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Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

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ACRONYMS AND ABBREVIATIONS

AMC	Advance Market Commitment
AMR	Antimicrobial resistance
APIs	Active pharmaceutical ingredients
BARDA	Biomedical Advanced Research and Development Authority
CDC	US Centers for Disease Control and Prevention
CFCs	Chlorofluro carbons
DDD	Defined Daily Dose
DMS	Diagnostic Market Stimulus
DNDi	Drugs for Neglected Diseases Initiative
EMA	European Medicines Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	US Food and Drug Administration
FDC	Fixed Dose Combination
FIND	Foundation for Innovative New Diagnostics
G20	The Group of 20 (Argentina, Australia, Brazil, Canada, China, France, Germany, India, Indonesia, Italy, Japan, South Korea, Mexico, Russia, Saudi Arabia, South Africa, Turkey, United Kingdom and United States, plus the European Union)
G7	The Group of Seven (Canada, France, Germany, Italy, Japan, United Kingdom, and United States)
GARD	Global Antibiotic Research & Development
Gavi	Gavi, the Vaccine Alliance
GBP	British Pound
GDP	Gross domestic product
GHRF	Global Health Risk Framework for the Future
GHSA	Global Health Security Agenda
GLASS	Global Antimicrobial Resistance Surveillance System
HCAI	Healthcare-associated infection
IDA	International development assistance
IMI	Innovative Medicines Initiative
IPC	Infection prevention and control
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
MDR	Multi-drug resistant
MPP	Medicines Patent Pool
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSF	Médecins Sans Frontières (Doctors without Borders)
ND4BB	New Drugs For Bad Bugs
NGO	Non-government organisation
NIH	US National Institutes of Health
OECD	Organisation for Economic Cooperation and Development
OIE	World Organisation for Animal Health
OTC	Over-the-counter
PD	Pharmacodynamics
PK	Pharmacokinetics
PMDA	Pharmaceutical and Medical Devices Agency (Japan)
R&D	Research and development
SARS	Severe Acute Respiratory Syndrome
SDGs	UN Sustainable Development Goals
TB	Tuberculosis
UDR	Usual drug resistance
UK	United Kingdom
UN	United Nations
US	United States
USD	US Dollar
WHA	World Health Assembly
WHO	World Health Organization
3Ps	'Push, Pull, Pool' initiative for TB drug development

FOREWORD BY JIM O'NEILL

When I was asked to chair the Review on Antimicrobial Resistance (AMR), I was told that AMR was one of the biggest health threats that mankind faces now and in the coming decades. My initial response was to ask, 'Why should an economist lead this? Why not a health economist?' The answer was that many of the urgent problems are economic, so we need an economist, especially one versed in macro-economic issues and the world economy, to create the solutions.

I have very much kept this in mind ever since that first conversation and it has framed my team's approach.

It is now clear to me, as it has been to scientific experts for a long time, that tackling AMR is absolutely essential. It needs to be seen as the economic and security threat that it is, and be at the forefront of the minds of heads of state, finance ministers, agriculture ministers, and of course health ministers, for years to come.

As has now become widely cited, our very first paper outlined a world in 2050 where AMR is the devastating problem it threatens to become unless we find solutions. I deliberately chose 2050 as it is the same timeframe associated with the so-called BRIC (Brazil, Russia, India and China) inspired world that I became well-known for. We employed two consultancy teams, KPMG and Rand, to undertake detailed scenario analyses, which provided the basis for our conclusions. As is now quite well known, we suggested that without policies to stop the worrying spread of AMR, today's already large 700,000 deaths every year would become an extremely disturbing 10 million every year, more people than currently die from cancer. Indeed, even at the current rates, it is fair to assume that over one million people will have died from AMR since I started this Review in the summer of 2014. This is truly shocking. As well as these tragic human costs, AMR also has a very real economic cost, which will continue to grow if resistance is not tackled. The cost in terms of lost global production between now and 2050 would be an enormous 100 trillion USD if we do not take action.

> *"Indeed, even at the current rates, it is fair to assume that over one million people will have died from AMR since I started this Review in the summer of 2014."*

As with all forecasts of this sort, it is of course possible that our estimates may turn out to be too large, but we believe it is even more likely that they could be too small. This is because we did not even consider the secondary effects of antibiotics losing their effectiveness, such as the risks in carrying out caesarean sections, hip replacements, or gut surgery. And in the short 19 months since we started, new forms of resistance have emerged that we did not contemplate occurring so soon, such as the highly disturbing discovery of transferable colistin resistance, reported in late 2015.

Since setting out the scale of the problem if we do not act, we have been making recommendations on how we can avoid such a terrible scenario. Whatever the exact number, which of course we hope will never become a reality, the 100 trillion USD cost of inaction means that our recommended interventions are extremely good value for money on a relative basis.

There has already been some exciting progress since we began to set out our proposed solutions. In February 2015, we recommended that a dramatic boost in surveillance was needed to track resistance, especially in the emerging world. We are very pleased in this regard, that the UK government has initiated the ***Fleming Fund*** to improve disease surveillance focused on drug-resistant infections in low and middle-income countries, and has contributed 375 million USD to it. This work is incredibly important for tackling AMR and it must go hand in hand with the recent impetus to achieve truly effective global disease surveillance and to make sure that health systems are better prepared for epidemics.

We also recommended that more research funding is needed for AMR to kick-start early research into new antimicrobials and diagnostics. We are delighted that the UK and Chinese governments have each already agreed to contribute 50 million GBP (72 million USD) to a new ***Global Innovation Fund***. This Fund will need to grow internationally and partner with other existing sources of funding for AMR, to fill the gaps left by traditional funding streams and make sure existing and new funding streams are well coordinated for the benefit of researchers everywhere in the world.

It is greatly rewarding that many of our recommendations are already being taken forward, even before we published this, our final report. But so much more remains to be done over the rest of this year and the following years. We need to ensure that the appropriate global bodies are involved in reaching policy agreements, and I have spent considerable

time focusing on this over the last two years. Given my own background and the nature of the AMR challenge, it was obvious that the G20 Leaders as well as their Finance Ministers would need to play a central role, and we are pleased that the pieces are in place for successful progress. It is a historic opportunity for global governance that China is hosting the G20 in 2016 for the first time; it is in China's power to lead the world in tackling the AMR problem meaningfully and globally from their presidency onwards.

Four interventions are going to be particularly important, out of the 10-point plan for tackling AMR set out in our final report.

First, we need a ***global public awareness campaign*** to educate all of us about the problem of drug resistance, and in particular children and teenagers. I see this as an urgent priority and urge international campaign developers, industry experts, and non-governmental organisations to consider how they could help to support an urgent global campaign on AMR. I think this is something that could, and should, begin this summer if we are to really make progress on AMR, and it could be supported at the UN General Assembly in September.

Secondly, we need to tackle the supply problem: we need new drugs to replace the ones that are not working anymore because of resistance. We have not seen a truly new class of antibiotics for decades. It is in policymakers' hands to change this. We have recommended that countries must review carefully how they buy and price antibiotics, to reward innovative new drugs without encouraging unnecessary use of new antibiotics. In addition to this work at the national level, we need a group of countries such as the G20 to get together and provide for a reward to developers of new antibiotics after they are approved for use by patients. These ***market entry rewards***, of around one billion USD each would be given to the developers of successful new drugs, subject to certain conditions to ensure that the new drugs are not 'over-marketed' and yet are available to patients who need them wherever they live. It is great to see this idea already being discussed by senior G20 officials. I hope this discussion will translate into tangible action during their Heads of States' meeting in September.

Thirdly, we need to use antibiotics more sparingly in humans and animals, to reduce the unnecessary use that speeds up drug resistance. To do this, we need a step change in the diagnostic technology available. I find it incredible that doctors must still prescribe antibiotics based only on their immediate assessment of a patient's symptoms, just like they used to when antibiotics first entered common use in the 1950s. When a test is used to confirm the diagnosis it is often based on a slow technology that hasn't changed significantly since the 1860s. I can understand why this is the situation: there aren't enough good and rapid tests to confirm the professional judgment of the doctor, and the tests that are available are often more expensive than prescribing the drugs 'just in case'. Yet this is not acceptable: we need to encourage more innovation and, importantly, must ensure that useful products are used. I call on the governments of the richest countries to mandate now that by 2020, all antibiotic prescriptions will need to be informed by up-to-date surveillance information and a rapid diagnostic test wherever one exists. This will open the door to investment and innovation, by showing clever developers that if they build rapid tests they will find a market for them. Once the technology has improved, markets in developing countries can be supported with a system we have called a ***diagnostic market stimulus***, not dissimilar to the great work that Gavi, the Vaccine Alliance, has done to improve global child vaccination.

> *"I find it incredible that doctors must still prescribe antibiotics based only on their immediate assessment of a patient's symptoms, just like they used to when antibiotics first entered common use in the 1950s."*

Fourthly, we must reduce the extensive and unnecessary use of ***antibiotics in agriculture***. We first need to improve surveillance in many parts of the world, so we know the extent of antibiotic use in the agricultural sector. We have then proposed that targets should be set by individual countries for antibiotic use in agriculture, enabling governments to have the flexibility to decide how they will reach lower levels of use. Alongside this we need to make much faster progress on banning or restricting the use in animals of antibiotics that are vital for human health. I hope the United Nations meeting in September will take action on each of these points and make progress with the World Health Organization (WHO), Food and Agricultural Organization of the United Nations (FAO), and the World Organisation for Animal Health (OIE).

There are a number of ways to raise the funding required for action from the public or the private sector: the amounts are

very small in the context of both spending on healthcare and the costs of rising AMR if we do not act. Given that antibiotics are a shared resource that society and the pharmaceutical industry depend on, there is a strong case for pharmaceutical companies investing in AMR to sustain their own revenue from other sectors such as oncology or surgical operations. That is why I have proposed that governments should consider a small levy on the pharmaceutical sector, as one of the options to raise funding for the market entry rewards for new antibiotics. I would find such a funding mechanism particularly attractive if it could be applied on a 'pay or play' basis, where those firms who invest in R&D that is useful for AMR can deduct their investment from the charge owed by all players within the industry.

Although AMR is a massive challenge, it is one that I believe is well within our ability to tackle effectively. The human and economic costs compel us to act: if we fail to do so, the brunt of these will be borne by our children and grandchildren, and felt most keenly in the poorest parts of the world.

Chairing this Review has been one of the most stimulating things I have been lucky enough to do in my professional career, and in addition to many people to thank, I want to both thank and congratulate the UK Prime Minister, David Cameron, for having the foresight to establish this Review, as well as the UK Chancellor, George Osborne. I would also like to thank the helpful guidance of the Review's steering group – Dame Sally Davies, Dr Jeremy Farrar, John Kingman, Karen Pierce and Ed Whiting, as well as the enthusiasm of Dave Ramsden. And of course my Review team: Hala Audi, Jeremy Knox, William Hall, Anthony McDonnell, Anjana Seshadri, James Mudd, Nehanda Truscott-Reid, Olivia Macdonald, Dr Flavio Toxvaerd and Professor Neil Woodford.

May, 2016

EXECUTIVE SUMMARY

Following 19 months of consultation and eight interim papers, each focusing on a specific aspect of antimicrobial resistance (AMR), this report sets out the Review on Antimicrobial Resistance's final recommendations to tackle AMR in a global way, as commissioned by our sponsors, the UK Government and the Wellcome Trust.

The magnitude of the problem is now accepted. We estimate that by 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output are at risk due to the rise of drug-resistant infections if we do not find proactive solutions now to slow down the rise of drug resistance. Even today, 700,000 people die of resistant infections every year. Antibiotics are a special category of antimicrobial drugs that underpin modern medicine as we know it: if they lose their effectiveness, key medical procedures (such as gut surgery, caesarean sections, joint replacements, and treatments that depress the immune system, such as chemotherapy for cancer) could become too dangerous to perform. Most of the direct and much of the indirect impact of AMR will fall on low and middle-income countries.

It does not have to be this way. It is in policy makers and governments' hands to take steps to change this situation. Because microbes travel freely, some of the steps that are required will need to be taken in a coordinated way internationally. What is certain is that no single country can solve the AMR problem on its own and several of our proposed solutions will require at least a critical mass of countries behind them if they are to make a difference. Tackling AMR is core to the long-term economic development of countries and our well-being. Solutions to address it must have global access to healthcare at their heart and they must help us to stop wasting medicines that we rely on and yet are exhaustible.

To stop the global rise of drug-resistant infections, there is a supply and demand problem that needs to be fixed. The supply of new medicines is insufficient to keep up with the increase in drug resistance as older medicines are used more widely and microbes evolve to resist them. At the same time, the demand for these medicines is very badly managed: huge quantities of antimicrobials, in particular antibiotics, are wasted globally on patients and animals who do not need them, while others who need them do not have access.

Fundamental change is required in the way that antibiotics are consumed and prescribed, to preserve the usefulness of existing products for longer and to reduce the urgency of discovering new ones. Governments should be held accountable on this goal to reduce the demand for antimicrobials and in particular antibiotics, as should the main sectors that drive antibiotic consumption: healthcare systems, the pharmaceutical industry and the farming and food production industry.

Firstly, the specific steps to reduce demand are:

1. **A massive global public awareness campaign**

   We need to improve global awareness of AMR across the board, so that patients and farmers do not demand, and clinicians and veterinarians do not prescribe, antibiotics when they are not needed, and so that policy makers ensure that policies to tackle AMR are taken forward now. The cost of running a sustained public awareness campaign across the world would depend on its nature and scope. Based on estimates we have considered, it could cost between 40 and 100 million USD a year. It could be met by a mix of existing public health programmes in high-income countries, support for programmes in low and middle-income countries and corporate sponsorship for major events.

2. **Improve hygiene and prevent the spread of infection**

   Improving hygiene and sanitation was essential in the 19th century to counter infectious diseases. Two centuries later, this is still true and is also crucial to reducing the rise in drug resistance: the less people get infected, the less they need to use medicines such as antibiotics, and the less drug resistance arises. All countries need to act. Some in the developing world will need to focus on improving the basics first, by expanding access to clean water and sanitation. For other countries the focus will be to reduce infections in health and care settings, such as limiting superbugs in hospitals. The simplest way that all of us can help counter the spread of infections is by proper hand washing.

3. **Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment**

   There are circumstances where antibiotics are required in agriculture and aquaculture – to maintain animal welfare and food security. However, much of their global use is not for treating sick animals, but rather to prevent infections or simply to promote growth. The quantity of antibiotics used in livestock is vast. In the US, for example, of the antibiotics defined as medically important for humans by the US Food and Drug Administration (FDA), over 70 percent (by weight) are sold for use in animals. Many countries are also likely to

use more antibiotics in agriculture than in humans but they do not even hold or publish the information. The majority of scientists see this as a threat to human health, given that wide-scale use of antibiotics encourages the development of resistance, which can spread to affect humans and animals alike. We propose three steps to improve this situation. **First**, 10-year targets to reduce unnecessary antibiotic use in agriculture, introduced in 2018 with milestones to support progress consistent with countries' economic development. For this to succeed, governments must support and speed up current efforts, including those of the World Organisation for Animal Health (OIE) and others, to measure antibiotic use and farming practices. **Second**, restrictions on certain types of highly critical antibiotics. Too many antibiotics that are now last-line drugs for humans are being used in agriculture; action should be taken on this urgently by an international panel. **Third**, we must improve transparency from food producers on the antibiotics used to raise the meat that we eat, to enable consumers to make more informed purchase decisions.

Antibiotics can reach the environment in many ways such as through sewage systems (including from hospitals) and run-off from food-producing units such as farms, and can then pose potential problems for AMR. One area that has not received enough focus so far is the way that the active ingredients for antibiotics are manufactured, and particularly the impact of effluent from factories on AMR in nearby water systems. To tackle this we need regulators to set minimum standards for the treatment and release of manufacturing waste; and manufacturers to drive higher standards through their supply chains. Both must take responsibility and correct this unnecessary environmental pollution immediately.

4. Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals

Surveillance is one of the cornerstones of infectious disease management, yet has until recently been often ignored and remains under-resourced in the fight against AMR. Learning the lessons from Ebola, countries have started to increase funding in this area recently, in particular the US government via the Global Health Security Agenda (GHSA), the UK government with its announcement last year of the 375 million USD Fleming Fund in response to early recommendations made by this Review, and the World Health Organization (WHO) with its developing Global AMR Surveillance System (GLASS). With oversight from the WHO, governments must build on these efforts to collect data about the consumption of antimicrobials, the levels of resistance, and the underlying biological reasons for resistance, supporting countries that need it most in doing so. They must also put systems in place now that will make the most out of the 'big data' on drug resistance that will be generated on an unprecedented scale as diagnostic tools are modernised and cloud computing is embraced. These new tools are just round the corner, and lower income countries may be able to 'leapfrog' into using them to support surveillance in some circumstances.

5. Promote new, rapid diagnostics to cut unnecessary use of antibiotics

Rapid diagnostics could transform the way we use antimicrobials in humans and animals: reducing unnecessary use, slowing AMR and so making existing drugs last longer. It is not acceptable that much of the technology used to inform the prescription of important medicines like antibiotics has not evolved substantially in more than 140 years. Rich countries must lead the way to change this: they should make it mandatory that by 2020 the prescription of antibiotics will need to be informed by data and testing technology wherever available and effective in informing the doctor's judgement to prescribe. This will spur investment by giving diagnostics developers the assurance that effective tests will be used. Our proposed Global Innovation Fund for AMR would support early-stage research in this area. In low and middle-income countries where access and affordability are the main barriers, a diagnostic market stimulus would provide top-up payments when diagnostics are purchased, in a similar way that setting up Gavi, the Vaccine Alliance, in the early 2000's revolutionised global vaccine coverage in what was one of the best returns on investment to support economic development and wellbeing.

6. Promote development and use of vaccines and alternatives

Vaccines can prevent infections and therefore lower the demand for therapeutic treatments, reducing use of antimicrobials and so slowing the rise of drug resistance. Other alternative approaches to both preventing and treating bacterial infections are also being researched, and could provide alternatives to antibiotics in some cases in the future. We believe these approaches should be eligible for the same incentives that we recommend for antibiotic development. We therefore need to: 1) Use existing vaccines and alternatives more widely in humans and animals; 2) Renew impetus for early-stage research; and 3) Sustain a viable market for vaccines and alternatives.

7. Improve the numbers, pay and recognition of people working in infectious disease

Infectious disease doctors are the lowest paid of 25 medical fields we analysed in the United States. It is no surprise that there are not currently enough candidates to fill hospital training vacancies. A similar story applies to other professions relevant to tackling AMR, from nurses and pharmacists in hospitals trained to improve stewardship, to microbiologists and other laboratory scientists doing surveillance, diagnostic testing and R&D in academia, governments, public sector organisations or companies: focusing on AMR-related specialties is often less rewarding financially and in terms of prestige than other areas of science and medicine. To change this we need an urgent rethink and improved funding to improve career paths and rewards in these fields.

Secondly, we must increase the number of effective antimicrobial drugs to defeat infections that have become resistant to existing medicines.

8. Establish a Global Innovation Fund for early-stage and non-commercial research

There is insufficient private and public investment in R&D focused on tackling AMR. To support early-stage research, whether 'blue sky' or focused on neglected areas like pharmacology or diagnostics, we have proposed a Global Innovation Fund endowed with up to 2 billion USD over five years. Exciting progress has already happened during the lifetime of this Review, including the UK and China's nascent Innovation Fund focused on AMR, stepped up efforts in the US via the Biomedical Advanced Research and Development Authority (BARDA), and in Europe via the Innovative Medicines Initiative (IMI) and Joint Programming Initiative for AMR (JPI-AMR) programmes. The spirit of the Global Innovation Fund we envisage could be achieved by linking up and increasing the size of these initiatives. It is crucial however that it becomes more than the sum of its parts: funding both early-stage 'blue sky' science, and R&D that may not be regarded scientifically as 'cutting-edge', and which lacks a commercial imperative, in a way that breaks down barriers to entry and makes funding available in countries and for organisations that would not have had access to funding previously.

9. Better incentives to promote investment for new drugs and improving existing ones

For antibiotics, the commercial return on R&D investment looks unattractive until widespread resistance has emerged against previous generations of drugs, by which time the new antibiotic may no longer have patent protection or may soon lose it. The total market for antibiotics is relatively large: about 40 billion USD of sales a year, but with only about 4.7 billion USD of this total from sales of patented antibiotics (that is about the same as yearly sales for *one* top-selling cancer drug). So it is no wonder that firms are not investing in antibiotics despite the very high medical needs. This will not change until we align better the public health needs with the commercial incentives. Governments must change this at the national level by considering possible changes to their purchase and distribution systems for antibiotics, to find ways to support better rewards for innovation while helping to avoid over-use of a new product. This can be partly achieved through adjustments to national purchasing and distribution systems, to reflect the diversity of health systems around the world. At the same time, for the drugs that are most needed globally and for which global stewardship and global access are important, we need new ways to reward innovation while reducing the link between profit and volume of sales and ensuring that developers give access and promote stewardship globally. We have proposed a system of market entry rewards of around one billion USD per drug for effective treatments, whether they are based on new or old drugs that work against resistant pathogens in areas of most urgent need. As an example, tuberculosis, gonorrhoea, so-called 'Gram-negative' pathogens as well as some fungal indications are all recognised to represent a high area of need that are currently ill-served by antimicrobial development. Finally, harmonised regulations and clinical trial networks can play an important role in this area to lower drug development costs.

None of this will succeed without building a global coalition for action on AMR and we consider that to be our tenth recommended intervention.

10. Build a global coalition for real action – via the G20 and the UN

AMR is not a problem that can be solved by any one country, or even any one region. We live in a connected world where people, animals and food travel, and microbes travel with

them. Global action is therefore essential to make meaningful progress over the long-term. We call on the G20 and the UN to focus on this issue in 2016 and to take action on both the supply and demand of antimicrobials, sparking a step-change in the fight against AMR.

What global action on AMR would cost

Our broad estimate for the cost of taking global action on AMR is up to 40 billion USD over a 10-year period.

