerful incentive, but highly inefficient

We have also heard a number of calls for the use of so-called 'wildcard' patent extensions in the antibiotics field – whereby the developer of a qualifying antibiotic product would be awarded a voucher for, say, two years of additional market exclusivity, which can be applied to any product still under patent. This can be used by the company to which it is awarded, or sold on an open market. We believe that such vouchers would be lucrative for their holders, but inefficient and unnecessarily costly as a policy tool for stimulating antibiotic development.

Such schemes are sometimes presented as a 'low cost' way to raise a lot of money. However this is not true. Extending the patent term for another drug will keep the price of that drug far higher than they need to be – costs which may not be immediately visible but will nonetheless be borne directly by governments, insurers and patients. The fairness of funding antibiotic development through what is essentially an uncontrolled charge upon other treatment areas is highly doubtful.

It is not clear exactly how much a patent extension voucher would be worth, but a 2007 study[24] estimated that extending patent protection of the 10 highest selling drugs by two years would result in excess costs to the US healthcare system of 40 billion USD – equating to a cost of 4 billion USD through each antibiotic rewarded by the system. This would create an enormous revenue stream for pharmaceutical companies, but at a cost far greater per drug than other equally effective interventions to the pipeline.

But that said, the value of an individual voucher will be unpredictable, varying considerably based on how big the sales for the market leading drugs that are near the end of their patent are. This means that the funding is less reliable and that firms will earn differing amounts of money for something that is beyond their control. This volatility also has the potential to harm generic entry.

In summary, interventions which stimulate antibiotic development more directly – with reward linked transparently to the value and efficacy of the antibiotic produced – offer fairer, cheaper, more efficient and more transparent means of achieving the same end.

Priority regulatory review vouchers

In the past, steps to stimulate drug development in given areas have – particularly in the US – focussed on the role of an expedited review process to make it quicker, cheaper and easier to bring products to market. Initiatives for neglected tropical diseases and paediatric conditions have extended this concept to consider the role that transferable priority review vouchers can play – i.e. a 'ticket' for a priority review by the FDA which is earned by producing a qualifying product but which can be transferred or sold for use with any other drug.

Although neither the market distortions nor the marketable value are as great as those associated with the proposed comparable model of transferable vouchers for extended patent exclusivity, we believe that there is limited scope for further use of these to drive antibiotic development.

Firstly, the sums of money which such vouchers would generate for recipients are likely to be insufficient by themselves to offset the financial risk and uncertainty associated with antibiotic development. Secondly there is worrying potential for gaming. Even where qualifying criteria are well-defined, such a scheme can readily lead to a drug that has low societal value 'skipping the queue' and thus slowing down approval for drugs in other areas where the unmet clinical need is greater. Finally, in practical terms the burgeoning number of priority review schemes in use mean that the true value of 'priority' status risks being undermined: 56% of drugs approved by the FDA in 2012 received some sort of expedited approval, with nearly a quarter qualifying for two or more different schemes. This may be indicative of the success of priority review vouchers in stimulating drug development in important areas, but points to there not being significant scope to take the initiative further.

Adjustments to reimbursement systems

We have also explored areas where health system reimbursement arrangements may create perverse incentives, or undermine the functioning of a healthy market for antibiotics. There are obviously wide variations across the world, but some common themes.

Many health systems, for instance, have adopted tariff-based systems of reimbursement which see hospital providers paid a lump sum for a patient episode, depending upon that individual's

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24 Outterson K, Samora J B, Keller-Cuda K. Will longer antimicrobial patents improve global public health? The Lancet Infectious Disease 2007; 7: 559-566

symptoms and the treatment. All inpatient costs, including diagnostics and medication, are bundled into a single tariff price for a given 'diagnosis-related group' (DRG). Such systems are a popular – and largely effective – means of promoting efficiency and cost-control within healthcare systems.