Within this, we have estimated that it would cost about 16 billion USD to overhaul the antibiotics and TB R&D pipeline using new market incentives such as market entry rewards. Our costs are modelled on achieving 15 new antibiotics a decade, of which at least four would be breakthrough products targeting the bacterial species of greatest concern. We have also recommended setting up an AMR Global Innovation Fund endowed with two billion USD over five years.

It is more difficult to estimate the cost of supporting innovative new diagnostics and vaccines and then rolling them out, as the cost would depend very much on the type of products and the size of population who need them. At this stage of our work and based on roll out costs for other large public health programmes, we estimate that one to two billion USD a year to support take-up globally would make a very material difference in these areas.

Further economic analysis is needed urgently to understand the impact of reducing the unnecessary use of antibiotics in agriculture, whether that transition would impose a cost on the farming sector, how big, how distributed and for how long. So far most analysis has focused on high-income countries and therefore more analysis is needed of the impact in low and middle-income settings.

Finally, we recommend interventions that are not specific to AMR but happen to help address drug resistance, such as good general disease surveillance and better water and sanitation. These costs are part of normal investment to achieve good healthcare and so are not part of the package of global costs we describe here.

So in total, we estimate that the world can avert the worst of AMR by investing three to four billion USD a year to take global action. This is tiny in comparison to the cost of inaction. It is also a very small fraction of what the G20 countries spend on healthcare today: about 0.05 percent.

There are several ways to cover the cost of our interventions

Governments can afford to cover the cost of addressing AMR by allocating resources from existing health and economic development budgets: committing funds to AMR now will reduce the amount it costs later when it develops into an even bigger crisis, which will inevitably fall to governments. Most of the incentives we recommend are structured as 'payments for success' so they do not require upfront public investment into projects that may not deliver improvements.

Countries can also decide to create new streams of funding to contribute to AMR and these would not need to be the same everywhere, such as transferable vouchers to reward new antimicrobials, or taxes on antibiotics. These options all have their pros and cons and in the end will be reflected in the price society pays for healthcare.

What matters most now is that action starts quickly to reduce unnecessary use of antimicrobials and to revive investment in their development. In this respect, one funding option that could be particularly effective to shift supply-side resources towards AMR research is an antibiotic investment charge, which would be imposed widely on the pharmaceutical sector and applied on a 'pay or play' basis, meaning companies could either pay the charge or invest in R&D that is deemed useful for AMR. The money from companies who pay the charge would be used to improve the commercial market for the successful products such as news drugs, vaccines or diagnostics. This would push many more companies to invest in AMR, matching their short-term financial incentives better with the fact that the industry as a whole depends on effective antibiotics to sustain a range of areas from oncology to joint surgery.

Finally, we highlight principles for how these interventions should be delivered in practice, to limit new bureaucracy, and co-exist with current international institutions and national health systems. Until the new incentives are in place at a global level, it would be very useful for governments, charities and industry to try and test new ideas and models at a local level.

It is time to turn ideas into effective action and to solve the problem of drug resistance. Thanks to the courage and determination of a few leaders in this area, the problem of AMR will be discussed at the UN General Assembly later this year and continues to rise up the agenda for the G7 and G20 groups of countries. Leaders in these global forums must now rise to the occasion and agree on practical solutions.

Review on Antimicrobial Resistance

In 2014, the UK Prime Minister David Cameron commissioned the independent Review on Antimicrobial Resistance, Chaired by macroeconomist Jim O'Neill, to examine the growing threat of AMR from an economic perspective and to recommend solutions. The Review has been co-sponsored by the Wellcome Trust and the Department of Health. Over the last 19 months the Review has published eight thematic papers that address different aspects of the problem of AMR. These are as follows:

- *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*, December 2014
- *Tackling a global health crisis: Initial steps*, February 2015
- *Securing new drugs: The pipeline of antibiotics*, May 2015
- *Rapid Diagnostics: Stopping unnecessary use of antibiotics*, October 2015
- *Safe, secure and controlled: Managing the supply chain of antimicrobials*, November 2015
- *Antimicrobials in agriculture and the environment: Reducing unnecessary use and waste*, December 2015
- *Vaccines and alternative approaches: Reducing our dependence on antimicrobials*, February 2016
- *Infection prevention, control and surveillance: Limiting the development and spread of drug resistance*, March 2016

This is the final report that pulls together all our previous recommendations as a package of actions that we believe will be needed to tackle this rising threat.

TACKLING ANTIMICROBIAL RESISTANCE ON TEN FRONTS

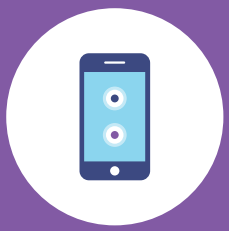
Public awareness

Sanitation and hygiene

Antibiotics in agriculture and the environment

Vaccines and alternatives

Surveillance



Rapid diagnostics

Human capital

Drugs

Global Innovation Fund

International coalition for action

Review on Antimicrobial Resistance

1.

THE PROBLEM: WHY TACKLING AMR IS ESSENTIAL

What is antimicrobial resistance (AMR)?

Antimicrobial drugs are medicines that are active against a range of infections, such as those caused by bacteria (antibiotics), viruses (antivirals), fungi (antifungals) and parasites (including antimalarials).

AMR arises when the micro-organisms which cause infection (e.g. bacteria) survive exposure to a medicine that would normally kill them or stop their growth. This allows those strains that are capable of surviving exposure to a particular drug to grow and spread, due to a lack of competition from other strains. This has led to the emergence of 'superbugs' such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and extremely drug-resistant tuberculosis, bacteria which are difficult or impossible to treat with existing medicines.

Resistance to antimicrobials is a natural process that has been observed since the first antibiotics were discovered – and, indeed, the genes that confer drug resistance upon some strains of bacteria pre-date antibiotics by millions of years. However, AMR has increasingly become a problem in recent times because overuse of antimicrobials has increased the rate at which resistance is developing and spreading, but we lack new drugs to challenge these new superbugs. This results in us facing a growing enemy with a largely depleted armoury.

In the past, resistant infections were associated predominantly with hospitals and care settings, but over the last decade resistant infections have been seen in the wider community too. With resistance on the rise, we stand to lose the immense ground we have gained in the last century. This includes: 1) our fight against life threatening infectious diseases such as pneumonia, TB, HIV and malaria; 2) our battle against conditions such as cancer, where antibiotics are crucial in helping chemotherapy patients avoid and fight infection; and 3) huge advances in surgical procedures like organ transplants and caesarean sections, which have now become routine and relatively low risk, thanks to our ability to effectively stave off or treat acute infections with antibiotics.

Drug-resistant infections already cost too many lives today

We estimated in our first report, published in December 2014[1], that in total about 700,000 people die every year from drug-resistant strains of common bacterial infections, HIV, TB and malaria. This number is likely to be an underestimate due to poor reporting and surveillance. Nearly 200,000 people die every year from multidrug-resistant and extremely drug-resistant tuberculosis (TB) alone[2]. In India, antibiotic-resistant neonatal infections cause the deaths of nearly 60,000 new-borns each year[3]. A current death toll on this scale means that more than one million people have lost their lives to drug-resistant infections in the 19 months since we published our first report.

Our ability to cure infections that were once considered benign is already damaged. For instance, the rapid development of drug-resistant strains of gonorrhoea combined with the fact that we do not have a rapid diagnostic test to guide doctors' choice of prescription, means we are down to using our 'last line' antibiotic to treat gonorrhoea[4]. After this antibiotic fails, there are no more treatment options on the shelf. For other infections, doctors running out of better options are using antibiotics that were once avoided due to their bad side effects. This is the case with colistin, for example, which can cause kidney failure and so was never given to patients for many years. Over the past decade however, it has re-entered use as a last resort treatment for patients with particularly hard-to-treat Gram-negative bacterial infections[5], and already colistin resistance is emerging.

The economic impact is also already material. In the US alone, more than two million infections a year are caused by bacteria that are resistant to at least first-line antibiotic treatments[6], costing the US health system 20 billion USD in excess costs each year[7].

1 Review on AMR, *Antimicrobial resistance: Tackling a crisis for the health and wealth of nations*, 2014.

2 WHO, Tuberculosis Factsheet, Online, Available at: http://www.who.int/mediacentre/factsheets/fs104/en/

3 Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance – the need for global solutions, *The Lancet Infectious Diseases* 2013; 13: p.1057-98.

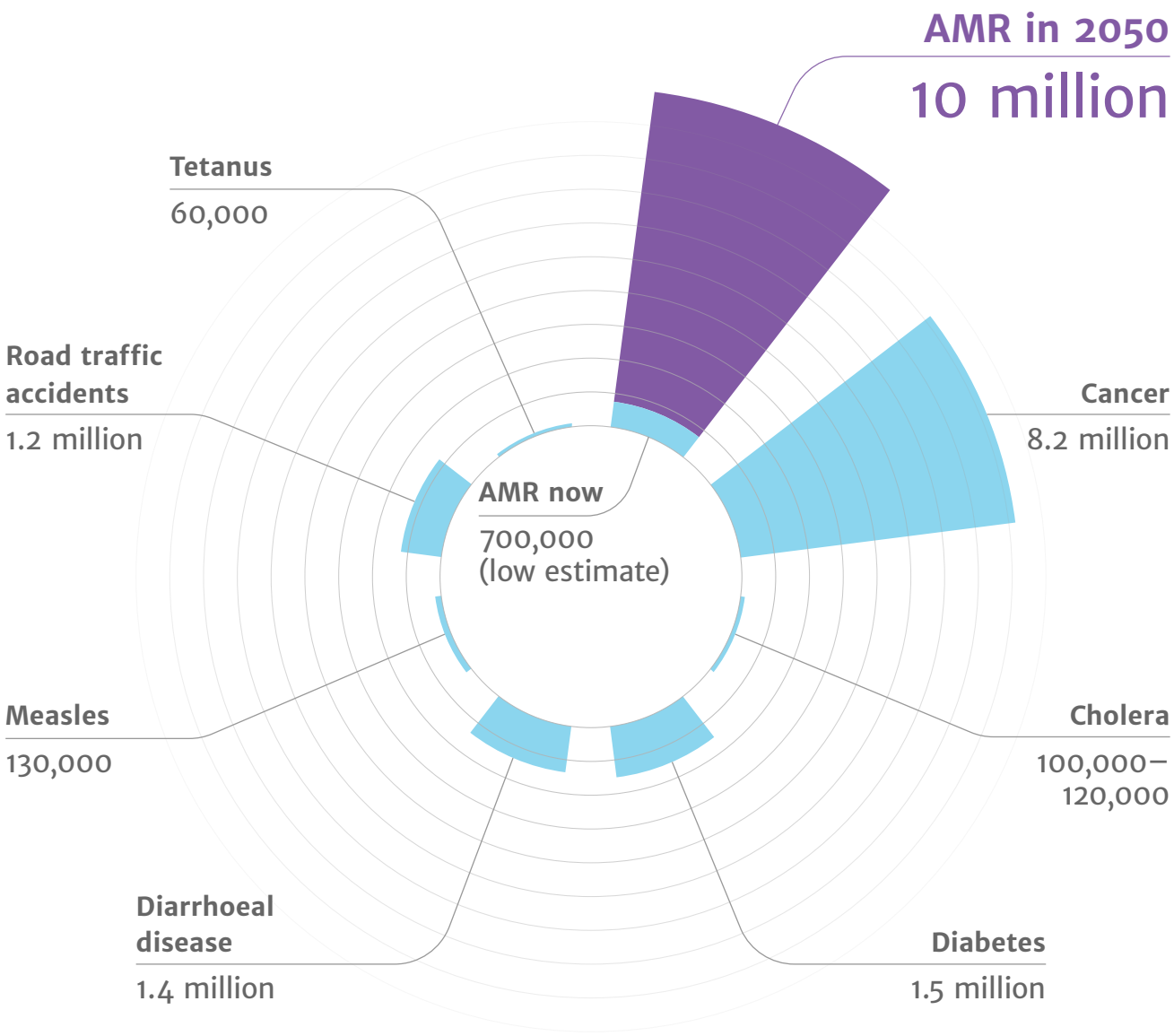
4 Davies SC. *Annual report of the Chief Medical Officer 2011: Volume 2*. London: UK Department of Health. 2013.

5 Boucher HW, Talbot GH, Bradley JS, Edwards JR Jr, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America, *Clinical Infectious Diseases*, 2009; 41, 1-12.

6 Centres for Disease Control and Prevention, Antibiotic Resistant threats in the United States, 2013, US Department of Health and Human Services.

7 Smith R, Coast J, The true cost of antimicrobial resistance, *BMJ*, 2013, 346, f1493.

DEATHS ATTRIBUTABLE TO AMR EVERY YEAR



Sources:
Diabetes: www.whi.int/mediacentre/factsheets/fs312/en/ Cancer: www.whi.int/mediacentre/factsheets/fs297/en/
Cholera: www.whi.int/mediacentre/factsheets/fs107/en/ Diarrhoeal disease: www.sciencedirect.com/science/article/pii/S0140673612617280
Measles: www.sciencedirect.com/science/article/pii/S0140673612617280 Road traffic accidents: www.whi.int/mediacentre/factsheets/fs358/en/
Tetanus: www.sciencedirect.com/science/article/pii/S0140673612617280

Review on Antimicrobial Resistance

This challenge will only get worse in the future if we do not act now

Based on scenarios of rising drug resistance for six pathogens to 2050, we estimated that unless action is taken, the burden of deaths from AMR could balloon to 10 million lives each year by 2050, at a cumulative cost to global economic output of 100 trillion USD. On this basis, by 2050, the death toll could be a staggering one person every three seconds and each person in the world today will be more than 10,000 USD worse off[8].

It is impossible to predict the path of emerging drug resistance, but it is a trend that has largely run only in one direction so far. What we can be certain of is that, in the absence of interventions to slow the emergence of resistance, and increase the supply of new antibiotics, the impacts will be felt not just in isolated areas but at a far more fundamental level, across our societies and healthcare systems.

As the antibiotics available to us become less effective, so the risks of many treatments which rely upon antibiotics becomes higher. This will progressively undermine the viability of interventions that many may not directly associate with antibiotics. Cancer chemotherapy or organ transplantation are just two examples of medical treatments that leave the patient highly vulnerable to bacterial infections. Most invasive surgery (particularly 'dirty' procedures, such as those involving the gut) is today routinely and dependably 'de-risked' by effective antibiotic prophylaxis and by the availability of reliable therapy for infections that do occur despite best practices. Intubated patients in intensive care facilities already experience very high rates of infection, including drug-resistant ones, as a result of the ventilation that they receive – and the mortality risk associated with this will rise further if treatment options for such infections deplete. These secondary impacts are difficult to quantify but they threaten to dramatically change healthcare as we know it today.

This field suffers from decades of under-investment by companies and governments

The post-World War II period saw a 'golden era' of antibiotic discovery, with a steady stream of new products reaching the market through the late 1940s to the early 1970s. But this rate of discovery has fallen dramatically since the 1980s. Even when a tiny number of 'new' antibiotics have reached the market over the past two decades, they have originated from breakthroughs made many decades ago. One reason for this is that discovering new antibiotics is harder today than it once was, particularly those active against the drug-resistant Gram-negative infections that are of great concern. The 'low-hanging fruit' of easily-isolated natural antibiotic products is gone and early genomic screening techniques, when first used in the 1990s, failed to deliver on their promise of a revolution in antibiotic discovery[9].

This scientific hurdle is exacerbated by the decline in investment by both industry and public funders. This owes much to the perception that emerged during the second half of the 20th century that the greatest challenges to public health, at least in the developed world, no longer lay in infectious diseases, but in non-communicable diseases. This perception that infectious disease is somehow 'yesterday's problem' has led to an over-adjustment in terms of research priorities in favour of non-communicable diseases, and ultimately a neglect of R&D, with the notable exception of HIV/AIDS research. This was compounded by the fact we failed to take into account the impact of zoonotic diseases and a rise in global transmission rates as travel increased.

In the private sector, pharmaceutical companies have divested from their antibiotics research teams steadily, to the benefit of areas that may not be 'easier' but that definitely have a higher commercial return. In oncology, for instance, there were close to 800 new products in the development pipeline in 2014, of which around 80 percent were potentially 'first-in-class'[10] – compared to a total antibiotics pipeline today of fewer than 50 products. Moreover, the rate of new product registrations in oncology since 2010 has been twice as high as it was in the 2000s[11] – demonstrating the impact of a significant and sustained industry focus on a scientifically challenging but commercially lucrative disease area. Antibiotics also attract a very small – and shrinking – share of venture capital funds. Of 38 billion USD venture capital invested into pharmaceutical R&D between 2003 and 2013, only 1.8 billion USD was invested into antimicrobials research, with total investments falling by more than a quarter over that period, despite the issue of drug-resistance becoming worse and, at least recently, becoming better known by the public[12].

The same story is true in the allocation of public research funds by governments. For example, the US National Institutes of Health (NIH), the world's largest single funder of health research, allocated just 1.2 percent of its grant funding to

8 Based on United Nations report World Population Prospects: The 2015 Revision, 2015, which cites current world population of 7.3 billion and projected world population in 2050 of 9.7 billion.

9 Payne DJ, Gwynn MN, Holmes DJ, Pompliano D, Drugs for bad bugs: Confronting the challenges of antibacterial discovery, *Nature Reviews Drug Discovery*, 2007, 6.

10 PhRMA, Medicines in development 2014: Cancer, PhRMA, 2014.

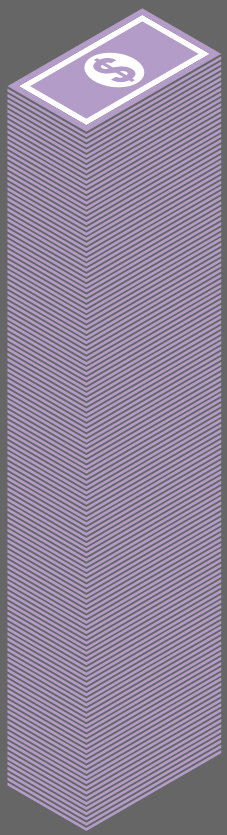
11 Kinch MS, Patridge E, Plummer M, Hoyer D, An analysis if FDA-approved drugs for infectious disease: antibacterial agents, *Drug Discovery Today*, 19, 9, 1283-7.

12 Renwick MJ, Brogan DM, Mossialos E, A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics, *The Journal of Antibiotics*, 2016, 69, 73-88.

ANTIMICROBIAL R&D IS NOT ATTRACTIVE TO VENTURE CAPITALISTS

Less than 5%

of venture capital investment in pharmaceutical R&D between 2003 and 2013 was for antimicrobial development.



Total venture capital investment

$38bn

Antimicrobial venture capital investment

$1.8bn

Source: Renwick MJ, Simpkin V, Mossialos E, International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development, The Need for a One Health – One Europe – One World Framework, Report for the 2016 Dutch Presidency of the European Union.

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AMR-related research between 2009 and 2014, compared to 18.6 percent (more than five billion USD annually) to cancer research[13]. This trend has begun to turn in some areas, with the US Government and initiatives such as the European-based Joint Programming Initiative on AMR (JPIAMR) helping to channel more public funding into AMR research. Two key programmes specifically supporting antibiotic development, the US Biomedical Advanced Research & Development Agency (BARDA) Broad Spectrum Antimicrobials programme, and the European Innovative Medicines Initiative (IMI) New Drugs For Bad Bugs (ND4BB) programme, together provide direct financial support to nearly 20 percent of all antibiotics currently under development globally, and half of those targeting Gram-negative bacteria[14]. Nonetheless, there remains much more to do to close the profound gap with funding for R&D in non-communicable diseases – something we will address in the next chapter.

Finally, this lack of investment and interest by companies and governments has in turn contributed to a decline in the attractiveness and prestige of the field. Academic careers do not reward the skills required for antibiotic discovery, where advancement and prestige is driven by publishing in journals seen as focused on 'cutting-edge science' – not something often associated with microbiology[15].

There is no excuse for not taking action now

There is no excuse for inaction given what we know about the impact of rising drug resistance. The reality is that governments will sooner or later bear the cost of AMR: they can either do so proactively by taking action now and pay less for better outcomes, or remain unprepared and end up spending much more taxpayer money on far worse outcomes further down the line.

Governments always have to make very difficult financial allocation choices. Understandably, they often find it easier to react to visible and immediate threats rather than longer term and less visible problems even if the latter are very large, such as AMR.

When threats such as SARS, Swine Flu and Ebola arise, governments spend vast sums, often in haste and with vision clouded by the imperative to respond to an acute global health crisis. For instance, the US Government appropriated 5.4 billion USD in a single year to underwrite its response to the Ebola epidemic globally and domestically; while the UK spent 1.9 billion USD tackling the 2009 swine flu outbreak. These crises were of course impossible to predict and required a quick response with large sums of money, from a position of relative weakness – but the vast sums involved illustrate the almost uncontainable cost of responding to a major health crisis once it reaches an acute phase. In contrast, the unfolding global threat of rising drug resistance is essentially predictable, and the costs that we present here for mounting an effective *pre-emptive* response to it are substantially lower than the expense of responding once it becomes a true public health emergency.

This principle of investing prudently to pre-empt future health challenges is well-established. A seminal World Bank report in 1993[16] demonstrated the enormous returns on investing in improved health, with more recent studies underlining how relatively low-cost investments in global health security can yield substantial dividends. For instance, the recent Commission on a Global Health Risk Framework for the Future estimated that global investment of 4.5 billion USD a year would mitigate the risk of pandemic disease threats that could cost the world 60 billion USD annually[17]. The most critical lesson that the global community can learn from this, and from the real experience of responding to Ebola and other health crises like it, is that the most powerful and cost-effective response is to anticipate the future threat and to act upon the conditions allowing it to unfold.

> *"The reality is that governments will sooner or later bear the cost of AMR: they can either do so proactively by taking action now and pay less for better outcomes, or remain unprepared and end up spending much more taxpayer money on far worse outcomes further down the line."*

13 Review on AMR, *Tackling a global health crisis: initial steps*, 2015.

14 Eichberg MJ, Public funding of clinical-stage antibiotic development in the United States and European Union. *Health Security* 2015, 13, 3, 156-165.

15 Zorzet A, Overcoming scientific and structural bottlenecks in antibacterial discovery and development, *Uppsala Journal of Medical Sciences*, 2014, 199, 170-5.