However, for patients with bacterial infections (particularly where these are acquired within the hospital), the cost-control pressures associated with tariff-based reimbursement enforce existing incentives for hospitals to resist using more expensive (but possibly more effective) antibiotics rather than generic ones in treating the infection.

Calls have been made to either make DRG reimbursement more generous for bacterial infections; or to 'unbundle' novel antibiotics from the DRG entirely and reimburse providers separately for their use – as is done with some 'high cost' drugs and technologies already. We believe that there may be merit in exploring such an approach for antibiotics to help support the market for new, high quality products which offer clear benefits to patients. We look forward to hearing, and contributing to, the emerging policy discussions – particularly those being led by policy-makers in the US – about the potential that changes to reimbursement systems like this offer. But there may be limitations to the effectiveness of such an approach: the additional payment may not be passed on to developers via higher prices, for instance, and there are risks that it may undermine good infection control and antibiotic stewardship practices within hospitals.

APPENDIX C:

MODELLING THE ANTIBIOTIC DEVELOPMENT PROCESS

In order to quantify the effects that different types of incentive would have on the development pipeline for antibiotics, we developed an economic model of the drug discovery process. This builds on similar efforts previously by the Eastern Research Group (ERG) in the US[25], and the Office of Health Economics in the UK.

Our model is not intended to perfectly represent the highly complex drug discovery process, as obviously each drug and company will be different. However, it was designed to help determine the relative effectiveness – and cost effectiveness – of different policy interventions to stimulate antibiotic development.

Cost and revenue assumptions

In gathering information for this process we sought data on typical costs of the antibiotic development process (including marketing, manufacturing and regulatory costs) from a number of sources:

- IMS Health UK;
- a literature review;
- large and small pharmaceutical companies.

Data on typical estimated antibiotic sales volumes and revenues were provided by companies. We understand that both costs and revenues will differ significantly by drug, but worked with the companies to establish ranges that would reflect what typical development costs and patterns of sales could be expected to look like[26].

Non-cost development assumptions

The model's underpinning assumptions for factors other than development costs and revenues were defined on the following basis:

- Based on the ERG report and academic literature, we assumed that the annual discount rate used by a company would be 11%.
- The typical duration of each phase of the R&D process came from information we were given from pharmaceutical companies and ERG.
- The probability of success of each stage of development was based on research commissioned from IMS Health (on observed rates of success), and those assumptions used by the ERG modelling. In our base case we used an average the two. We felt that the IMS data may overstate the probability of success in the development of novel classes of antibiotics because most of the drugs in their sample were follow-on products (reflecting patterns of antibiotic research in recent years.)[27]

What the model does

We have made the model available in Microsoft Excel format via our website, www.amr-review.org

First, this model allows the user to choose a high, medium or low setting for all the assumptions on R&D cost, probability of success and discounting rate. Depending on these settings, the implied cost of buying out the patent of a drug changes, as does the cost of rewarding the drug developer at the end of the development process.

Secondly, the model also allows the user to assess the impact of different interventions on the total cost of drug development.

Thirdly the model looks at the cost of a complete market buyout where drugs are then sold at cost and a hybrid model where there is a lump sum as well as sales.

25 Sertkaya et al 2014

26 Several companies generously shared data on development costs and sales projections which they regard as commercially confidential. This has been invaluable as part of the modelling process, but we are limited to publishing this data on an aggregated and non-identifiable basis.

Summary of inputs

Outlined here are the inputs used in our model.
These assumptions are based on the sources outlined above, and represent what we believe is currently spent on typical development projects in these areas.