16 World Bank, *World Development Report 1993: Investing in Health*, 1993, New York: Oxford University Press

17 Commission on a Global Health Risk Framework for the Future, *The Neglected Dimension of Global Health Security: a Framework to Counter Infectious Disease Crises*, 2016.

Guiding principles for developing our recommendations

We have followed six simple guiding principles, of equal importance, to develop our package of recommendations across 10 areas. These are:

1. The solution to the problem must work for the world and benefit as many people as possible, not one country or one group of countries.

2. The solutions should be cost-effective, affordable and support economic development.

3. AMR is a global problem and some of the solutions have to be implemented collectively but we seek to avoid creating new institutions except in the rare cases when they are really required. Whenever possible our interventions coexist seamlessly with current international institutions and national health systems.

4. The solutions should aim to increase the number and types of organisations and individuals undertaking research relevant to AMR, and reduce barriers to entry, including in countries that have a less established pharmaceutical research industry.

5. The solutions should make best use of the respective strengths of the public sector, the private sector, civil society and academia.

6. The solutions should identify market failures and address them by allocating resources and risk effectively, via price mechanisms where possible or regulation if required.

The sixth principle, about allocating risk effectively, is important for R&D in drug discovery. It is important in clinical research to not stop supporting a project that is likely to come to fruition, so you want organisations to continue research that looks promising. However it is equally important to stop supporting unpromising projects, and replace them with new ones that might bring success. Governments often struggle to do this, as cancelling a project that does not look promising leaves them open to the charge of having wasted public money, so they often fund a small number of projects, and continue to support them even when their odds of success become too low for funding to make sense. In contrast, the private sector can do better funding a large number of early-stage projects, then dropping those that do not look promising, enabling them to back those that do. The environment that they operate in is less critical of failure, considering it as part and parcel of the process of finding and pursuing opportunities with the potential to generate high financial returns. The same can be true for non-profit funders, though their measure of success or returns will typically relate to their respective missions.

It is important that changes to funding systems harness the ability that the private and the not-for-profit sectors have for taking on risk and acting flexibly. On the other hand, governments can borrow more cheaply than industry and may be best placed to make long-term investments.

Like governments, civil society organisations and not-for-profits often have goals that align well with public need, and they can be much more flexible than governments. They can thus be very good at undertaking research. However resource constraints, and a lower reward for winning, as well as a desire not to be seen to have "wasted" their funds can leave them less well placed than the private sector to take risks.

An outline of the market failures affecting AMR

Economists use the term 'market failure' to describe situations where supply and demand do not come together efficiently and effectively. The main failures in the case of AMR are externalities, imperfect information, and an unwillingness to pay for public goods.

Externalities

An externality is the cost or benefit to a third party for a decision over which they have no control. For example, when a factory pollutes a river, it may save money, but everyone who relies on the river downstream suffers. Governments often intervene to tax or regulate goods that have negative externalities, like pollution. Antibiotic consumption fits in this category: individuals take and may benefit from the antibiotics but the resistance to which they contribute impacts all of society. Governments often subsidise goods that have positive externalities like education, which helps increase overall economic development, or vaccines, which help prevent other people from getting sick. Antibiotics can also be said to have some positive externalities too, where taking them kills the infection and stops it spreading to other people – although the negative externality of resistance is more pronounced.

At the moment the negative externalities of antibiotic consumption are not regulated strongly and that has led to their overuse in patients and animals. Diagnostics to make sure the right antibiotics are taken at the right time are either not available or used insufficiently because of financial and cultural barriers at the point of use. For instance, it would cost more in time and money for a doctor to test a patient before prescribing an antibiotic, instead of prescribing it 'just in case it is needed'. This is exacerbated by the fact that antibiotics are often very cheap – cheaper even than a low-cost test.

Imperfect information

Problems of 'imperfect information' occur when two parties have different information about the same issue. There are two such instances where this arises in the use of antimicrobials.

The first is that doctors may not realise a patient has a resistant infection and may prescribe a drug that does not work. That will delay the patient receiving second-line treatments and mean they are ill for longer, during which time they might pass the infection on to others. Poor information also leads to doctors prescribing antibiotics to patients with viral infections and prescribing second or third-line antibiotics where a first-line would be effective. Diagnostic tools are crucial in addressing this lack of information.

The second information problem is that it is very difficult to predict how resistance will evolve over time. In the context of current financial rewards, this makes it hard for pharmaceutical companies to predict how many people will need their new antimicrobial in future, which can fatally undermine their economic case for investing in developing it. Because of this uncertainty, these companies do not invest enough in these areas until there is already a resistance problem – by which time a new drug will be an urgent need, and yet could be 10-15 years away from coming to market.

Public goods

Public goods are things that benefit a wide group of people, where that group does not directly pay for their production. One example is a light house, which benefits ships sailing at night but where the running costs and upkeep are not paid for directly by the ship owners. Governments have traditionally funded lighthouses or they have become linked to privately owned ports which can charge boat owners for entry, helping to cover running costs.

The story is similar for antimicrobials; a large proportion of the medical industry relies on the ability to manage infections with antibiotics to sell their products. AMR increases the risks associated with surgery, chemotherapy and other interventions or treatments and may thus reduce the number of people having these. This will impact the sales of products such as artificial hips and chemotherapy drugs, as well as health outcomes for patients. As with lighthouses, there is a rationale for the pharmaceutical industry and society at large (represented by governments) to correct this need for collective funding.

Tackling the rise of drug-resistant infections requires international collective action across a range of different sectors[18]. But what is striking is that this is not as difficult as it may seem. In this report we describe specific and feasible interventions that either improve the supply of new antimicrobial medicines or reduce the demand for existing ones, prolonging their life. These interventions are the Review's way of breaking up the problem of AMR into manageable parts. They are wholly consistent with the five objectives that were laid out by the 194 member states of the World Health Organisation in the Global Action Plan on AMR agreed in May 2015[19].

18 Hoffman SJ, Outterson K. What will it take to address the global threat of antibiotic resistance?, *Journal of Law, Medicine and Ethics*, 2015, 43(Supp.3), 6-11.

19 World Health Organisation, Global Action Plan on Antimicrobial Resistance, WHO, 2015. The five pillars are:

1.to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;

2.to strengthen the knowledge and evidence base through surveillance and research;

3.to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;

4.to optimize the use of antimicrobial medicines in human and animal health;

5.to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions

2.

WE MUST REDUCE THE DEMAND FOR ANTIMICROBIALS SO THE CURRENT STOCK OF DRUGS LASTS LONGER

At the heart of the problem of rising drug resistance is rapidly growing global demand for antibiotics, something that is necessary to improve access to life-saving medicines with economic development, but all too often reflects excessive and unnecessary use rather than genuine medical need. More consumption of antibiotics directly leads to more drug resistance. Thus, by reducing unnecessary consumption, we can have a powerful impact on resistance. Doing so is particularly important because its effect is lasting (all other things being equal), preserving the effectiveness of existing and new drugs and slowing the rate at which they need to be replaced with even newer products.

In this section we detail seven interventions required to reduce the unnecessary use of antibiotics and other antimicrobial drugs (the last two - vaccines and improving human capital – are both a demand and a supply intervention). In all cases, it is crucial that the focus remains on reducing unnecessary use; access to drugs that patients actually need should not be reduced. In summary, we need access not excess.

We need to:

1. Undertake a massive global public awareness campaign
2. Improve hygiene and prevent the spread of infection
3. Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment
4. Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals
5. Promote new, rapid diagnostics to cut unnecessary use of antibiotics
6. Promote development and use of vaccines and alternatives
7. Improve the numbers, pay and recognition of people working in infectious disease

> *"More consumption of antibiotics directly leads to more drug resistance. Thus, by reducing unnecessary consumption, we can have a powerful impact on resistance."*

LOWERING DEMAND FOR ANTIMICROBIALS AND REDUCING UNNECESSARY USE

Public awareness

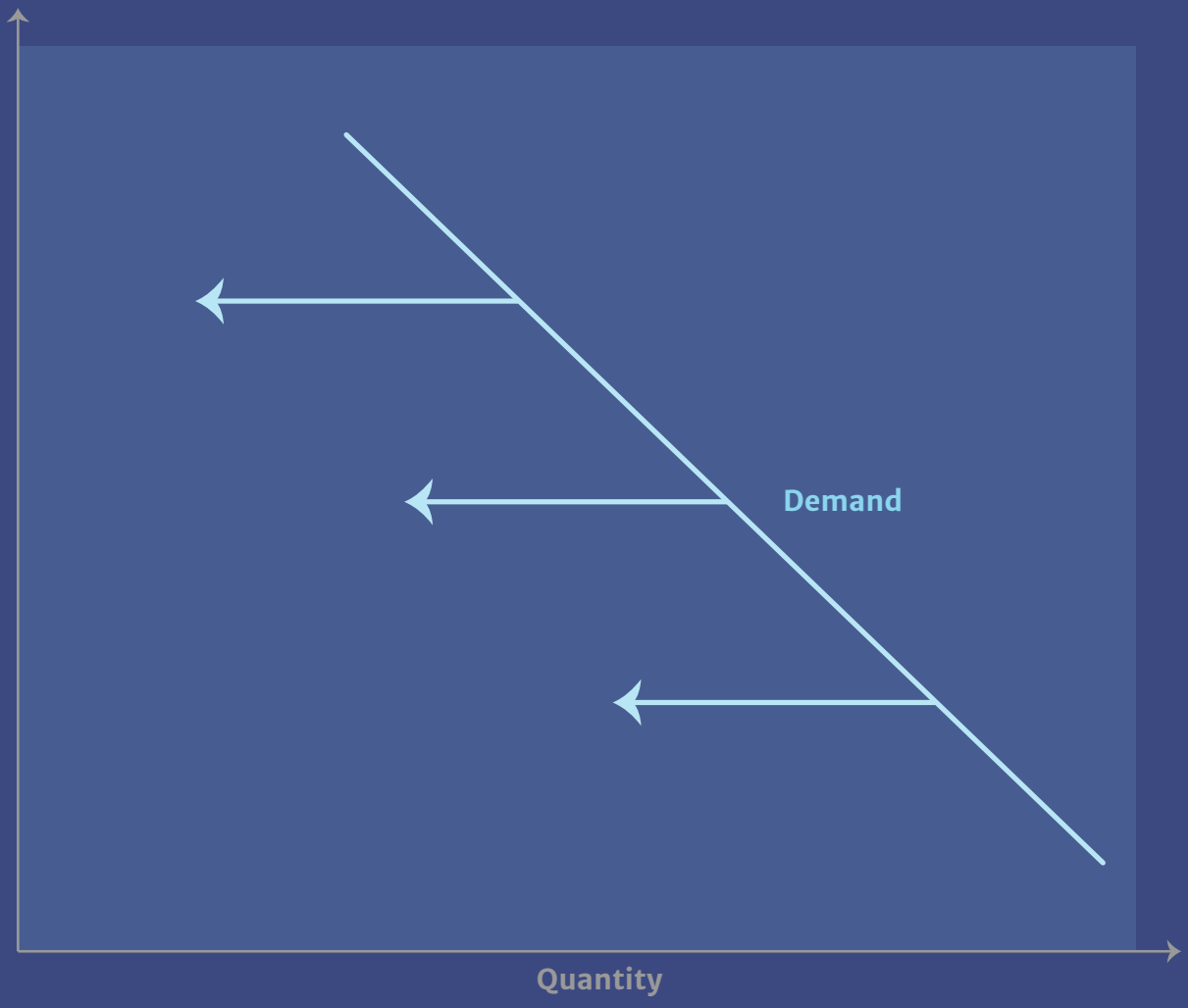
Sanitation and hygiene

Antibiotics in agriculture and the environment

Vaccines and alternatives

Rapid diagnostics

Human capital



Review on Antimicrobial Resistance

Intervention 1:
A global public awareness campaign

> *A crucial part of tackling this challenge is to create the circumstances for behavioral change. From reducing smoking rates, to convincing people to wear seatbelts, effective public campaigns have repeatedly changed social attitudes and improved human health. In this case, a public health campaign has the potential to build understanding and change behavior, helping to avoid a future catastrophe that could see 10 million people dying every year.*
>
> Donald A. Baer, Worldwide Chair and CEO, Burson-Marsteller

Why we need to act

Patients often demand antibiotics and other medicines from their doctors, or buy them over-the-counter (OTC), without knowing whether they need them and understanding the implication of unnecessary use of antimicrobials.

Recent studies have shown that misconceptions about resistance, its development and impact, are rampant and that this is seen all over the world, with people often not knowing what AMR is or believing that humans rather than microbes build up resistance[20,21]. A campaign that convinces people not to demand antibiotics from their doctor or buy them OTC without a genuine need, as well as farmers not to use them unnecessarily in agriculture, will play an important part in stopping the unnecessary use that is driving so much of the world's resistance problems.

Studies have shown that public awareness or behaviour change campaigns can be very cost-effective and lead to lasting changes, when run well. One study showed that in Belgium, campaigns to reduce antibiotic use during the winter flu season, resulted in a 36 percent reduction in prescriptions. Over 16 years, the cumulative savings in drug costs alone amounted to around 130 Euros (150 USD) per Euro spent on the campaign[22]. Results such as this demonstrate the potential impact of such campaigns, if done alongside measures that sustain the change over time.

Raising public awareness and understanding is therefore a crucial pillar of our recommendations for tackling AMR. Targeting interventions towards specific professions, such as healthcare prescribers[23] and farmers or food producers is also central to this approach.

What we need to do

The design and implementation of sustained public awareness campaigns to change behaviours and have positive impacts on health outcomes is crucial. A single global campaign is unlikely to make sense, given the complexity of national and regional messages. Instead there should be a common set of core messages that are globally consistent, with recognisable and iconic themes and symbols. Each country or region would then deliver the message locally in a way that is tailored to their particular audience and use locally relevant channels of communication, which might include social media through the internet, text messaging, TV and radio adverts. Alternatively, more traditional means such as posters and leaflets in hospitals, clinics, pharmacies, etc., as well as using celebrities, sports stars and other high profile figures to raise the profile of this issue. Any campaign needs to account for local infrastructure and social norms. For instance, simply telling farmers to reduce the amount of antimicrobials they give their animals, without ensuring their incentives are aligned to do this, and without technical assistance, will not yield the changes that we need.

How much would it cost?

The costs of running a campaign will vary hugely based on the size of the campaign that is run. Campaigns are significantly more expensive in higher-income countries. For this reason we believe that an appropriate global body should lead work to co-ordinate and encourage campaigns in high-income countries whilst also funding and supporting them directly in low-income settings. There will also be opportunities to campaign in low budget ways by enlisting the support of large organisations, possibly using corporate sponsorships – involving, for example, bold messages during national and global sporting events from football to cricket, or the Olympic Games.

Based on estimates we have considered, such a campaign could cost between 40 and 100 million USD a year. However since the cost of a global campaign depends on the scale of the intervention and the optimal 'level' for such an intervention is difficult to prescribe, it should be for global bodies and experts to consider the size and scope of such an ambitious campaign.

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20 Wellcome Trust, Exploring the consumer perspective on antimicrobial resistance, June 2015.

21 WHO, Antibiotic resistance: Multi-country public awareness survey, 2015.

22 Goossens H, 2016, Personal communication.

23 Gjelstad S, Høye S, Straand J, Brekke M, Dalen I, Lindbæk M. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study), BMJ, 2013, 347.

Labelling of medicines and food: the power of transparency to change behaviours

Convincing the public that we should stop using antibiotics unnecessarily would not be effective if most people cannot recognise which drugs are antibiotics in the first place. Labelling of antimicrobials, especially antibiotics, is crucial. We call on governments and international health organisations to agree global labelling standards for antibiotics. India has led the way so far with its idea of a 'Red Line Campaign' for antibiotics packaging, launched earlier this year. This idea should be considered as a starting point, the labelling and symbols used improved if needed, and then expanded globally. Common labelling standards of this type could become a condition of sale of antibiotics around the world.

We also call on producers, retailers and regulators to agree standards for 'responsible antibiotic use'. These standards could then be developed and implemented as an internationally recognised label, or used by existing certification bodies. Similarly, the improved transparency and labelling could be a powerful tool in driving changes by the global pharmaceutical industry to ensure robust oversight of their supply chains for antimicrobials, ensuring that their manufacture does not involve the release of dangerous levels of antibiotic active pharmaceutical ingredients (APIs) into the environment.

Patients as consumers: shifting public demand for antibiotics

Over-the-counter sales

In much of the world, legislation prevents the sale of antibiotics and other antimicrobials 'over-the-counter' (OTC), i.e. without a prescription from a doctor, but these regulations may be weakly enforced in some countries and non-existent in many others. Systematic figures on non-prescription sales of antibiotics are hard to come by, but in parts of Southern and Eastern Europe 20 to 30 percent of antibiotics are believed to be consumed without prescription, while in some parts of Africa this figure rises to 100 percent[24].

There are circumstances in which OTC sales may have a place. For instance, in resource-constrained settings, OTC sales may be the only route for people to access the medicines they need. In this context, improving access to healthcare is far more important than a regulatory crackdown on OTC sales. In high-income healthcare systems, the advent of new rapid diagnostics (discussed elsewhere in this report) might actually present opportunities for OTC sales to be facilitated by pharmacists able to provide a full and confident diagnosis at point of sale, without the need for a prescription from a doctor.

As an overarching principle, however, strong regulatory responses are needed from governments and regulators to establish and enforce strict controls on OTC sales, while having regard to the need for sustainable access.

Internet sales

The internet provides further opportunities for non-prescription sales of antibiotics on an unprecedented scale. Consumers anywhere in the world are now only a few clicks away from online pharmacies, some of whom are willing to ship antibiotics anywhere in the world without prescription. Increasing use of electronic prescribing provides opportunities for legitimate internet sales, but decisive action is needed to restrict the activities of unscrupulous and currently unregulated online vendors.

The regulatory response to this is more complex than for 'bricks and mortar' pharmacies, but no less crucial. A coordinated, global effort is required by domestic regulators and international bodies (like INTERPOL or the World Customs Organization) working in harmony to limit opportunities for unregulated online sales within countries and across international borders.

24 Morgan DJ, Okeke IN, Laxmanirayan R, Perencevich EN, Weisenberg S, Non prescription antimicrobial use worldwide: a systematic review, *Lancet Infectious Diseases*, 2011, 11, 9, 692-701.

Intervention 2:
Improve sanitation and prevent the spread of infection

> ***The basics of public health – clean water, good sanitation and hygiene, infection prevention and control and surveillance – are as critical for reducing the impact of antimicrobial resistance as they are for infectious disease control. While we also need new technologies and medicines, and better use of existing medicines, we cannot let attention to fundamental public health practices suffer, or else antimicrobial resistance will continue to thrive.***
>
> Dr Keiji Fukuda, the Director General's Special Representative for Antimicrobial Resistance at the World Health Organization (WHO)

Why we need to act

To reduce our unnecessary use of antibiotics and limit the impact of drug-resistant infections, one of the most fundamental steps that can be taken is to break the chain of transmission of infections. By preventing infections from occurring, we reduce the need for treatment and limit the opportunities for drug-resistant strains to develop. This principle applies both to human and animal health, although our focus in this section is on the former.

In the community

In the 19th century, long before the advent of antibiotics, some of the earliest public health interventions by governments in the US and Western Europe focused on investing in public infrastructure such as sewerage and sanitation. These investments yielded dramatic benefits for rapidly-growing urban populations and laid the foundations for the 'epidemiological transition' that saw non-communicable illnesses overtake infectious diseases as the most common cause of death in these regions before the First World War.

While these investments in sewerage and sanitation infrastructure were a key feature in the development of the economies of many higher-income countries, today's rapidly-growing middle-income countries have not always made comparable investments.

This partly reflects the challenges of keeping up with rapid urbanisation and economic growth. However, it is also likely to reflect the fact that effective antibiotics are available today, in a way they were not in the early 20th century. This has led us to overly rely on the curative potential of drugs, at the expense of a prudent focus on prevention.

As a result, infectious diseases continue to profoundly affect many parts of the world, with unsanitary living conditions acting as a catalyst of rapid person-to-person spread. This directly increases the burden of bacterial infections and directly contributes to the development of antibiotic resistance. In addition, inadequate access to safe water and sanitation also indirectly contributes to the rise of drug resistance by driving the spread of non-bacterial infections for which antibiotics will often be inappropriately prescribed.

In this respect, AMR is intrinsically an issue of economic development: the emergence and spread of drug resistance is both driven by issues like access to safe water and sanitation that represent key challenges for low and middle-income countries, as well as being a headwind to human and economic development.

This can be illustrated with the example of the burden of diarrhoeal conditions. These impose a substantial burden in low and middle-income countries: they claim 1.1 million lives each year, and represent the second most common cause of death amongst children. 60 percent of this disease burden is associated with inadequate access to safe water and sanitation[25]. Around 70 percent of episodes of diarrhoeal illness are caused by viral, rather than bacterial infections[26], against which antibiotics are ineffective – and yet antibiotics will frequently be used as a treatment. The volume of antibiotic consumption associated with preventable diarrhoeal illness is therefore substantial: modelling commissioned by the Review suggested that across four middle-income countries (India, Indonesia, Nigeria and Brazil), close to 500 million courses of antibiotics are each year used to treat diarrhoea. With universal access to improved water and sanitation, though, this would be reduced by some 60 percent[27].

In healthcare settings

The impact of drug-resistant infections is often worst in healthcare settings such as hospitals, because they are high-risk environments for the spread of bacterial infections of all types. Across developed countries, between seven and 10 percent of all hospital inpatients will contract some form of

25 Review on AMR, *Infection prevention, control and surveillance: Limiting the development and spread of drug resistance*, 2015.

26 Review on AMR, *Infection prevention, control and surveillance: Limiting the development and spread of drug resistance*, 2015.

27 Analysis commissioned by the Review.

BETTER WATER AND SANITATION REDUCES ANTIBIOTIC CONSUMPTION

In the four middle-income countries studied, introducing water and sanitation infrastructure could substantially reduce the number of related diarrhoea cases treated with antibiotics.

60%

potential decrease in the number of cases of water and sanitation-related diarrhoea being treated with antibiotics

Analysis commissioned by the Review.

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healthcare-associated infection (HCAI), a figure that rises to one patient in three in intensive care units (ICUs)[28]. These levels of incidence are even higher in low and middle-income settings, where healthcare facilities can face extreme constraints, sometimes as fundamental as access to running water for cleaning and handwashing.

As with infections acquired in the community, HCAIs foster drug resistance, and impose a human and economic burden in terms of clinical outcomes and higher healthcare costs. For example, one common hospital-acquired 'superbug', MRSA, can have a mortality rate more than double that of the easier-to-treat Methicillin-susceptible strains of the same species of bacteria, and be more than twice as expensive for a hospital to treat[29].

Some basic principles about how to stop the spread of infections in hospitals and other care settings, like nursing homes for the elderly, are well understood. Handwashing by clinicians between contact with patient is recognised, for instance, as being one of the single most effective means of preventing HCAIs. However, despite being such a simple and powerful intervention, actual adherence to proper hand hygiene can be remarkably low: only 40 percent on average[30]. Beyond this, there are substantial evidence gaps as to 'what works', and what is cost-effective – particularly in the case of new technologies which may offer substantial benefits in things like hand hygiene and the cleaning of care facilities. And to compound this, infection prevention and control (IPC) is too often seen as a cost pressure, rather than a means to deliver better value and better outcomes for patients; managers and senior clinicians often give it insufficient focus as a result.

What we need to do

First, IPC needs to be embedded as a priority for health systems at all levels.

This requires a return to the attitudes of the pre-antibiotic era, when infection prevention was recognised as a priority, because cures were limited.

When in the past governments, regulators and other health system leaders have established reducing levels of HCAIs as a system-wide priority, it has delivered results. MRSA reduction targets in the NHS in England, for instance, led to very substantial declines in rates in hospitals. Top-down priority-setting can play a valuable role in bringing this issue higher up the priority list, so long as they are in the form of carefully-designed targets that promote cooperative working across a health system.

Second, funding is needed to support studies that evaluate the efficacy and cost-effectiveness of IPC interventions, and which explore ways of changing behaviours.

Third, the benefits of improvements to water and sanitation in slowing the development of drug resistance need to be properly reflected in investment decisions by governments in low and middle-income countries

Investment in water and sanitation infrastructure delivers profound benefits for a population's health and prosperity, and should be seen as a vital foundation for sustainable economic growth. Using data published by the World Bank and the WHO, we have found that when income is controlled for, increasing access to sanitation in a country by 50 percent is correlated with around nine and a half years of additional life expectancy for its population.

Efforts to support global improvements in access to clean water and sanitation such as the 'Swachh Bharat Abhiyan' ('Clean India Mission') programmes are a huge step in the right direction for economic development and will be vital in countering the threat of AMR.

"Using data published by the World Bank and the WHO, we have found that when income is controlled for, increasing access to sanitation in a country by 50 percent is correlated with around nine and a half years of additional life expectancy for its population."

28 WHO, Report on the Burden of Endemic Health care-Associated Infection worldwide, 2011, ISBN 978 92 4 150150 7.

29 Filice GA, Nyman JA, Lexau C et al. Excess costs and utilization associated with methicillin resistance for patients with *Staphylococcus aureus* infection, *Infection Control and Hospital Epidemiology*, 2010, 31(4).

30 Erasmus V, Daha T J, Brug H, Richardus J H, Behrendt M D, Vos M C, et al., Systematic review of studies on compliance with hand hygiene guidelines in hospital care, *Infection Control and Hospital Epidemiology*, 2010, 31, 3, 283-294.

Intervention 3:
Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment

> ***"The antibiotic usage in food animals is indeed becoming a global issue associated with food safety and public health. All countries in the world should use the antibiotics in food animals more prudently and rationally. Concerning the antibiotics used as feed additives in food animals, now it is the time to act globally to restrict or prohibit the use of antibiotics in feeds for the purpose of growth promoter or disease preventing, and this should be done on the basis of the evaluation of risk assessments of such antibiotics."***
>
> Dr Jianzhong Shen, one of the authors of the Lancet report on the discovery of transferable colistin resistance in humans and animals in China

Agriculture

Why we need to act

There are clearly circumstances where antibiotics are required in agriculture and aquaculture. Their proper use can maintain animal health and welfare, as well as food security. However, much of their global use is not for treating sick animals, but instead either to prevent infections (sometimes to compensate for poor farming practices) or simply to promote growth. The quantity of antibiotics used in livestock is vast, and often includes those medicines that are important for humans. In the US, for example, of the antibiotics defined as medically important for humans by the FDA, over 70 percent of the total volume used (by weight) are sold for use in animals[31]. Many other countries are also likely to use more antibiotics in agriculture than in humans but they do not even hold or publish the information. There is also growing concern about the use of antimicrobials, particularly antifungals, in crop culture.

Many scientists see this as a threat to human health, as well as a threat to animal health and food security, given that wide scale use of antibiotics encourages the development of resistance that can spread to affect humans and animals alike. In our December 2015 paper, we reviewed 280 published, peer-reviewed research articles that address the issue of antibiotic use in agriculture. We found that 139 of these were published by academics; of these, only five percent concluded that there was no evidence of a link between antibiotic use in animals and resistance in humans, while nearly three quarters concluded that there is evidence of such a link.

In addition to this, large numbers of animals living in close proximity, or in non-hygienic conditions can act as a reservoir of resistance and accelerate its spread. There are often many opportunities in intensive farming environments for drug-resistant bacteria to be transferred between, for example, thousands of chickens being reared in the same indoor enclosure[32].

Although gaps in the evidence undoubtedly remain, there is an increasingly robust consensus that unnecessary use of antibiotics in animals and agriculture is a significant concern for human health. There is a compelling case for action now to reduce unnecessary use, as there also is in the unnecessary human use of antibiotics.

The issue of antibiotic use in agriculture and its impact on drug resistance has been recognised by the WHO as part of its Global Action Plan, requiring its member countries to develop National Action Plans to tackle AMR which incorporate considerations of animal usage. It has also been recognised by both the UN's Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE). We urge all three organisations to continue to work together through their Tripartite Agreement and to take the lead in accelerating international action in this area.

It seems clear to us that the poorest countries in the world are a group that will need help in this area from external development agencies. The World Bank with its experience in similar fields, along with other international NGOs and development agencies, together have an important role to play in providing support to help train veterinarians, guide development of regulatory frameworks for antibiotics, build laboratory and surveillance capacity, improve farming practices, and other similar methods of capacity-building.

Given that the countries of the G20 account for 80 percent of total world meat production[33], a large part of antibiotic consumption in livestock and the likelihood of generating drug resistance, currently rests with them. Therefore we feel this

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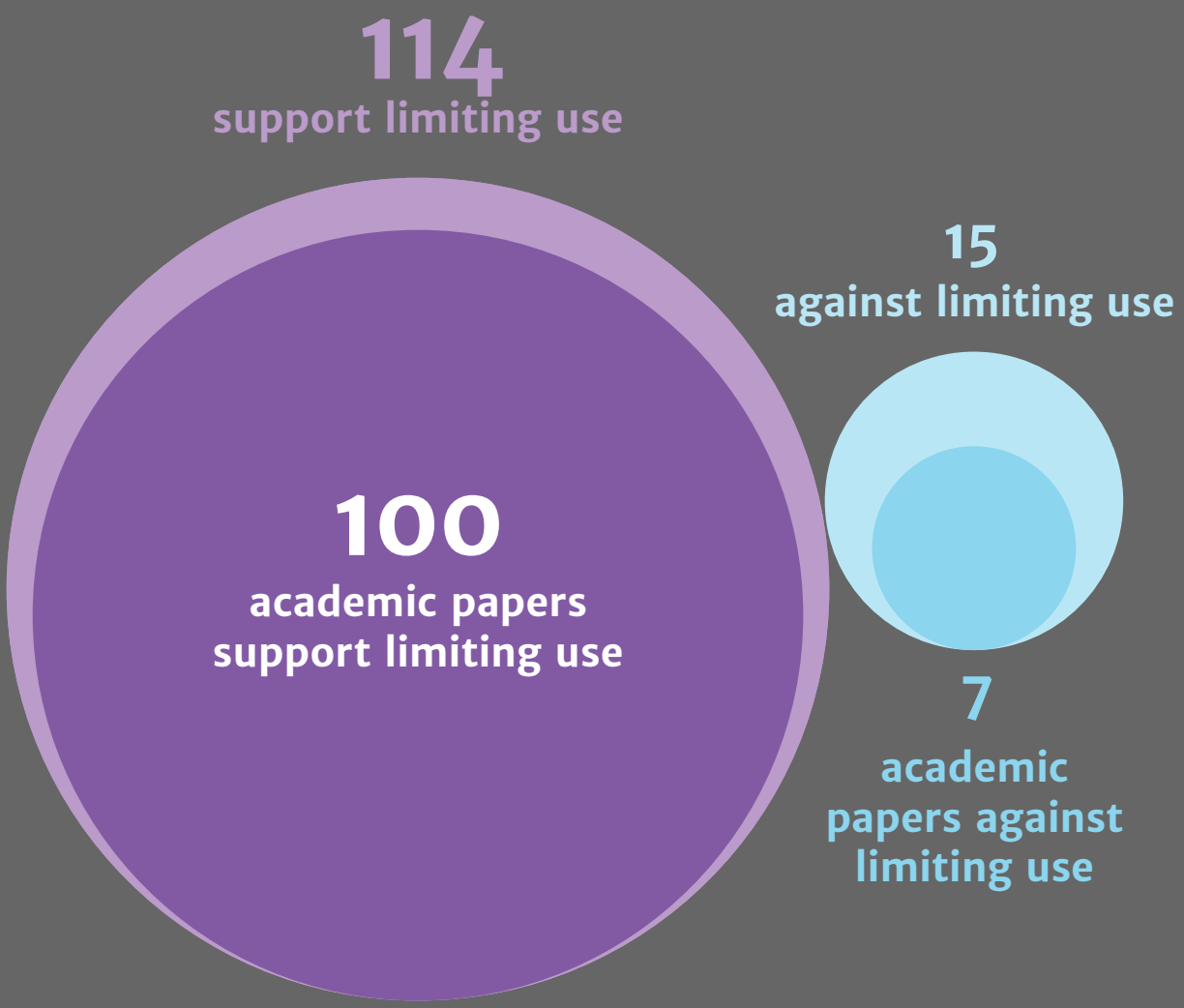
31 Animal consumption figure of 8,893,103kg from FDA, 2012. Human consumption of 3,379,226kg in 2012 based on calculations by IMS Health. The figures are rounded from 72.5 percent used in animals and 27.5 percent used in humans.

32 Davis MF, Price L, Liu C, and Silbergeld EK. An ecological perspective on U.S. industrial poultry production: the role of artificial ecosystems on the emergence of drug-resistant bacteria from agricultural environments, *Current Opinion in Microbiology*, 2011, 14, 3, 244-250.

33 FAO data, FAOSTAT, 2016.

MOST PUBLISHED PAPERS PROVIDE EVIDENCE TO SUPPORT LIMITING USE OF ANTIBIOTICS IN AGRICULTURE



Based on a representative sample using the 280 papers from the NCBI's PubMed database found with the search terms " "drug resistance, microbial" AND "agriculture" "; 88 of which were deemed not to be applicable as they did not address antibiotic use in agriculture. Papers were categorised as 'supportive' if they provided evidence to support limiting antibiotics in agriculture, 'against' if they provided evidence that we should not be concerned with limiting antibiotics in agriculture and 'neutral' if they did not explicitly take a stance. There were 63 papers that were categorised as neutral. Of the papers classified as neutral, 36 were written by academics. Academic papers are defined as those that were exclusively written by academics.

Source: Review's own analysis.

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is an issue that the G20 must take a lead on, alongside wider international efforts through the UN, WHO, OIE and FAO.

> *"There is an increasingly robust consensus that unnecessary use of antibiotics in animals and agriculture is a significant concern for human health."*

What we need to do

We propose three broad steps to improve this situation:

1. **10-year targets to reduce unnecessary antibiotic use in agriculture, introduced in 2018 with milestones to support progress consistent with countries' economic development.** In order to reduce global use of antibiotics in agriculture there is a strong case for targets on use at the country level, taking into account countries' production systems.

2. **Restrictions and/or bans on certain types of highly critical antibiotics.** Too many antibiotics that are last-line drugs for humans are being used in agriculture, sometimes without even professional oversight. These need to be the prime focus of efforts to reduce consumption in animals and action should be taken on this now.

3. **Improve transparency** from food producers on the antibiotics used to raise the meat that we eat, to enable consumers to make more informed purchase decisions.

1.

TARGETS / LIMITS TO REDUCE ANTIBIOTIC USE IN AGRICULTURE, INTRODUCED IN 2018

All antibiotic use increases the chance of resistant bacteria developing and spreading, and a ban on the use of antibiotics for growth promotion for example, while a significant step forward, alone would not solve the problem. It is also difficult for regulators to know how an antibiotic is being used. For example, antibiotic use declared to be prophylactic may increase when use for growth promotion is banned, as some users may try to 'game the system'. Providing targets allows countries to decide on a local level how they can best reduce unnecessary use of antibiotics in farming. We described our rationale for targets in more detail in our paper, *Antimicrobials in agriculture and the environment: reducing unnecessary use and waste*[34].

We have made proposals on how these targets could be structured but an expert international group is needed to guide countries and help them develop these proposals into ones that are ready to be implemented within the next two years. There are many questions, which it is beyond the scope of the Review to address, but which now need to be given urgent consideration by the global agricultural and veterinary community. These include:

- **How should the targets be calculated?** Our lead proposal is that this should be on a mg / kg basis for livestock and fish. However, one other option might be to measure usage on a 'defined daily dose' (DDD) basis. The methodology to set such targets will need careful consideration, such as whether antibiotic classes should be treated differently, and whether targets should be broken down by animal type – e.g. poultry, cattle, etc. - or broken down even further to give more specificity by species.

- **What levels should countries aim to reach?** We highlighted the success of Denmark as one of the largest pork exporters in the world. They have a highly productive farming system with levels of antibiotic use of less than 50 mg / kg. We therefore see this as a broadly reasonable target for high-income countries to aim for in the short-term. However, further consideration needs to be given to such targets and how they vary globally, not least since some countries are already below this level, whilst for others it would require substantial change and investment. There will not be a one-size-fits-all target, but all countries need to play their part in reducing use.

- **How long should be given to reach these targets?** We have proposed that targets could be set with a 10-year horizon, with benchmarks to encourage regular progress. Since there is a need for continuing, even indefinitely, efforts to optimise antibiotic use in animals, we envisage that new targets should be set, after these initial ones, to continue progress. We recognise that low and middle-income countries are likely to need more time to reach the same levels of use as high-income countries, and that developing further economic analysis on the switching costs in these countries in particular might assist with design and implementation. We believe that targets should be set globally within two years, beginning by 2018, but encourage countries that have good data on antibiotic use to already begin work on what appropriate targets would look like now.

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34 Review on AMR, *Antimicrobials in agriculture and the environment: reducing unnecessary use and waste*, 2015.

Gaps in data – surveillance and economic costs

In agriculture, there are large gaps in our data which we need to urgently improve, in parallel to setting initial targets. We discuss two of these gaps below and further detail is provided in a new paper published by Professor Anthony So et al[35], which is published on the Review website.

First, we need better collection of data to allow monitoring of the types and quantities of antibiotics being used in agriculture, as well as better data on the emergence and spread of drug resistance in animals. Collecting this information should be a priority over the next two years and would help inform further work on global targets or limits on antibiotic use in agriculture.

Across all settings, but especially resource-limited ones, the collection of such data should prioritise that which will move policymakers to act. For example, the growing resistance in food animals to last-line antibiotics for human medicine might serve as a wake-up call for action. As a recent US Department of Agriculture study showed, producers using antibiotics for production purposes rather than treatment would realise only a decline of less than one per cent in the value of what they produced[36]. Such studies and those demonstrating the cost-effectiveness of alternatives may be important in other settings.

The international community should also prioritise resources towards bolstering data collection in those countries and sections of the industry that will have the greatest global impact. By 2030, industrialised countries will have three times the level of meat consumption than developing countries, and together, the United States and China are projected to comprise 40 percent of the world's antimicrobial use in livestock production[37]. Therefore the largest markets need to be at the forefront of action in order to make real progress on this issue.

We encourage countries and regions where these types of surveillance data are already more routinely available to take a lead in global efforts to gather and bring together more complex data, such as use by species, routes of administration, and prevalence of drug-resistant bacteria in the food chain.

Elsewhere in this paper we describe what is needed to improve surveillance of AMR more generally. The 265 million GBP (375 million USD) Fleming Fund already announced by the UK Government (to improve AMR surveillance in low and middle-income countries) is an excellent starting point in this effort, but further sustained funding and collaboration is needed across human and animal populations to improve data on antibiotic use and resistance.

Second, we need better data on antibiotic use and farming practices across a variety of country settings, to enable modelling of the economic costs of transitioning to lower levels of antibiotic use in farming. On the producer side, this would include the impact of antibiotics used for both growth promotion and prophylaxis in different countries and regions – most of the evidence we have at the moment demonstrates this impact in high-income countries and focuses on growth promotion so this work needs to be broadened. It would also include an analysis of the costs of using alternative products, and of improving hygiene and other aspects of animal husbandry. Finally, benchmarking such efforts across multiple farming operations in each country (with data confidentiality ensured) could provide an economic motivator for farmers to move towards efficiently raising healthy animals with fewer antibiotics.

In line with the Global Action Plan, the OIE is collecting data on the use of antimicrobials in animals with the support of FAO and WHO. We hope this will go some way to fill the gaps in the animal sector, but these efforts need to be supported and accelerated where possible given the urgency of the AMR threat.

35 So AD, Ramachandran R, Love DC, Korinek A, Fry JP, Heaney CD et al, A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production, 2016, Available online on Review website: www.amr-review.org

36 Stacy Sneeringer, James MacDonald, Nigel Key, William McBride, and Ken Mathews. Economics of Antibiotic Use in U.S. Livestock Production, ERR-200, U.S. Department of Agriculture, Economic Research Service, November 2015.

37 Laxminarayan, R., T. Van Boeckel and A. Teillant (2015), "The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector", OECD Food, Agriculture and Fisheries Papers, No. 78, OECD Publishing.

HOW COUNTRIES COULD ACHIEVE TARGETS

In our paper, *Antimicrobials in agriculture and the environment: reducing unnecessary use and waste*[38], we discussed in detail how governments might use regulation, taxation and subsidies of alternatives to lower antibiotic use. It may be that governments choose to use a combination of all three.

However, one area that we believe needs particular focus in the context of animal use is vaccines. We already have a number of vaccines that are used in livestock and increasing the uptake could save significant amounts of antibiotic use, reducing the likelihood of drug-resistant bacteria developing, while improving animal health by preventing infections. The work of the OIE and others on prioritising diseases for which vaccines could reduce antibiotic use in swine, poultry and fish, would be a good starting point to focus efforts.

To increase vaccine coverage in agriculture and aquaculture, particularly in low and middle-income countries, consideration should be given to whether there is a case for creating a similar model to Gavi, which has had considerable success at expanding the coverage of vaccines on the human side. In addition to this more attention needs to be given to generating new vaccines.

As well as vaccines there are of course many other ways to reduce antibiotic use in agriculture and aquaculture, including changes in production practices and animal husbandry systems to improve hygiene, and reorganising the planning of production sites to reduce disease[39]. Improving vets' and farmers' awareness of AMR and education around appropriate antibiotic use will also be important, and we discuss a global awareness campaign earlier in this paper. These and other areas need to be explored by countries to optimise use and help them to achieve their targets.

The assumption behind how total reduction targets would work is that when farmers are put under pressure to reduce antibiotic consumption, they will prioritise reducing sub-therapeutic use (i.e. use as prophylaxis or for growth promotion), rather than therapeutic use to care for sick animals. Previous research has found that using sub-therapeutic antibiotics in agriculture could give an economic benefit of as little as five percent[40]. Our work suggests that the economic value to the farmer of using antibiotics to treat sick animals is comparatively higher. For this reason we see the potential for total use targets to encourage the reduction of non-therapeutic use, rather than depriving treatment to sick animals.

2.

RESTRICTIONS OR BANS ON CERTAIN TYPES OF HIGHLY CRITICAL ANTIBIOTICS

As well as reducing overall volumes of use, there is a strong case for some antibiotics not to be used in agriculture at all, or only to be used under very strict conditions, particularly the drugs we rely the most on in human medicine to treat very sick patients. This is because use of antibiotics in animals can impact on their efficacy in humans. This was recently shown with colistin, which is now a last-line antibiotic for humans, but has been used widely in animals in many countries, and only occasionally in humans. We need to be much quicker at recognising when such drugs become critical for human use and taking appropriate action on their use in agriculture. It is also important to recognise that drug resistance can extend beyond a particular drug to classes of drugs, and cross-resistance can even develop to multiple drugs beyond those directly administered. This represents another reason why surveillance is so important so that the appropriate national and international authorities are able to spot these occurrences and take action where necessary.

There has already been a substantial amount of work done internationally to define which antibiotics are highly critical for human health and map these to use in agriculture. However there is no single harmonised definition. The WHO[41], the European Medicines Agency (EMA)'s Antimicrobial Advice Ad Hoc Expert Group (AMEG)[42], the OIE and the FDA each have their own methodology. We believe that different criteria create the potential for loopholes and inconsistencies on a global scale.

We need to urgently agree upon a harmonised approach to identify those antimicrobials of greatest importance for human health, and whose use in animals represents the greatest risk. We believe this can and should happen within the next year and that a harmonised list should inform future bans or restrictions on the antibiotics that are most critical, such as colistin. This builds on the EMA's recent draft strategy for veterinary antimicrobial use[43] which suggests restricting the use of products critical to human health to instances where no alternative treatment exists.

In order to monitor and provide appropriate oversight of antimicrobial use in agriculture, many countries, especially some low and middle-income countries will need to develop better systems of veterinary oversight. We recognise that this will take time, but improving the capacity to implement standards in many countries will be essential to long-term progress on reducing unnecessary use.