Length of trials

Phase	Length of trials	Time between phases
Preclinical	5 years 6 months	none
Phase one	11 months	3 months
Phase two	1 year 1 and a half months	6 months
Phase three	1 year 10 months	6 months
Approval	9 months	none
Post-approval paediatric and follow on trials	3 years	none

Probability of success

	Base case assumption (average of two)	ERG modelling assumptions	IMS observed data
Preclinical	17.3%	35.2%	9.3%
Phase one	33.0%	33.0%	33%
Phase two	59.3%	50.0%	75%
Phase three	75.8%	67.0%	85.7%
Approval	79.7%	85.0%	75%

27 IMS data may also exclude some preclinical stage failures, leading to a tendency to overestimate the probably of early stage success. However we felt that this bias may be offset by the exceptionally high rates of failure of antibiotic discovery based on genomic screening, which may account for a disproportionate number of projects in their sample.

Cost of research costs

	Base case assumption	Lower bound estimate	Upper bound estimate
Preclinical	$10,688,946	$10,033,419	$12,814,435
Phase one	$10,072,046	$6,982,404	$15,082,141
Phase two	$26,312,760	$17,273,318	$47,221,654
Phase three	$96,295,600	$64,919,901	$117,874,527
Post-approval paediatric and follow on trials	$146,295,599	$114,919,901	$167,874,527
Notes	Based on average inputs from eight sources	This was the 25th percentile from the inputs	This was the 75th percentile from the inputs

Other costs

Approval fees	$3,676,466
Marketing costs (for life of drug)	$401,000,000
Basis	Based on a literature review and discussions with industry experts

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However, please note that the views and opinions expressed in this report represent those of the Review on Antimicrobial Resistance, and do not necessarily reflect those of the individuals and organisations named below.

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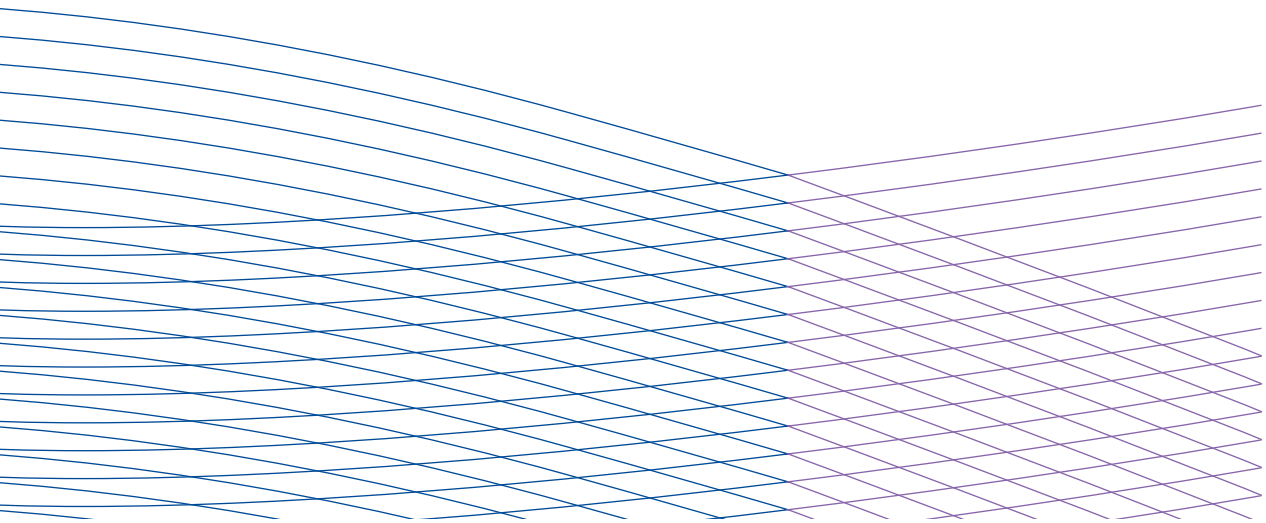
Review on Antimicrobial Resistance

Tackling drug-resistant infections globally



The UK Prime Minister commissioned the Review on Antimicrobial Resistance to address the growing global problem of drug-resistant infections. It is chaired by Jim O'Neill and supported by the Wellcome Trust and UK Government, but operates and speaks with full independence from both.

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