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38 Review on AMR, *Antimicrobials in agriculture and the environment: reducing unnecessary use and waste*, 2015.

39 Midtlyng, PJ, Grave, K, Horsberg, TE, What has been done to minimize the use of antibacterial and antiparasitic drugs in Norwegian aquaculture?, *Aquaculture Research*, 2011, 42, s1, 28–34.

40 Laxminarayan R, Van Boeckel T, Teillant A, The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector, OECD Food, Agriculture and Fisheries Papers, 2015, No. 78, OECD Publishing.

41 World Health Organization, Critically Important antimicrobials for human use, 3rd revision, Geneva, 2011.

42 European Medicines Agency, Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals, 2014.

43 Committee for Medicinal Products for Veterinary Use (CVMP), CVMP strategy on antimicrobials 2016–2020 (draft), European Medicines Agency, 2015.

3.

IMPROVE TRANSPARENCY

Recent months have seen a series of announcements by companies, including food retailers, wholesale producers and fast food chains, of antibiotic reduction targets for their supply chains[44]. This is driven, often to a significant extent, by consumer pressure and preferences. For example, although still a small proportion of the overall market, sales of 'antibiotic-free' chicken in the US rose by 34 percent in 2013[45]. However, as well as consumer pressure, there is growing pressure from investors on food companies and restaurant chains to reduce unnecessary use of antibiotics in their supply chains[46]. This pressure from investors and long-term asset managers to raise the importance of responsible antibiotic use could play a crucial role in changing behaviours to address AMR.

Indeed changes, led voluntarily by the industry, might be one of the most practical ways to reduce antibiotic use in the short-term. To broaden this effort, mandatory transparency requirements for producers and retailers as to how antibiotics have been used in their supply chains could have a real impact. This could include labelling that refers to antibiotic use. This would improve consumer knowledge and help them make more informed decisions. This would not necessarily be a 'raised antibiotics-free' label; a 'responsible use' label might be more appropriate. Although in order for lasting change to be made third-party validation and support from independent institutions to monitor progress would be beneficial.

We call on producers, retailers and regulators to agree standards for 'responsible use'. These standards could then be developed and implemented as an internationally recognised label, or used by existing certification bodies.

Priority actions this year, including further analysis of the costs

Efforts to reduce unnecessary use of antibiotics in agriculture will continue for many years. Indeed, much work will need to be undertaken to apply best practices in production to reduce unnecessary use of antibiotics, and to ensure that the veterinary workforce to implement such practices is in place. However there are three tangible steps that we believe should be made this year:

1. **A detailed economic analysis of the transition costs to lower antibiotic use in farming practices in different regions / countries.** As we have discussed, a number of high-income countries have shown that it is possible to have relatively low levels of antibiotic use and be highly productive. More analysis is needed of the costs, in particular for low and middle-income countries, of transitioning to similarly low levels of use while maintaining animal welfare. This will help inform the detail of appropriate targets / limits and also provide more information to farmers and food producers of the actual economic benefits and costs of antibiotic use in the production system. We call on international organisations, such as the OECD or the World Bank, that have the appropriate expertise, to take forward this work as soon as possible.

2. **We need to improve surveillance and standards for data collection in many regions, in order to improve the data on antibiotic use in agriculture and across supply chains.** We call on the UN, with the support of the WHO, FAO and OIE, to focus on the gaps in surveillance of antibiotic use in agriculture and resistance in animals this year, and to develop a harmonised protocol for data collection and standards for reporting on AMR. This would need to be done in collaboration with work being done to improve surveillance on the human side. This will not only continue to improve our understanding of the health threat this problem poses, but importantly it will enable countries without current data on use to move towards setting targets / limits on use of antimicrobials in the future. We also encourage countries that already have such data available to consider how they can make progress in reducing antibiotic use now.

3. **We need the WHO, FAO and OIE to commission an expert group to agree a harmonised list across the relevant regulatory bodies and international organisations, of those antibiotics that are critical for humans**, as well as recommending which should be banned or restricted in agriculture. We call on governments to support this process.

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44 See Consumer Reports report (Consumer Reports, Meat on drugs: the overuse of antibiotics in food animals & what supermarkets and consumers can do to stop it,' Consumer Reports, 2012, Available at: https://www.consumerreports.org/content/dam/cro/news_articles/health/CR%20Meat%20On%20Drugs%20Report%2006-12.pdf.) on prevalence of antibiotic free meat in 123 major US supermarkets and the National Defence Research Council's case study (.NDRC, Case study Going mainstream: Meat and poultry raised without routine antibiotics use, 2015, Available at: http://www.nrdc.org/food/files/ antibiotic-free-meats-CS.pdf.

45 Wall Street Journal, Meat companies go antibiotics-free as more consumers demand it, November 2013, [Online] Available at: http://www.wsj.com/articles/meatcompanies-go-antibiotics-free-as-more-consumers-demand-it-14150718O2.

46 Farm Animal Investment Risk and Return (FAIRR), $1 trillion investor coalition demands corporate action on 'Systemic Overuse' of antibiotics- Press release, 2016, A Coller Initiative.

Reduce Environmental pollution

Why we need to act

Antibiotics can reach the environment through three principal channels: animal waste, human waste and manufacturing waste. They can contaminate soil, crops and water sources and encourage the development of drug resistance amongst the pathogens with which they interact. It is difficult to predict how quickly they degrade, as they are very diverse chemically – an area where gaps in our understanding need to be addressed to help us identify the antibiotics of greatest risk in an environmental context.

Animal waste

Studies suggest that 75–90 percent of tested antibiotics are excreted from animals un-metabolised[47], and enter sewage systems and water courses. We believe that tackling the source of this issue, much of which is due to unnecessary use of antibiotics in animals, is crucial. Beyond this, further consideration is also needed of measures to limit the sale and agricultural use of by-products which may contain antimicrobials, such as manure from animals that have been treated with antibiotics[48].

Human waste

The majority of antibiotics consumed by humans are also excreted un-metabolised[49]. As with animals, we believe that reducing inappropriate use of antibiotics is the key, tackling the problem at its source. However, inappropriate disposal of antibiotics, for instance by flushing them down the toilet, also plays a role[50], whilst the problem is particularly severe in the waste of patients in hospital settings. Multiple studies have found significant concentrations of antibiotics in hospital effluent in countries as diverse as Germany[51] and India[52]. Public awareness is instrumental to changing behaviours at the domestic and individual level, whilst the recognition (and prioritisation) of the issue by health system leaders is necessary to drive changes in how hospital waste is managed. In countries where resources are limited, tackling the treatment of hospital waste as a priority would likely yield the greatest benefits on this front.

Manufacturing waste

The way that antimicrobials are produced, and the by-products which result, is an issue which has too often been neglected to date in discussions about AMR. The remainder of this section outlines the source of this issue and our proposed solutions for tackling it.

Active pharmaceutical ingredients (APIs) are the biologically-active ingredients in a pharmaceutical drug. In the case of antimicrobials, most are manufactured in China and India, where local companies are able to manufacture these raw ingredients to global standards at substantially lower costs than in Europe or other high-income locations. These APIs are then sold in bulk to pharmaceutical companies who make end products for patients globally. However, there is growing evidence that some API manufacturers do not adequately treat waste products, with the result that antibiotic APIs are released into the local environment, usually as waste water. This acts as a driver for the development of drug resistance[53], creating environmental 'reservoirs' of antibiotic-resistant bacteria[54],[55].

For example, an important study by Swedish researchers in 2007 examined a wastewater treatment plant in India that received effluent from 90 bulk API manufacturers. It revealed that shocking levels of APIs were being discharged into a nearby river. It also showed that the concentration of ciprofloxacin, a commonly used antibiotic, exceeded levels toxic to some bacteria by 1000-fold – a far higher concentration of the antibiotic than would routinely be found in the blood of a patient taking the drug[56]. Similar studies have been undertaken at sites elsewhere in Asia and Europe[57].

Failing to solve this problem does most harm in the short-term to the health of people living near manufacturing sites who are exposed to polluted water. In a way, they are paying a price for the supply of cheap antibiotics upon which much of the world relies. But in the long-term, we know that resistance spreads and this will contribute to the global problem.

What we need to do

We recommend two complementary approaches to reducing this problem of environmental pollution.

1.

ESTABLISH MINIMUM STANDARDS TARGETING THE EMISSION OF MANUFACTURING WASTE CONTAINING APIs

There are currently no, or very few, standards for API discharge and limited systematic monitoring of discharge anywhere in the world[58]. We recommend the introduction of minimum regulatory standards for relevant APIs in liquid waste, and potentially also

47 Marshall, BM, Levy SB, Food animals and antimicrobials: impacts on human health. Clinical Microbiology Reviews, 2011, 24, 718–733.

48 Sengeløv G, Agersø Y, Halling-Sørensen B, Baloda SB, Andersen JS, Jensen LB, Bacterial antibiotic resistance levels in Danish farmland as a result of treatment with pig manure slurry, *Environment International*, 2003, 28(7).

49 Kümmerer K, al-Ahmad A, Mersch-Sundermann V, Biodegradability of some antibiotics, elimination of the genotoxicity and affection of wastewater bacteria in a simple test, *Chemosphere*, 2000, 40, 7, 701–10.

50 Center for Disease Dynamics, Economics & Policy, State of the World's Antibiotics, 2015, Washington, D.C.

51 Kümmerer, K. Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources—a review, *Chemosphere*, 2001, 45, 957–69.

52 Diwan V, Tamhankar AJ, Khandal RK, et al, Antibiotics and antibiotic-resistant bacteria in waters associated with a hospital in Ujjain, India, *BMC Public Health*, 2010, 10, 414.

53 Sum of Us, Changing Markets and Profundo, Bad Medicine: How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs, 2015.

54 Bengtsson-Palme J, Boulund F, Fick J, et al, Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India, *Frontiers in Microbiology*, 2014, 5, 648.

solid waste. Responsibility for compliance would sit with API manufacturers and would be assessed through independent risk assessments. We are aware that there has been relatively limited research into what level of API residue should be set as a regulatory maximum discharge for each API. We would encourage further scientific research into this across antibiotic classes but, in the meantime, recommend basing initial standards on levels set out in existing literature[59].

2.

ENCOURAGE THE PHARMACEUTICAL INDUSTRY TO DRIVE HIGHER STANDARDS THROUGHOUT THEIR SUPPLY CHAINS

We recognise that adoption of new international regulations can take time. Given this, we believe there is an onus on the industry itself to drive change, through pharmaceutical companies requiring higher standards from their supply chain partners, and/or buyers integrating environmental considerations into their reimbursement appraisals, particularly for high-volume generic products. We note, for instance, the efforts of the Antibiotic Stewardship Council, which is comprised of major industry players, to improve manufacturing practices. There are good examples of instances in other sectors where industry and non-government stakeholders have driven change (e.g. palm oil), as well as those where regulation took a leading role (e.g. CFCs).

Confidence that self or third-party regulation has been followed could be provided through improved transparency regarding pharmaceutical companies' sourcing of APIs. This could feed into industry labelling, similar to that used in consumer-facing industries to denote good practice, for example the Marine Stewardship Council (MSC) or Forest Stewardship Council (FSC) symbols on fish and wood respectively.

Improved manufacturing practices, for example the use of enzymes, can increase yields and lower energy, chemical and solvent needs whilst also reducing API waste. However, we recognise that a bigger impact, at least in the context of current practices, is likely to be through API waste treatment. The significant majority (more than 95 percent[60]) of antibiotic API manufacturing waste is in liquid form. This can be addressed by on-site, waste water treatment plants. There are two advantages of having plants on site. Firstly, it addresses the issue of environmental waste at source, leaving less space for contamination downstream. Secondly, it means that control and responsibility (not just accountability) remain with the API manufacturer, who can be effectively monitored by external agencies with respect to compliance. There is also scope to improve treatment of solid waste but, given the relative scale of the problem, we recommend prioritising tackling liquid waste.

A new regulatory regime, provided it was consistently implemented and enforced across districts and countries, could raise the bar across the industry and confer neither advantage nor disadvantage to any particular player in their negotiations with suppliers and customers.

How much would it cost?

The number of tonnes of APIs produced per year and the current costs associated with this production are not known. There has also been limited research into what level of APIs in manufacturing waste should be considered unsafe. As such, the cost and impact of improving treatment of liquid waste – through the construction and operation of on-site, dedicated waste water treatment plants (including waste water testing) – are difficult to quantify. We believe there is a strong case for more research into this area, to inform mandatory or voluntary standards for each class of APIs.

In the absence of sufficient third party research into the matter, we think the following estimates, based on the experiences of a major industry player, serve as a useful starting point for further investigation. These suggest that it could cost in the region of 180 million USD per year (or 0.50 USD/ kilogram of APIs produced) to prevent an estimated 30,000-70,000 tonnes of waste with antimicrobial activity generated by the antibiotic supply chain from reaching the environment. This quantity represents 10-20 percent of the total antimicrobial activity produced in manufacturing sufficient APIs to support estimated global antibiotic consumption of around 250,000 tonnes a year[61]. Though that 10-20 percent is much lower than the 50%+ figures, for the proportion of antibiotics excreted by humans and animals, the fact that this waste is released by a small number of production facilities (around 200 globally[62], mostly in India and China) rather than broadly spread across the global human and animal population, means that local environments, particularly water courses downstream of production facilities, can show marked concentrations of antimicrobial activity and risk becoming breeding grounds for resistance.

55 Flach CF, Johnnin A, Nilsson I, Isolation of novel IncA/C and IncN fluoruquinoloneresistance plasmids from an antibiotic-polluted lake, *Journal of Antimicrobial Chemotherapy*, 2015, 70, 10, 2709-17.

56 Larsson, DGJ, Pollution from drug manufacturing: Review and perspectives, *Philosophical Transactions of the Royal Society B*, 2014, 369.

57 Li D, Yang M, Hu j et.al, Determination and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and receiving river, *Environmental Toxicology and Chemistry*, 2008, 27, 80-86.

58 Agerstrand M, Berg C, Björlenius B et al, Improving Environmental Risk Assessment of Human Pharmaceuticals, *Environmental Science*, 2015, 49, 5336-5345.

59 Bengtsson-Palme J, Larsson DGJ, Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International*, 2015, 86, 140-149.

60 Industry estimate.

61 Sarmah AK, Meyer MT, Boxall AB, A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment, *Chemosphere*, 2006, 65, 5, 725-59.

62 Thomson Reuters Newport database.

Intervention 4:
Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals

> ***Without good surveillance, we cannot effectively counter the threat that antimicrobial resistance poses to health systems and people all over the world. It is also vital that countries work together to make sure old and new technologies are rolled out in a way that supports better global "One Health" AMR surveillance including animals and the environment.***
>
> Yasuhisa Shiozaki, Minister of Health, Labour and Welfare for Japan

Why we need to act

Surveillance is the foundation of infectious disease management, yet is often ignored or given less importance than treatment in the fight against infectious diseases. In our report in March 2016[63], we showed that information from surveillance systems would provide benefits at multiple levels. At the local level, information would help improve patient health. At the national level, surveillance data would help inform health policies and responses to health emergencies. Finally, at the global level, it would provide early warnings of emerging threats and help identify long–term trends.

Surveillance for AMR should ideally include three strands of data that need to be analysed in tandem to fully understand the epidemiology of AMR. The first is monitoring data on consumption of antibiotics in both humans and animals, which would give us better information on the extent of antibiotic use, in which areas, and which would help understand the link between antimicrobial use and the development of resistance. The second is data on resistance rates for various drug–bug combinations and their impact on patients' health. The third is molecular biological data to explain the biological basis of resistance, through characterisation of the types of resistant bacteria and the genetic reasons for their resistance. This information should be gathered within a 'one health' perspective, covering animals and humans to provide a complete picture of consumption and resistance rates as well as the environment, to monitor base levels of antimicrobial resistance as well as the impact of antimicrobial manufacturing. Although some of this will take time, efforts should start urgently.

> *At the local level, information would help improve patient health. At the national level, surveillance data would help inform health policies and responses to health emergencies. Finally, at the global level, it would provide early warnings of emerging threats and help identify long–term trends.*

What we need to do

We need to continue improving our monitoring and understanding of infectious disease globally, and ensure that the surveillance of drug–resistant infections is included in these systems. To achieve this, action is needed in two ways.

First, the WHO, FAO and OIE, regional bodies and philanthropic organisations need to continue playing a coordinating role in developing a global surveillance network and governments and national authorities need to increase funding to develop and expand their current networks. Efforts are underway to improve surveillance of infectious diseases in general and the monitoring of drug resistance specifically, with important work being led by the WHO through the Global Antimicrobial Resistance Surveillance System (GLASS), the OIE through their database on use of antimicrobials in animals with the support of FAO and WHO, regional blocs, and philanthropic organisations such as the Institut Pasteur and the Gates Foundation, with wide international networks on the ground. Countries have also increased funding in this area recently, in particular the US government via the Global Health Security Agenda (GHSA), and the UK Government with its announcement last year of the 265 million GBP (375 million USD) Fleming Fund – the latter being a direct response to early recommendations made by this Review. These initiatives, as well others, aim to increase international cooperation, and support capacity–building in low–income countries. But huge gaps need to be addressed if we are to have comprehensive, reliable information on the development and spread of drug resistance globally and how it is affecting patients.

Second, governments and globally–representative bodies need to find ways to incentivise and remove barriers to safe, secure and appropriate sharing of data of use to global surveillance efforts. One particular challenge is to ensure that health systems, doctors and researchers are able to make the most of the 'big

63 Review on AMR, *Infection prevention, control and surveillance: Tackling the development and spread of resistance*, 2016.

HOW SURVEILLANCE CAN IMPROVE HEALTH OUTCOMES

Review on Antimicrobial Resistance

data' that will be generated as diagnostic tools are modernised and cloud computing is embraced. These new tools are just around the corner, and even less developed countries may be able to 'leapfrog' into using them. So questions about how data are owned, used and shared need to be answered now if the full potential of this information revolution is to be harnessed in our battle against AMR. Additionally, governments need to examine regulations and incentives for private players such as private laboratories, hospitals and pharmaceutical companies to encourage them to enter the field of surveillance and share the data that they collect, both on consumption and resistance rates. This presents a rich potential source of information that would generate more representative data.

How much would it cost?

It is exceptionally challenging to establish a firm estimate of the costs of implementing a comprehensive, global surveillance system tracking antibiotic use and rising drug resistance across both the human and animal populations, and in the environment.

First, there is a lack of data on current surveillance capabilities across the world, which are extremely variable with some countries and regions having advanced systems in place, some with insufficient laboratory capability for participating in surveillance, and some regions where there is simply no infrastructure or routine testing being carried out.

Second, there is very little information to set out what type of system we would need to provide good quality data for surveillance that would also benefit the patient.

Third, in the regions where resistance testing is conducted, it is often part of larger surveillance systems that are intrinsic parts of the wider healthcare infrastructure.

Fourth, AMR is not limited to a single pathogen or case definition, unlike diseases such as polio, gonorrhoea or influenza, for which surveillance systems have existed for a while. It is therefore challenging to extrapolate the costs of AMR surveillance from the cost of already existing surveillance networks.

However, we believe that improving the surveillance of AMR is vital. The recent GHRF report, recommended a total investment of 4.5 billion USD per year to improve national pandemic preparedness capabilities, including significant improvements to global disease surveillance capabilities as part of wider enhancements to emergency response capabilities[64]. We support the recommendations of the report and believe that a global commitment to investing on this scale is crucial to enable health systems to better respond to the threat of infectious diseases as a whole.

The work of the WHO in setting up the GLASS, the work of the Fleming Fund in the UK, and the surveillance-focused strands of the GHSA, will play important roles in providing financial and technical support for building laboratory and surveillance capabilities in low and middle-income countries.

64 GHRF Commission (Commission on a Global Health Risk Framework for the Future). *The neglected dimension of global security: A framework to counter infectious disease crises*, 2016.

Intervention 5:
Promote new, rapid diagnostics to reduce unnecessary use of antimicrobials

> *"Today, antibiotics are rarely prescribed based on a definitive diagnosis. Diagnostic tests can show whether or not an antibiotic is actually needed, and which one. Having rapid, low-cost, and readily available diagnostics is an essential part of the solution to this urgent problem."*
>
> Dr Margaret Chan, Director General of the World Health Organization

Why we need to act

The vast majority of antimicrobial, and especially antibiotic prescriptions are made outside the hospital, by doctors without using a diagnostic tool, by pharmacists or by self-medicating patients buying antibiotics OTC. When doctors and other medical professionals decide whether to prescribe an antibiotic, they usually use so-called 'empirical' diagnosis: they will use their expertise, intuition and professional judgement to 'guess' whether an infection is present and what is likely to be causing it, and thus the most appropriate treatment. In some instances, diagnostic tools are used later to confirm or change that prescription. This process has remained basically unchanged in decades: most of these tests are lab-based, and would look familiar to a doctor trained in the 1950s, using processes that originated in the 1860s. Bacteria must be cultured for 36 hours or more to confirm the type of infection and the drugs to which it is susceptible. An acutely ill patient cannot wait this long for treatment, and even when the health risks are not that high, most doctors' surgeries and pharmacies are under time, patient and financial pressure, and must address patients' needs much faster.

Huge quantities of antimicrobials, in particular antibiotics, are wasted globally on patients who do not need them, while others who need them do not have access. Fundamental change is required in the way that antibiotics are consumed and prescribed, to preserve the usefulness of existing products for longer and to reduce the urgency of discovering new ones. Rapid point-of-care diagnostic tests are a central part of the solution to this demand problem, which results currently in enormous unnecessary antibiotic use.

Rapid diagnostics would be able to reduce use of antibiotics by letting doctors know if a patient has an infection and if this infection is viral or bacterial, meaning that antibiotics will only be given out to patients who need them. In the future rapid diagnostics should be able to test for resistance allowing doctors to give patients the most appropriate available medicine for them. This will not only improve direct outcomes, but it can also stop transmission rates by shortening the time that people are infectious for, and improving infection control and will allow us to protect our most valuable drugs by only using them when no other drugs will work. The information garnered from rapid diagnostics, might eventually allow doctors to improve treatment and infection control to such an extent that this places negative selective pressure on resistance pathogens, thus reducing resistance in older drugs[65].

The reason why the science and technology have changed so little is mainly a lack of a market for new diagnostic tests, due to what economists would call externalities.

The use of diagnostics represents a classic example of a 'public good': the benefits are better antibiotic conservation and slower development of resistance and accrue to society at large over time, while the near-term costs are incurred by individual doctors or patients. It is simply more expensive and more time-consuming for a doctor or a patient to use a diagnostic than to use a drug 'just in case' it is needed, even if a test could help save costs and reduce waste at a health system-wide level, and help preserve the usefulness of antibiotics for all, over the longer-term. Many drug companies, meanwhile, including those producing affordable generic antibiotics, have no commercial interest in the advent of rapid diagnostics, which would act to limit the number of antibiotics prescribed. So it is not hard to see why diagnostic innovation has been so slow, with limited financial incentives to sell or buy these innovative products. Initiatives, such as the UK Longitude Prize, and prizes in the US and the EU have been important catalysts in raising attention for the need for rapid point-of-care diagnostics. But to sustain innovation in the medium and long-term, and to encourage uptake of the resultant technology, bolder and more sustained intervention is needed.

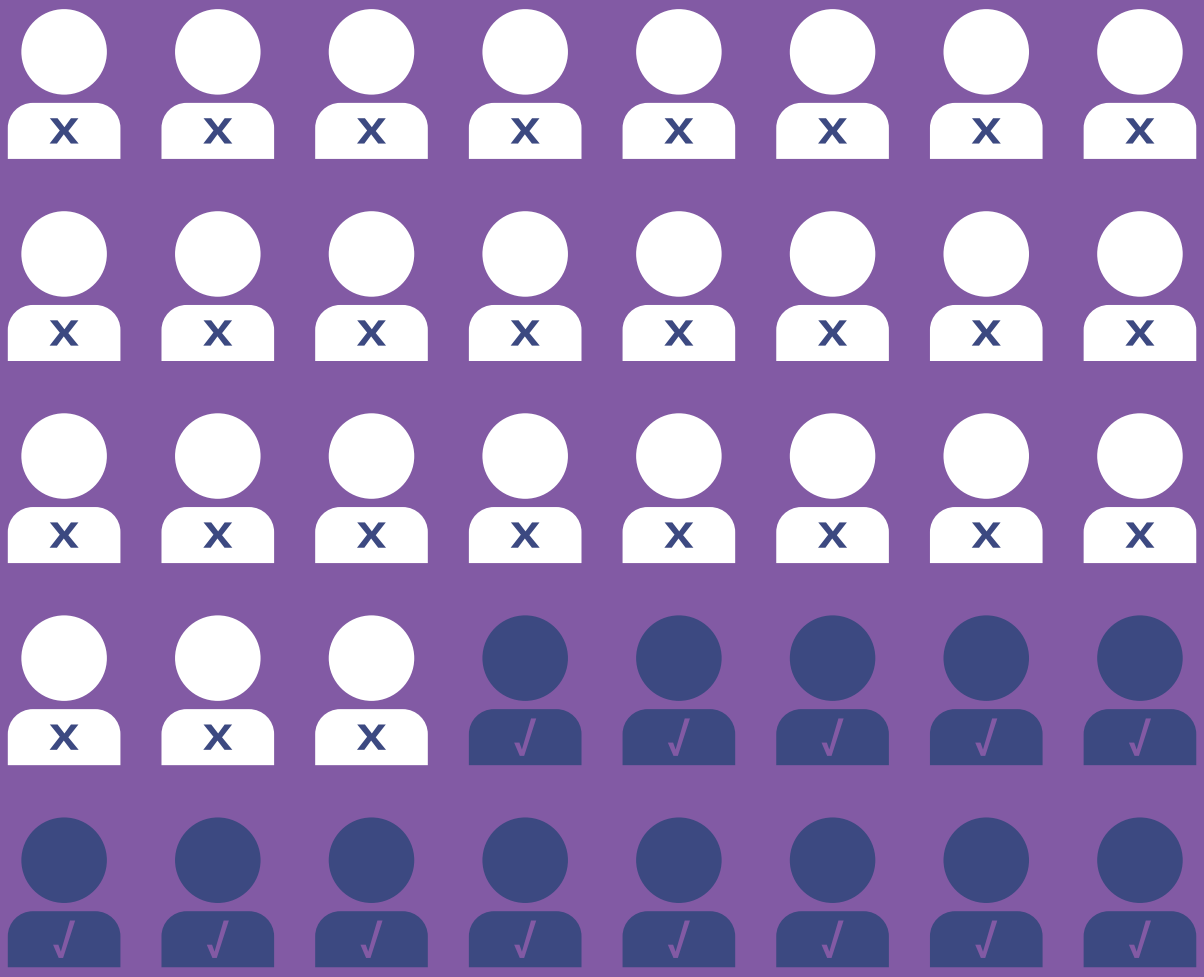
65 McAdams D, Extending the Antibiotic Era: Genomics and the Changing Game of Antibiotic Resistance, Working paper, 2016, Duke University.

RAPID DIAGNOSTICS WOULD REDUCE UNNECESSARY PRESCRIPTION

Out of 40m people who are given antibiotics for respiratory issues, annually in the US:

27m
get antibiotics unnecessarily

13m
who need antibiotics get them



Data extracted from: Shapiro D J, Hicks L A, Pavia A T, Hersh A L. *Antibiotic prescribing for adults in ambulatory care in the USA*, 2007–09. Journal of Antimicrobial Chemotherapy 2013.

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> *The vast majority of antimicrobial and especially antibiotic prescriptions are made outside the hospital, by doctors without using a diagnostic tool, by pharmacists or by self-medicating patients buying antibiotics OTC.*

What we need to do

Three specific measures must be adopted urgently.

First, high-income countries must lead the way to change how antibiotics are used. They should make it mandatory that by 2020 the prescription of antibiotics will need to be informed by data and testing technology wherever it is available and effective in informing the doctor's judgment to prescribe. To support this, governments, regulators and other health system leaders should consider incentives to facilitate the uptake and use of rapid point-of-care diagnostics in primary and secondary care. This will ensure that current diagnostics are used more often and will spur investment in further innovation by giving developers assurance that if their tests are effective enough, they will be used.

Second, we need a multinational effort to fund early research in this area – which could see new technology emerging from start-ups and newer companies in the emerging markets. We recommend that our proposed Global Innovation Fund for AMR (see below) should support this early research.

Third, in low and middle-income countries where access and affordability are the main barrier, a Diagnostic Market Stimulus (DMS) would provide top-up payments when diagnostics are purchased, in a similar way that Gavi has revolutionised global vaccine coverage. A similar approach could also be adopted to support uptake of vaccines that are relevant to AMR where affordability is an issue.

Finally, it is worth noting that the rapidly-advancing boundaries of computer learning and artificial intelligence could be put to good use in changing antibiotic prescribing – something that is already being done in other areas of medical practice, analysing and interpreting vast quantities of clinical data to support better clinical decision-making in real time.

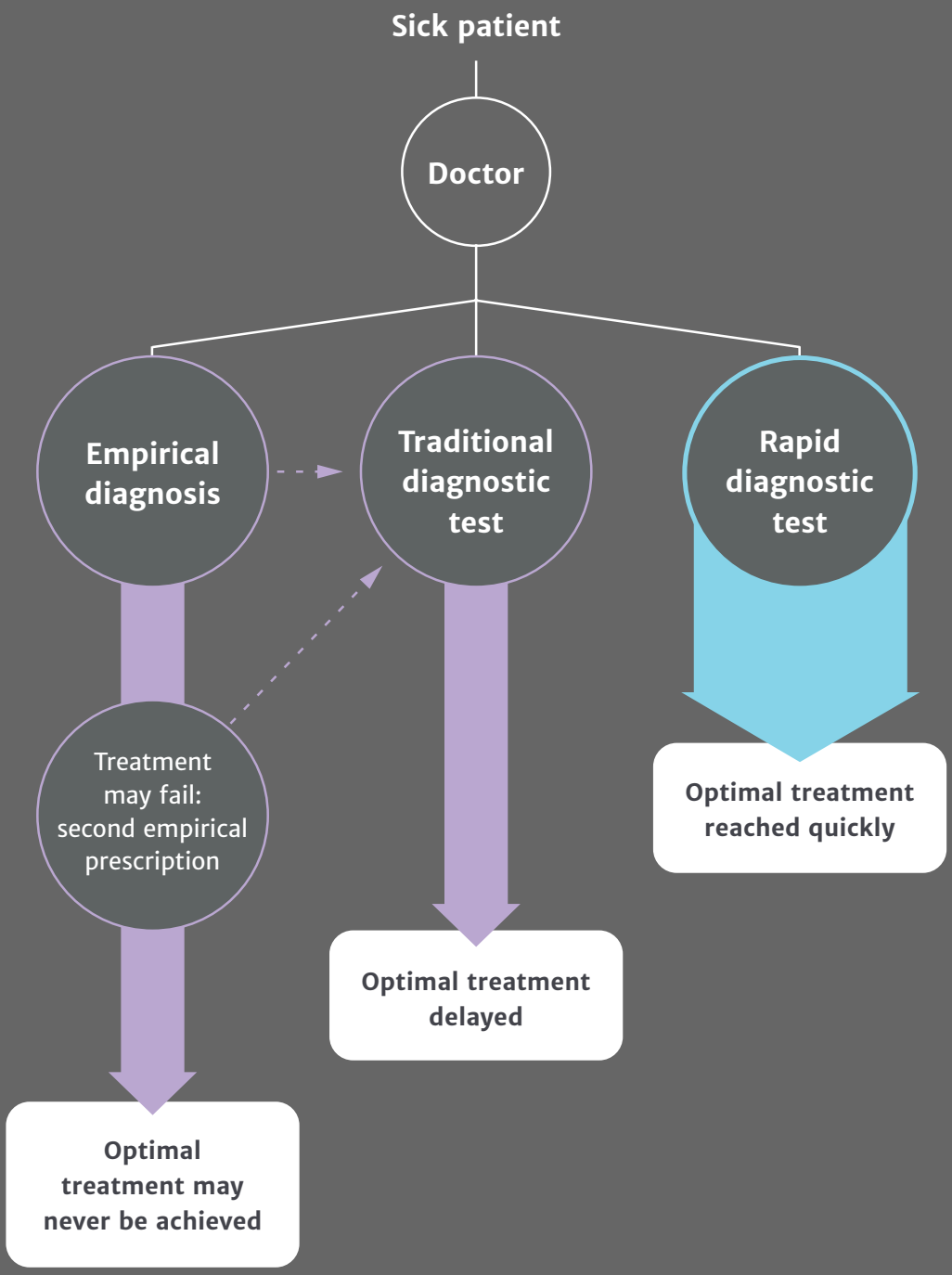
How much would it cost?

The cost of diagnostics will vary over time depending on the quality and quantity of diagnostics that are available. In a world where diagnostics can be produced very cheaply, or where there are a small number of diagnostics coming though, the cost is likely to be small. However, if diagnostics come along that are expensive to make and use, but can make a large difference in the fight against AMR, then subsidies are likely to be far higher, but justifiably so.

We estimate that the average cost per decade to roll-out diagnostics in low and middle-income countries using a DMS will range from 0.5 to 1 billion USD a year, based on the cost and usage of current diagnostics for TB, gonorrhoea, malaria and HIV. This should not be considered a precise estimate of the cost of a DMS, and we encourage continued research in this area.

> *High-income countries should make it mandatory that by 2020 the prescription of antibiotics will need to be informed by data and testing technology wherever it is available.*

NEW RAPID DIAGNOSTICS WOULD OPTIMISE TREATMENT



Review on Antimicrobial Resistance

A case study using gonorrhoea

The 70-year history of antibiotics has been marked by the continual and seemingly inevitable rise of antibiotic resistance. Gonorrhoea, a sexually-transmitted bacterial infection, illustrates very well our constant 'battle' to overcome resistant bacteria and so treat drug-resistant infections. Penicillin was first used to treat gonorrhoea in 1943 and was highly effective, but even by 1955 doctors had to increase their dosage 10 fold in order to combat growing resistance. By the mid-1960s tetracyclines had started to replace penicillin as resistance continued to increase. In the 1980s and 90s doctors began to switch again to fluoroquinolones such as ciprofloxacin. However these too eventually could not be used because of rising resistance rates, leading to the recommendation from the WHO in 2004 that cephalosporins should be used in all cases[66]. Currently the recommendation is for 'last-resort' dual therapy with injectable ceftriaxone and oral azithromycin. We have no obvious drugs left to use against gonorrhoea if these fail, and because of this it is internationally considered to be an urgent priority as resistance to both of these agents heralds potentially untreatable infections.

While doctors have stopped prescribing many older drugs due to resistance, this does not mean that these drugs would never work. On the contrary as of 2013, 70 percent of gonorrhoea cases in England and Wales were treatable with oral ciprofloxacin and over 80 percent with penicillin. But a 20 or 30 percent chance that the treatment would fail is too high for doctors to give these drugs to their patients; instead they normally stop prescribing first-line drugs for gonorrhoea once resistance rates exceed five percent. Given the combination of the shortage of new drugs for gonorrhoea, old drugs that would often work if we could use them, and existing molecular diagnostics that are relatively widely used, we felt that it would make for a good case study of the impact that a new rapid diagnostic for predicting resistance could have.

There are three benefits to introducing a new diagnostic in this area. The first is that patients would be diagnosed and treated appropriately faster than they are at present. Secondly, this would reduce transmission because people would be infected for shorter lengths of time. Finally, we could begin re-using old drugs, which would increase the size of our arsenal and simultaneously reduce the selective pressure for resistance to ceftriaxone, prolonging its effectiveness.

In order to best understand this we asked Dr Katy Turner from the University of Bristol[67] to examine the benefits of a diagnostic for gonorrhoea, quantifying them where possible. She found that rolling out a rapid diagnostic would reduce the average time it takes for patients to receive treatment in the UK by over two days. This would improve medication rates as doctors could prescribe appropriate treatment on the spot, and would reduce transmission as people would more often be treated successfully before they had unprotected sex again. Secondly a diagnostic that could predict resistance to older agents could reduce the number of ceftriaxone courses by more than 66 percent as most people would be given either penicillin or ciprofloxacin. This would reduce selective pressure on ceftriaxone, which would likely have huge benefits in fighting resistance, although it is more difficult to quantify how this would play out over time.

Finally, Dr Turner found that while there would be some cost savings from bringing in the resistance diagnostic, due to fewer appointments for patients, such savings were likely to be lower than the cost of the diagnostic. This diagnostic does not currently exist, so we can only guess how much it would cost, but if priced at 50 GBP (75 USD) per test, it would cost the UK an additional 70 million GBP (100 million USD) per year to introduce the diagnostic. Whilst the price of testing for resistant gonorrhoea is high, because the overall proportion of infection in those tested is low, the benefit from preventing or even slowing increases in resistance to ceftriaxone is nonetheless substantial, since the costs of developing new antibiotics are huge and, more importantly it takes around 10 years for new drugs to reach market.

This example highlights the paradoxical problem of new diagnostics; in the short-term it is often cheaper for healthcare providers and commissioners to rely on the current methods of diagnosis rather than to adopt new strategies. However, if we accept the financial 'hit' and introduce the new tests, by preserving useful treatments for gonorrhoea and lowering infection rates, the longer-term payoff to society would be large. This is why we believe it makes sense for governments to intervene in the market so that the external benefits of diagnostics are properly captured.

66 Barry P, Klausner J, The use of cephalosporins for gonorrhea: the impending problem of resistance, *Expert Opinion on Pharmacotherapy*, 2009, 10, 4.

67 Turner K, Christensen H, Adams E, McAdams D, Fifer H, McDonnell A, Woodford N, Analysis of the potential impact of a point-of-care test to distinguish gonorrhoea cases caused by antimicrobial-resistant and susceptible strains of *Neisseria gonorrhoeae*, (In preparation), 2016.

Intervention 6:
Promote development and use of vaccines and alternatives

> ***Tackling antimicrobial resistance requires a wide range of approaches and developing alternatives to antibiotics, in humans and animals, is critical to the fight. Vaccines have a vital role to play in combatting drug resistance, by preventing infections in the first place.***
>
> Dame Sally Davies, Chief Medical Officer for England

Why we need to act

Since the earliest immunisation programmes were launched in the mid-19th century, vaccination has profoundly changed the global infectious disease landscape, saving countless lives and fundamentally shifting patterns of disease transmission.

However, costs and poor health infrastructure in low and middle-income countries can make rolling out vaccines difficult and more expensive[68]. Gavi, the Vaccine Alliance, has made impressive progress in countries that might otherwise struggle to fund such programmes. By providing vaccines to 296 million children, Gavi has helped avert an estimated four million deaths[69] over the five-year period from 2010 to 2015. Their and others' introduction of Advanced Market Commitments (AMCs) have also created a market for products needed in lower-income countries, for which there were not previously commercially viable markets. Similarly impressive efforts have been made by both UNICEF and the WHO to broaden their monitoring process to include newer vaccines, for example those against *Streptococcus pneumoniae* and rotavirus, and underutilised vaccines.

Historically, vaccine programmes have been very cost-effective, often saving society more than 10 times their original cost[70], and averting more than a 100 million cases of childhood illness over 90 years[71].

New vaccines relevant to AMR are generally more complex and so more costly to develop than their forebears and may tackle smaller patient populations than the examples mentioned above. However, it is clear that they too could play a pivotal role in responding to the challenges of infectious disease and rising drug resistance. For this reason we believe this area is under researched and would like to see a greater level of investment, with funding from governments, charities and international organisations where necessary.

What needs to be done

Spending on vaccine R&D lags behind that on new drugs, and the share of the global pharmaceutical market attributable to vaccines is only three percent[72]. In the current global healthcare paradigm, far more effort and reward goes to treatment than to prevention.

In our report *Vaccines and Alternative approaches: Reducing our dependence on Antimicrobials*, we made three key recommendations with respect to vaccine innovation and uptake:

1. Use existing products more widely in humans and animals.

2. Sustain a viable market for vaccines.

3. Renew impetus for early research in vaccines useful for AMR.

Use existing vaccines more widely in humans and animals

There are many areas where we have existing vaccines that work, such as for pneumococcal infections which are caused by the bacteria *Streptococcus pneumoniae*, including pneumonia, meningitis, ear and sinus infections, and bloodstream infections. The WHO estimates that 14.5 million episodes of serious pneumococcal infections occur each year in children aged less than five years, resulting in over 800,000 deaths[73]. By increasing the use of vaccines in this area, for example, pneumococcal conjugate vaccines, we could not only save a large number of these lives but reduce selective pressure that causes resistance to the drugs we use to cure these infections. A 2011 US study found that the use of such vaccines led to a 64 percent reduction in antibiotic-resistant pneumococcal infections among children and a 45 percent decrease among adults over 65 years of age[74]. Despite this, access in low and middle-income countries was low, due to the higher price of the vaccines, though Gavi has done great work to improve access in this area. Similar schemes should be introduced to increase access to other vaccines that are underutilised both now and in the future.

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68 Médecins sans Frontières, The Right Shot: Bringing down barriers to affordable and adapted vaccines, 2015, 2nd Ed.

69 Gavi and Bill & Melinda Gates Foundation Joint Impact Modelling, Number of future deaths averted as a result of pentavalent, pneumococcal, rotavirus, yellow fever, meningitis A, Japanese encephalitis, Human papillomavirus, typhoid and rubella vaccination in 73 Gavi eligible countries (as of 2010).

70 Zhou F, Shefer A, Wenger J et al, Economic evaluation of the routine childhood immunization program in the United States, *Pediatrics*, 2009, 133, 4.

71 Scuffham PA, West PA, Economic evaluation for the control and management of influenza in Europe, *Vaccine*, 2002, 20, 19-20, 2562-78.

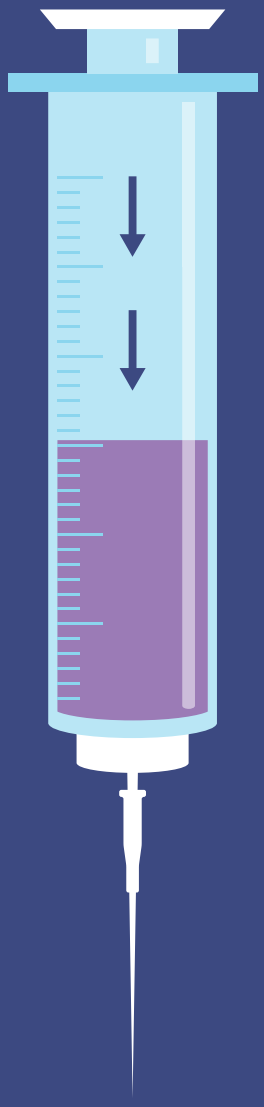
72 Sahoo A, Vaccines 2011: market analysis, key players and critical trends in a fast-changing industry, 2008, Kalorama Information.

73 O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates, *Lancet*, 2009;374:893–902.

74 Hampton LM, Farley MM, Schaffner W, et al. Prevention of antibiotic-non susceptible *Streptococcus pneumoniae* with conjugate vaccines, *Journal of Infectious Diseases*, 2012, 205, 401–411.

INCREASING COVERAGE OF VACCINES CAN REDUCE ANTIBIOTIC USE

Universal coverage by a pneumococcal conjugate vaccine could potentially avert 11.4 million days of antibiotic use per year in children younger than five, roughly a 47% reduction in the amount of antibiotics used for pneumonia cases caused by *S. pneumoniae*.



47%
reduction in antibiotic use

Source: Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J, Klugman K, Davies S, Access to effective antimicrobials: A worldwide challenge, Antimicrobials: access and sustainable effectiveness, *Lancet*, 2016, 387: 168–75.

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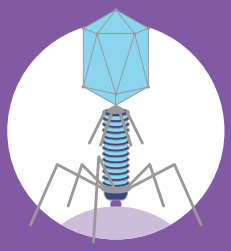
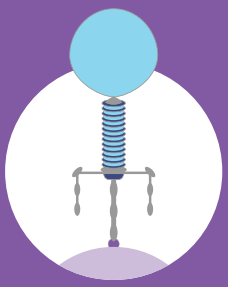
ALTERNATIVE PRODUCTS TO TACKLE INFECTIONS

A selection of alternative products that are under development, which could be used for prevention or therapy.



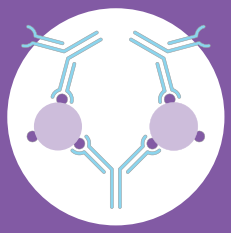
Phage therapy

Natural or engineered viruses that attack and kill bacteria



Lysins

Enzymes that directly and quickly act on bacteria



Antibodies

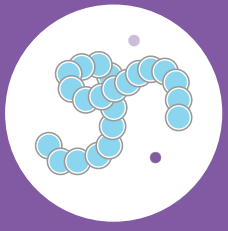
Bind to particular bacteria or their products, restricting their ability to cause disease

Probiotics

Prevent pathogenic bacteria colonising the gut

Immune stimulation

Boosts the patient's natural immune system



Peptides

Non-mammalian animals' natural defences against infection

Review on Antimicrobial Resistance

Sustain a viable market for vaccines

We have no licensed vaccines for any of the bacterial species that are considered by the US Centers for Disease Control and Prevention (CDC) to represent our most 'urgent' AMR threats[75]. In some cases, however, there are promising clinical candidates against these bugs, many of which are most prevalent – at least in their most dangerous forms - in hospital settings such as *Clostridium difficile* and *Pseudomonas aeruginosa*. With a 10 percent mortality risk from *C. difficile* and 453,000[76] annual infections in the US alone, the benefits of a vaccine would be huge. An estimated 35 million people aged over 65 are admitted to hospital per year in the US and EU[77]. This is a group at particular risk of infection. Prophylactic vaccination of 75 percent of these patients at 50 USD per course[77] would imply an annual addressable market of 1.3 billion USD or more. A similar, though more modest, argument can be made for *Pseudomonas aeruginosa*, which causes 51,000 healthcare associated infections a year in the US, of which 13 percent[78] are estimated to be multidrug-resistant.

These examples have clear commercial potential, but the route to market may be undermined by fragmented purchasing arrangements – even in high-income settings. Whereas commercially successful vaccines administered on a population-wide basis are often supported by clear national-level purchasing commitments from governments and national health bodies, more targeted vaccines to prevent healthcare-acquired infections lack a clear position in such national programmes.

More challenging from the perspective of existing market rewards are those infections for which there are limited effective treatments, but where the addressable market for vaccination is not sufficiently large to establish a clear commercial case without additional intervention such as carbapenem-resistant *Acinetobacter*.

In such circumstances, additional 'pull' funding could be required to take innovation right through to market. The size of the stimulus required would depend on the nature of the innovation, but could need to be in the multiple hundreds of millions of dollars. Depending on the characteristics of the vaccines in question, such 'pull' funding could be structured as Advanced Market Commitments (to promote broad uptake in mid to large sized populations) or as market entry rewards (to ensure availability for smaller populations at high risk).

Renew impetus for early research in vaccines useful for AMR

For some infections, the lack of candidates in clinical development can be viewed as being due more to the scientific challenges of vaccine development (and of targeting specific pathogens in doing so) than to commercial ones. A key example is gonorrhoea. This is a reason we suggest greater investment in early-stage research and human capital in order to help overcome scientific challenges.

How much would it cost?

We believe that advanced market commitments such as Gavi's should be funded to allow the roll out of vaccines, in low and middle-income countries as well as guarantee a market for those who come up with promising vaccines but do not want to take the risk of expensive production unless they are sure a market exists. Similar guarantees make sense in high-income settings, however these should be funded by national governments and healthcare systems rather than a global payer.

Like diagnostics, the costs of vaccines will fluctuate depending on the quality and quantity of products available, and so we cannot give a precise estimate for future costs at this time, and more research is needed in this area.

Alternative approaches

We have discussed in detail the potential for vaccines to reduce the need for antibiotics. However, there are a wide array of other possible alternatives currently being researched and developed. Some alternatives aim to prevent infection, as vaccines do, others to replace antibiotics as treatment, and still others to make antibiotics more effective or reduce the likelihood of resistance arising by being taken alongside them. We believe that alternatives should be eligible for the same incentives as vaccines or antibiotics, where they fulfill the same role in combating AMR.

A recent pipeline review[79] drew particular attention to the following alternatives, which have the potential to come to market within the next 10 years: antibodies, probiotics, lysins, wild-type and engineered bacteriophages, immune stimulation, and peptides[80].

75 Centers for Disease Control, Antibiotic resistance threats in the United States, 2013, U.S Department of Health and Human Services.

76 Lessa FC, Mu Y, Bamberg WM, Zintars GB, Dumyati GK, Dunn JR, et al, Burden of *Clostridium difficile* infection in the United States, *The New England Journal of Medicine*, 2015, 372, 825-834.

77 BofA Merrill Lynch Global Research

78 Centres for Disease Control and Prevention, Antibiotic Resistant threats in the United States, 2013, US Department of Health and Human Services.

79 Czaplewski L, Bax R, Clokie M, et al. Alternatives to antibiotics – a pipeline portfolio review, Lancet Infectious Diseases, 2016, Published Online January 12, 2016, http://dx.doi.org/10.1016/ S1473-3099(15)00466-1.

80 Peptide types include: antimicrobial, host defence, innate defence and antibiofilm peptides.

Intervention 7:
Improve the number, pay and recognition of people working in infectious disease

> *Infectious Diseases and Microbiology are among the least subscribed specialties in medicine and research, this leading to a shortage of key personnel on the frontlines of the challenge of drug-resistant infections. This needs to change immediately if we are to turn the tide against rising resistance.*
>
> Dr Jeremy Farrar, Director, Wellcome Trust

Why we need to act

All of the interventions we recommend to address AMR by reducing unnecessary use of antimicrobials and increasing the number of new products available to treat infections depend on having a vibrant, well-trained and empowered workforce to implement them.

Infectious disease specialists, microbiologists and all the professional staff who support them in the clinical setting from nurses to infection control specialists and pharmacists, are the cornerstone of reducing unnecessary use of antimicrobials. Yet there is a shortage of professionals working in this field, and the extent to which they are undervalued compared with peers working in other disciplines is a major concern. As an example, we highlighted in our second interim report in February 2015[81] that infectious disease doctors are the lowest paid of the 25 principal medical specialties in the US. Course registration data for 18 of these fields showed that infectious disease was the second least popular for specialist trainees, and one of only two in which there were fewer applicants than training places available. Furthermore, there are often key gaps in the basic and ongoing training provided to doctors in other medical specialties, who are likely to routinely be responsible for prescribing antimicrobials for their own patients.

On the research side, so crucial to the development of new drugs, there is a similar pattern, whereby microbiology and the skills required to discover and develop new antimicrobials are seen as less prestigious and rewarding than many other fields. We reviewed citations in biomedical journals – a key measure and driver of academic activity in a field – and found that articles on infectious diseases receive markedly fewer citations than most other medical fields. Specialist microbiology journals also lack the impact or perceived prestige of publications in other areas, with no microbiology journal ranked in the top 30 most influential biomedical journals by their '*h*-index' scores (a common measure of impact). This is at once both a driver and a reflection of the fact that microbiology is often not seen as 'exciting' or 'cutting-edge' for academic scientists, whose careers are widely judged by the impact and perception of the papers that they publish.

These patterns have led to an exodus of expertise both at the frontline of the battle with drug resistance – in healthcare settings and in surveillance efforts – and in the academic research settings from which breakthroughs in the treatment and understanding of AMR will originate. Similar issues exist in alternative avenues of research[82], which may too be relevant for AMR. Indeed, in many of these areas, product development has never been well remunerated and collaboration networks are limited, meaning the knowledge and evidence base is small and fragmented.

Besides this problem of the relative shortage of specialists in key fields related to AMR, there are far more pervasive and basic shortages of doctors, nurses, dentists and veterinarians in many parts of the world – something that itself exacerbates the problem. The WHO estimates that 44 percent of its member states have fewer than one physician per 1,000 population, while the minimum number of skilled healthcare professionals recommended by the organisation is 2.3 per 1,000[83]. This affects the emergence of drug resistance by creating fundamental barriers to access to proper medical care, forcing individuals towards self-medication and the use of antimicrobials sold OTC. In the case of animal health, many countries need more, and better trained veterinarians to help guide farmers and food producers to reduce unnecessary use of antimicrobials in animals.

Improving access to good medical care for all, is of course not just important for AMR, it is an integral part of countries' development process – something which should ultimately be about improving people's lives. It is thus encouraging to see how many low and middle-income countries are focusing on improving health systems and achieving universal healthcare coverage as national priorities. But as governments develop their health systems and move towards universal health coverage (UHC), proper attention needs to be given to some key considerations around AMR. For instance, in some parts of the world doctors' low basic pay leads to them being incentivised to sell drugs, including antibiotics, through bonus schemes; and in low and middle-income settings, increases in so-called 'co-payments' for accessing healthcare services are associated with

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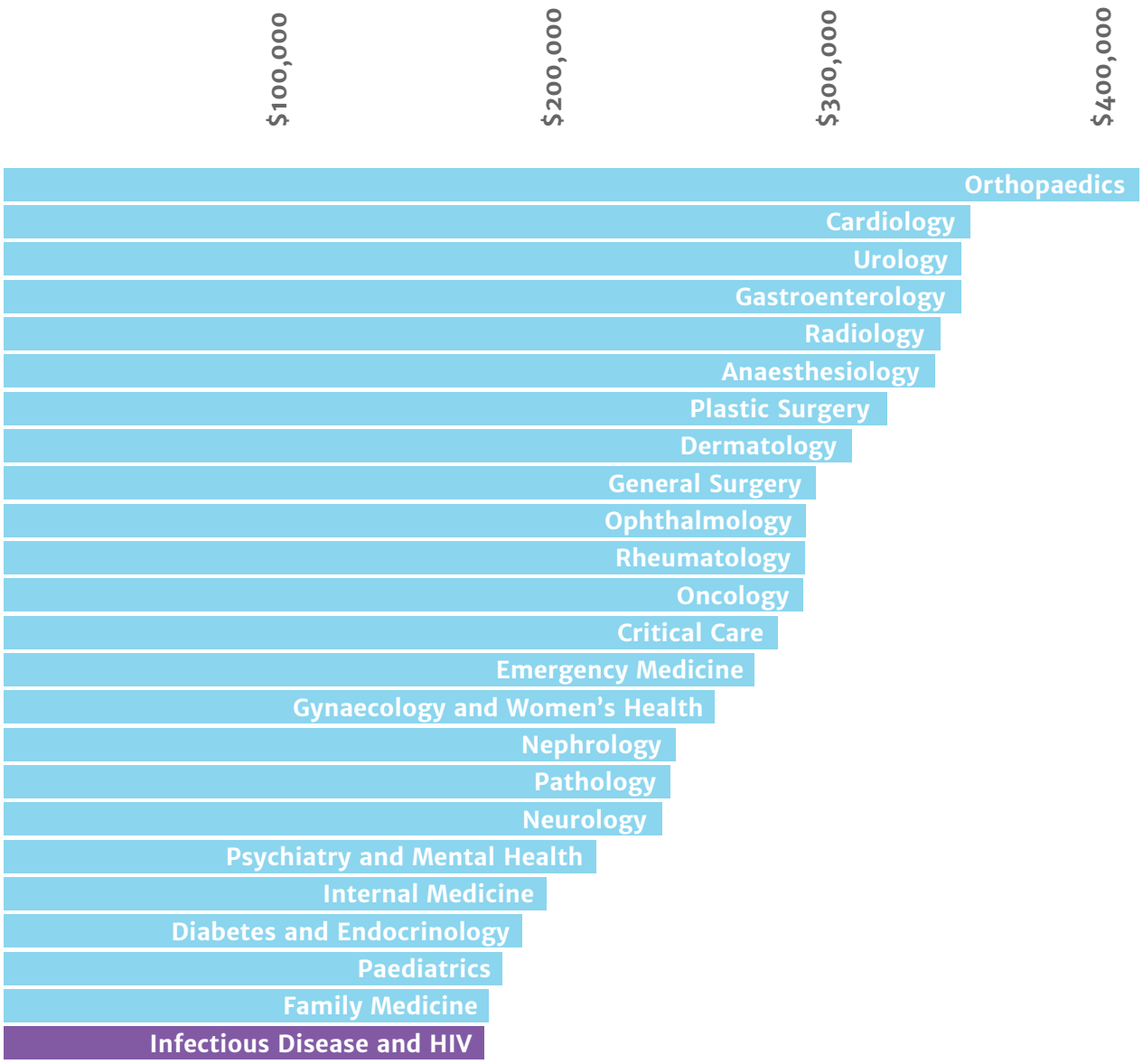
81 Review on AMR, *Tackling a global health crisis: Initial steps*, 2015.

82 Includes phage therapy, lysins, antibodies, probiotics, immune stimulation and peptides.

83 WHO website, 2016, Available online: http://www.who.int/gho/health_workforce/physicians_density/en/

DOCTORS WORKING IN INFECTIOUS DISEASE AND HIV EARN LESS

Doctors' annual pay for working in infectious diseases and HIV in 2012 compared with other medical fields in the US.



Source: Medscape.

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rising drug resistance as poorer patients increasingly turn to illicit OTC purchases of antibiotics[84].

What needs to be done

Governments, healthcare system leaders, and private actors (such as clinicians' professional bodies) should expand funding and opportunities to increase the number and capacity of essential health workers on the frontline of fighting resistance. Countries need to invest in people in these fields, thinking hard about training and rewarding them adequately.

As for getting academics and researchers back into the field of AMR research, this will need an impetus from funders, the availability of long-term research funding prospects, and better career recognition. Different health systems may have different ways to make this happen, including possibly creating centres of excellence that serve as knowledge and recognition platforms to support research focused on addressing AMR and reward research that improves public health.

Finally, we need more people in the human and animal healthcare settings who are experts in AMR and infectious disease. These include key frontline personnel such as doctors, nurses, veterinarians, dentists, microbiologists, and epidemiologists among many others. In some countries, like India, there is a good general understanding of infectious disease amongst the frontline doctors, but the number of specialists is low. In the UK the number of specialists is higher but far less emphasis is placed on understanding infectious disease amongst doctors in other fields. Both of these skills are important in a healthcare setting to improve antimicrobial prescribing and to truly get on top of the problem of resistance. Reviewing the literature it is clear that infectious disease experts improve the quality of prescribing, reducing unnecessary usage and protecting last-line drugs[85]. A literature review in 2014 on the impact of infectious disease specialists on antibiotic prescribing patterns in hospitals found that not only were infectious disease specialists associated with lower antibiotic use, they were also associated with reduced length of stay, reduced mortality, a reduction in the prevalence of multi-resistant bacteria and a reduction in the overall costs of antibiotics[86]. Specialists are thus important not only for preventing resistance, but also for improving patient care and can save hospitals money. Infectious disease specialists often also play a role in running an organisation's infection control programme, either through direct supervision or consultative advice[87]. More emphasis is needed to increase the knowledge and understanding of infectious disease.

How much would it cost?

Investing in healthcare workers and similar fields for AMR will require significant investment, which has traditionally been the domain of governments, and public and private healthcare providers amongst others. A WHO report, published over a decade ago, estimated that making up the shortfall in healthcare workers through training until 2015, would cost anywhere between 1.6 million USD per country per year, to almost two billion USD a year, in a large country such as India[88]. Though there has been an improvement in human resources for health since then, this has been a slow process. With an increasing global population leading to an increased burden on healthcare systems, with (the WHO estimating that there would be a shortage of 12.9 million health-care workers by 2035)[89], it is crucial that this investment be made a priority by health authorities, especially among low and middle-income countries that are moving towards UHC.

84 Alsan M, Schoemaker L, Eggleston K, et al., Out-of-pocket expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis, *Lancet Infectious Diseases*, 2015, 15, 1203-10.

85 Moleski RJ, Andriole VT, Role of infectious disease specialist in containing costs of antibiotics in the hospital, *Reviews of Infectious Diseases*, 1986, 8, 3, 488-493.

86 Pulcini C, Botelho-Nevers E, Dyar OJ, et al. The impact of infectious disease specialists on antibiotic prescribing in hospitals, *Clinical Microbiology and Infection*, 2014, 20, 963-972.

87 Petrak RM, Sexton DJ, Butera ML et al., The value of an infectious disease specialist, *Clinical Infectious Diseases*, 2003, 36, 1013-1017.

88 WHO, The World Health Report 2006- Working together for health, 2006.

89 WHO, A universal truth: No health without a workforce, 2014.

3.

WE MUST INCREASE THE SUPPLY OF NEW ANTIMICROBIALS EFFECTIVE AGAINST DRUG-RESISTANT BUGS

We need a better supply of new drugs across a range of diseases where drug resistance is on the rise. We draw out the following needs in order of priority for the main infectious diseases, based on the current level of investment in R&D and the strength of the different pipelines. This order of priorities explains why many of our proposed solutions focus on TB, antibiotics and antifungal medicines. These priorities will change over time as the AMR threat evolves and will need to be reconsidered and resources allocated accordingly.

Urgent need and current funding structures inadequate	Urgent need but current funding structures largely adequate	Need will arise and require future consideration
• TB treatment regimen	• New malaria treatments	• HIV/AIDS drugs
• Antibiotics		
• Antifungal medicines		

AMR is inevitable. As people keep finding ways to kill the microbes that infect us, those microbes, through evolutionary processes, will mutate to counteract them. As discussed above, we can reduce the build-up of resistance by reducing unnecessary use of antimicrobials and in particular antibiotics. This is important because the supply of new antimicrobials is not necessarily inexhaustible, whilst their development is increasingly expensive. Even if we manage to reduce the unnecessary use of antimicrobials over the next decade, with a growing world population and continuing improvements in access to healthcare, the world will need a functioning R&D pipeline of new antimicrobials if we are to meet the Sustainable Development Goals (SDGs) agreed in the UN in 2015.

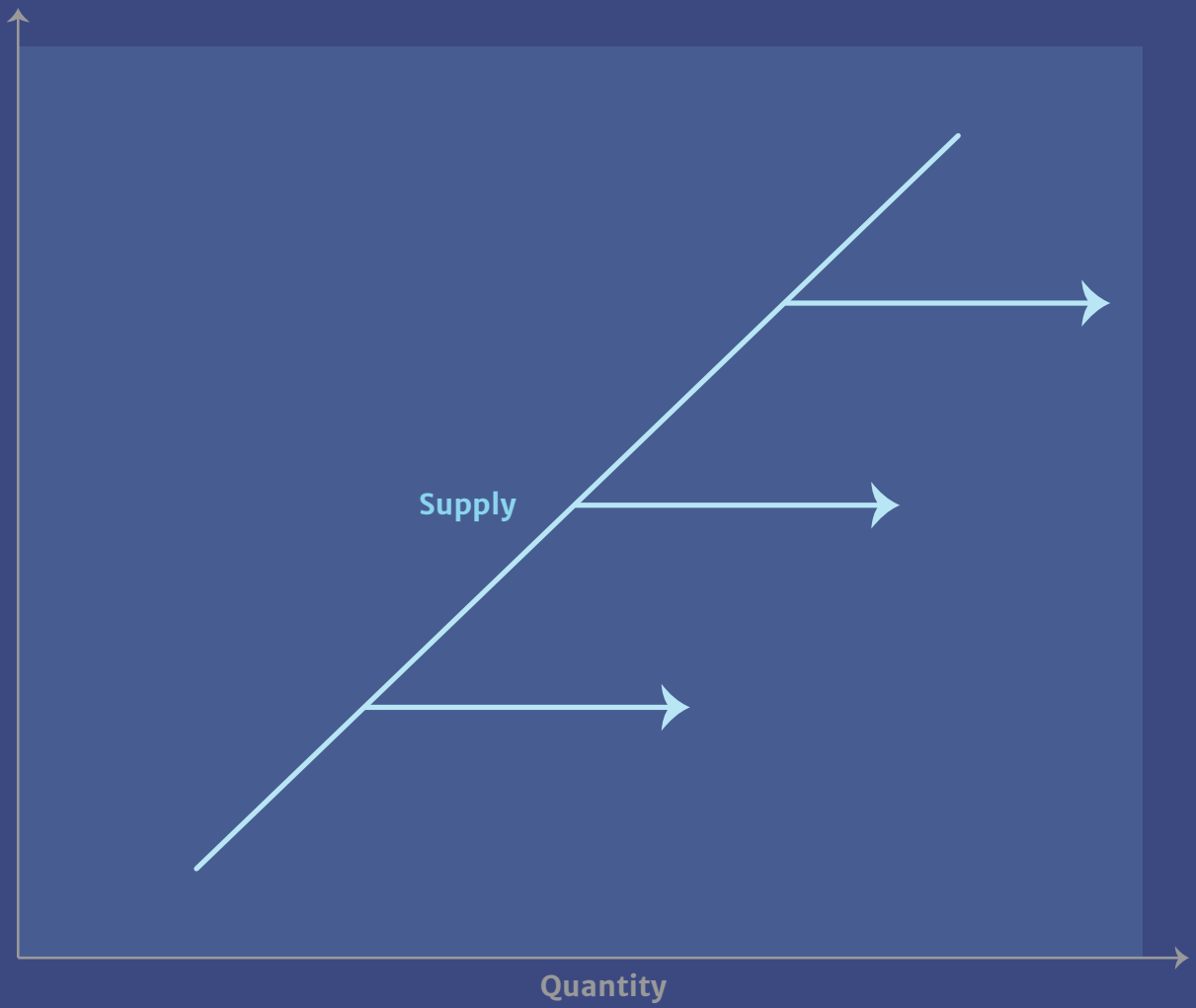
But achieving a functioning pipeline will depend on aligning public and private incentives to invest in R&D with public health needs, drawing on the expertise and creativity of research teams in all countries. Opening up the playing field, bringing down barriers to entry into research, and rewarding success wherever it comes from are crucial.

“This is important because the supply of discoverable new antimicrobials is not necessarily inexhaustible, whilst their development is increasingly expensive.”

INCREASING THE SUPPLY OF ANTIMICROBIALS TO KEEP UP WITH RISING RESISTANCE

Drugs
- $0.8 to $1.3 billion market entry rewards for antibiotics
- International clinical trial platform

Global Innovation Fund
- A global fund for early-stage research and R&D lacking a commercial imperative



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Intervention 8:
A Global Innovation Fund for early-stage and non-commercial R&D

Why it is needed

There is insufficient private and public investment in R&D in support of new drugs and other areas relevant to the global AMR challenge. The funding that does exist is not always as focused and coordinated (particularly across national borders) as it could be to maximise its impact.

We identified two key categories of research where existing funding arrangements may be inadequate:

1. **Early-stage, 'blue sky' scientific research in drug discovery and other areas relevant to AMR.** Cutting-edge scientific research, which is necessarily high-risk, is critical to making the breakthroughs needed in our understanding of drug resistance and in identifying the most promising avenues for further drug discovery and other areas relevant to AMR (for example, vaccines and alternative therapies). Many known avenues of research for AMR have failed; we need to go back to the drawing board and look for new ones. This type of research is a marginal commercial proposition at best, even when lucrative markets exist, which they often do not in areas relevant to AMR.

2. **Research that is less cutting-edge and which lacks a commercial imperative.** There are also areas of applied research that are not being taken forward, such as relatively simple research in the dosing of antimicrobials, as well as more difficult research questions into the combining or repurposing of old antibiotics or other drugs to yield benefits in terms of new or improved treatments. Such work is a typical 'blind spot' of current funding structures. It is not done by academics because it is not regarded as cutting-edge and is therefore of limited appeal to scientific researchers and funders. And it lacks a commercial imperative – as the outputs that it yields may not be patentable, or otherwise offer poor commercial returns.

To address these two issues and cover the blind spots left by the current level and structure of grant funding, we propose a Global Innovation Fund for AMR, endowed with 2 billion USD over five years. This is a very important element of the solution to increase the supply of new antimicrobials, as well as to support early research into new diagnostics, vaccines and alternatives. It cannot, however, be a substitute for correcting the market failures that persist in the antibiotics market in particular. We need this so-called "push" funding as well as "pull" incentives to provide a more attractive end market for new antibiotics and diagnostics, and to comprehensively and sustainably re-invigorate innovation in this field.

How it can be done

Public funding support for antibiotic discovery and development and other research related to AMR has seen some significant improvements in recent years, thanks to key initiatives in the US and Europe. BARDA's programmes in the US, and the IMI ND4BB programme in Europe, for example, have together been instrumental in supporting a number of companies' antibiotic R&D efforts. More broadly, the NIH and the JPIAMR have played important roles in improving support for other areas of research relevant to AMR. These programmes pre-date the Review's initial recommendations for the establishment of a global innovation fund, made in February 2015.

Since our initial recommendations, there have also been further encouraging developments in the priority afforded to AMR and to antibiotic R&D by key governments and funding bodies. For instance, over the past 12 months we have seen three major breakthroughs in terms of improving how funds are earmarked for research useful for AMR:

1. As well as substantially increasing funding allocated to existing NIH and BARDA activities related to AMR, the US Government in February 2016 announced the launch of the **BARDA Biopharmaceutical Accelerator**, which will see the agency partner with industry or non-profit organisations to incubate antibiotic research programmes through later stages of product development, with joint funding.

2. The **UK and Chinese governments** together announced in October 2015 a Global Innovation Fund to improve funding for AMR-related research. These countries have together committed 100m GBP so far (145m USD), a sum which is expected to increase as new partners join the initiative. The Bill & Melinda Gates Foundation has also committed its support.

3. A new not-for-profit product development partnership was launched in Geneva earlier this year: the **Global Antibiotic Research & Development (GARD) programme**, incubated by the Drugs for Neglected Diseases Initiative (DNDi) and supported by the WHO and several countries. This represents a potentially powerful means of filling specific gaps in R&D for AMR where a commercial incentive is lacking, particularly those in the second category of research defined above.

Despite such encouraging progress, there is more that can still be done to close the substantial gap in R&D funding between AMR and the best-funded areas of medical science. As initiatives such as these and the Global Innovation Fund flourish, it will be

critical to ensure that efforts are coordinated so as to leave no 'blind spots', and to better align spending with global priorities for R&D on AMR.

Low-cost and high impact measures are often overlooked: the example of old antibiotics

Much of the focus on antimicrobial R&D is rightly on providing incentives to develop new drugs to combat the problem of AMR. However, discovering and developing novel antimicrobials is an expensive and lengthy process even with the correct economic incentives in place. There may be lower hanging fruit to exploit today: namely, making sure we make use of all the diversity of antimicrobials that are already available, and that we use them correctly.

"**Forgotten antibiotics.**" Experts agree that using a diversity of antibiotics helps slow down the rise of resistance. Yet a study in 2012[90] found that in 38 high-income countries studied, **two thirds** of the antibiotics surveyed were **not available** in more than half of the countries. The main reason for this is that drugs manufacturers and distributors discontinue the stock where it is not profitable enough to maintain it. This situation is likely to be much worse in low and middle-income countries, which already bear the brunt of developing resistance. There must be ways for public health authorities to collaborate and address this problem, for instance by bringing advance orders together, to make sure old and useful antibiotics remain in stock and can be used against infections.

Knowing how to dose old antimicrobials. Another low hanging fruit in the fight against drug resistance is to make sure we use antimicrobials in the correct dosage. Using too low a dose – so called "sub-therapeutic dosage"- can speed up the development of drug resistance: it exposes the microbes to the drug without killing them, allowing them to develop resistance, multiply and spread. Yet incorrect dosages for antimicrobials are surprisingly common, especially for children, as many drugs are not available in paediatric dosages. A study in 2015 showed that nearly half the children in the sample were treated with sub-optimal dosages of commonly used antifungal agents[91].

A key driver of this routine non-optimal dosing is the lack of recent studies of the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics. More study would enable a better understanding of how the drug is broken down, absorbed and excreted. Understanding these things is crucial to determining what dose is optimal. Many PK and PD studies on antibiotics were carried out in the 1950s-60s when these antibiotics were discovered. However, with improved techniques and protocols for PK/PD studies, these antibiotics need to be re-evaluated to ensure that they are being used in the most efficient way possible. This type of research is not being done nearly enough at the moment.

It makes economic sense to devote innovation funding and research capacity to steps like this to rejuvenate old drugs and ensure better usage and dosing. Commercial and not-for-profit partners are ready to begin this type of work - which could be done in countries like South Africa, India, Brazil, China and Russia where the expertise and the patients exist and the need is pressing. Public or charitable funding is required and would have a relatively low cost for a high public health value, especially when compared with the cost of finding new drugs.

90 Pulcini C, Bush K, Craig WA et al., Forgotten antibiotics: An inventory in Europe, the United States, Canada and Australia, *Clinical Infectious Diseases*, 2012, 54, 2, 268-74.

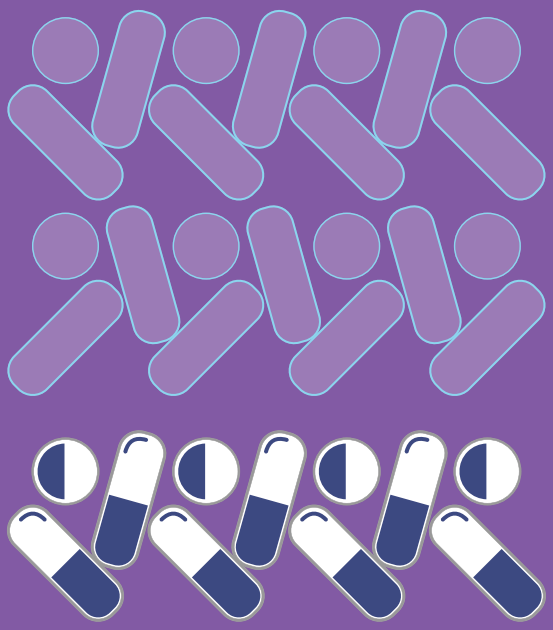
91 Lestner JM, Versporten A, Doerholt K, et al., Systemic Antifungal prescribing in neonates and children: outcomes from the Antibiotic Resistance and Prescribing in European Children (ARPEC) study, *Antimicrobial Agents and Chemotherapy*, 59, 2.

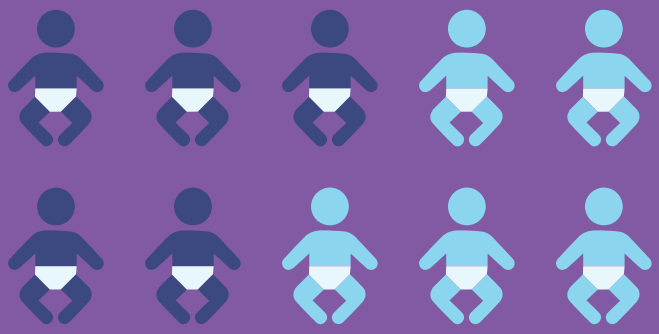
WE NEED TO USE EXISTING ANTIMICROBIALS BETTER

Improving availability of existing antimicrobials and using better dosing strategies would go a long way in helping current antimicrobials last longer.

2/3rd

A study in 2012 found that 2/3rds of selected antibiotics were not available in more than half the included countries.





1/2

A study in 2015 found that nearly half the children and newborns in the sample were treated with sub-optimal doses of commonly used antifungals.

Source: Pulcini C, Bush K, Craig WA et al., Forgotten antibiotics: An inventory in Europe, the United States, Canada and Australia, *Clinical Infectious Diseases*, 2012, 54, 2, 268-74, and Lestner JM, Versporten A, Doerholt K, et al., Systemic Antifungal prescribing in neonates and children: outcomes from the Antibiotic Resistance and Prescribing in European Children (ARPEC) study, *Antimicrobial Agents and Chemotherapy*, 2015, 59, 782-789.

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Intervention 9:
Better incentives to promote investment for new drugs and improving existing ones

> *"We have to dramatically shift incentives for pharmaceutical companies and others to create a long-term solution to this problem, with new rewards, funded globally, that support the development of new antibiotics and ensure access to antibiotics in the developing world."*
>
> George Osborne, Chancellor of the Exchequer, UK

Why it is needed

The current pipeline of new antibiotics shows that there is a mismatch between the drugs the world needs, given emerging levels of drug resistance, and the number and quality of new antibiotics that are being researched. 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 our analysis of the antibiotics pipeline – based on that of the Pew Charitable Trusts[92] – found that as of May 2015, there were only three compounds under development that 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. Furthermore, the total antibiotics pipeline currently stands at barely 40 products – far fewer than is needed to generate a flow of new products that is capable of matching the rise of drug resistance. Many of these are targeted at easier-to-treat infections of less overall concern in the context of the drug resistance challenge – such as skin infections caused by Gram-positive bacteria – whilst very few represent breakthroughs as likely first-in-class products[93].

These are patterns of development that can to some extent be explained by the considerable scientific challenges of antibiotic discovery and development – particularly when attempting to target Gram-negative bacteria. These scientific and technical challenges, and possible approaches to addressing them, are explored in detail in a recent 'roadmap' for antibiotic discovery published by the Pew Charitable Trusts[94]. These scientific and technical barriers will require focussed efforts to overcome. However, the state of the antibiotic pipeline at present is also shaped to an equal extent by two factors which can be addressed more directly through direct policy interventions:

- The lack of a dependable, commercially-attractive market for antibiotics that meet unmet medical needs, and;
- Practical and regulatory barriers to antibiotic development.

Antibiotic discovery and development is not an attractive proposition for commercial drug developers

A fundamental problem for the developer of a new antibiotic is that the volume of sales of a new-to-market antibiotic will be low during periods of 'usual drug resistance' (UDR) – that is, the period of time when older and cheaper generic antibiotics still work against most infections. During such periods, patented new drugs must compete with generics, which keeps the price low.

In addition to this, necessary stewardship efforts by public health authorities will actively limit the use of newer drugs, so as to slow the emergence of resistance to them and prolong their usefulness. This is very different to what happens in other therapeutic areas where a breakthrough product will most likely enter the market as the new 'first-line' treatment for a disease, capturing substantial market share and maximising sales during the early years of the product's life, when it is on patent and its developer is shielded from competition.

This combination of price pressure and low volumes makes antibiotics unattractive as a commercial proposition for drug developers.

In the current system, this changes only when resistance to existing generic products is already high at the point when a new drug comes to market. If the development cycle for antibiotics were short this would not be a problem, but a new medicine typically takes 10-15 years to go from discovery to the patient. This creates a time delay and means we need to invest ahead of rising resistance to avoid elevated mortality and morbidity while waiting for new drugs.

In other fields, this is less of a problem. With non-communicable diseases like diabetes, for instance, the availability of relatively reliable long-range epidemiological forecasts means that drug developers can predict with relatively high confidence future areas of unmet need. In the case of drug resistance, however, while the general upward trajectory is clear, the precise patterns of resistance and the unmet needs that they create are intrinsically uncertain. When they do emerge, they are likely

92 Pew Charitable Trusts, *Antibiotics Currently in Clinical Development*, 2015, Available at: http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development, Accessed May 2016.

93 Renwick MJ, Brogan DM, Mossialos E, A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics, *The Journal of Antibiotics*, 2016, 69, 73-88.

94 The Pew Charitable Trusts, *A Scientific Roadmap for Antibiotic Discovery*, Available at www.pewtrusts.org/antibiotic-discovery, Accessed May 2016.

MARKET ENTRY REWARDS WOULD HAVE A POWERFUL IMPACT ON ANTIBIOTIC R&D

Patented antibiotics form a small percentage of the total $40 billion per year antibiotics market, so $1.6 billion a year would have a material impact.

$4.7 bn

Patented antibiotics market

$1.6 bn

Market entry reward

Data and analysis by IMS Health, in the countries they had patent data for only 12.3% ($3.8bn) of sales were on patent while $26.9bn were off patent. We then presumed that this ratio remained the same in the 20% of countries they did not have patent data for, even though these countries tend to buy less patented drugs, making the above figures a high estimate of the patented market.

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to emerge more quickly than commercial drug developers can respond, unless there are good drugs already in reserve on the market or near to being launched.

In summary, without large-scale intervention, the commercial rewards necessary to reverse the long-term disinvestment from antibiotic research and development will not exist and the products that we need to respond to the emerging risks of greatest concern will not be developed.

Antibiotic research and development is hindered by regulatory challenges

The greatest cost associated with new antibiotic development is that of running clinical trials – particularly during the later stages of testing. Analysis undertaken by the Review found that on average more than 80 percent of the costs of bringing an antibiotic to market are related to clinical trials, or 65 percent of the cost when you adjust for the risk of failure, which more realistically captures the all-in cost of drug development.

It is right that testing and approval processes should be robust to prevent unsafe or ineffective drugs coming to market. However, antibiotics face some particular challenges, which have contributed to the progressive decline of R&D efforts.

For instance, even antibiotics intended for use as back-up defences for current generics to which resistance is rising need in principle to demonstrate clinical "superiority" versus the existing treatment. Identifying and enrolling large enough groups of patients with drug-resistant infections can be a technical and logistical challenge, not least due to limited diagnostics to identify patients quickly and dispersed populations.

Regulators in key jurisdictions – such as the FDA in the US, the Pharmaceutical and Medical Devices Agency (PMDA) in Japan, and the EMA in Europe – are already alive to these concerns and have taken important steps to address them, but more can be done to support antibiotic development by improving the regulatory process. Even when regulators manage to harmonise and simplify requirements for developers to bring new antibiotics to the market that are effective for those patients with a resistant infection, there remains a separate challenge which is the question of how to price these antibiotics. Healthcare providers and price setting authorities rightly require drug companies to present robust clinical evidence of the value of their drugs against comparators in order to price them. In other words, there is no escaping relatively large clinical trials. Reducing the cost of these – without compromising on quality and safety – will be an important part of reducing the cost of addressing AMR.

How it can be done

A global system of market entry rewards for antibiotics and alternative therapies

To transform the R&D landscape for antibiotics, a new system is needed that properly rewards the developers of new products that most effectively address both our current needs and those which will foreseeably arise in the future as AMR worsens. At the core of this challenge is the need to 'de-link' the profitability of an antibiotic from volumes sold, reducing uncertainty and enabling reward without encouraging poor stewardship.

Building on proposals set out in our report on the supply of new antimicrobials in May 2015[95], we believe that the most attractive, realistic model for achieving this is a system of 'market entry rewards' – large payments in the order of 800 million – 1.3 billion USD to the successful developer of a new antibiotic, which meets prospectively-defined criteria of 'unmet need'. Developers of alternative therapies aimed at tackling areas where there is unmet need due to rising AMR would also be eligible for these rewards.

Such rewards would be paid after a successful product comes to market and be proportionate to unmet medical need. This means that developers take the scientific risk rather than governments. Post-approval R&D may also be rewarded whilst sales efforts would be subject to strict conditions that balance affordable access with appropriate stewardship.

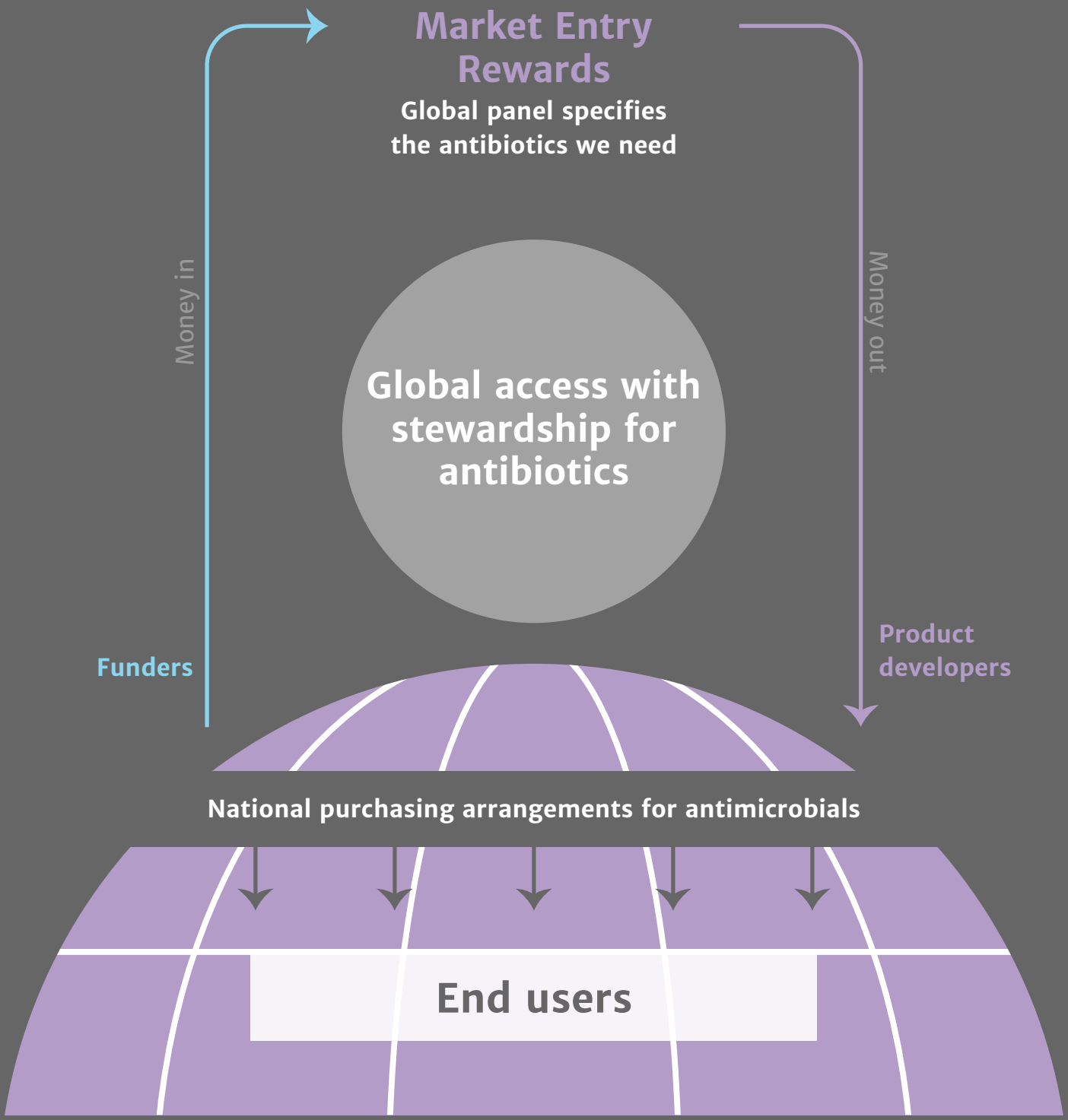
Our vision for this system of market entry rewards rests on the following key principles:

- **Developers should be actively guided towards the antibiotics that we most urgently need today, as well as those which we will most likely need tomorrow**. To do this consistently, target product profiles should be defined prospectively and stably over a horizon of several years. This is scientifically challenging, and may result in rewards going to products for which there is still only limited need when they reach market. But this is the most effective way to ensure that R&D is directed towards areas that pose the greatest risk for the future.

- **Payments should be free from political risk**. Long-term R&D

95 Review on AMR, *Securing new drugs for future generations: The pipeline of antibiotics*, 2015.

HOW A MARKET ENTRY REWARD FOR ANTIBIOTICS WOULD WORK



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investment decisions by companies need to be influenced by this intervention, therefore funding commitments must be made over the long-term, without the risk associated with political cycles at country level.

> *"Funding commitments must be made over the long-term, without the risk associated with political cycles at country level."*

- **Rewards should be linked to a product's value to society**. Drugs that meet the most acute unmet medical needs, most effectively, should be the most generously rewarded. At the same time, value criteria need to be transparently and objectively designed to provide certainty for product developers and global authorities alike. A points system, which addresses issues such as the level of unmet need, toxicity, efficacy, ability to counter resistance, etc., offers a promising basis for such an approach and ideas for implementing this system have started to emerge in the literature[96].

- **The payment should come as soon after a product reaches market as possible, but this may not be immediate and may not come all at once**. The high discount rate used by companies when calculating the current value of future payments means that this system will deliver better value for money the sooner after launch a reward is paid. However, some of the criteria for the points-based system described above may take some time to evaluate – meaning that a payment may only be made two or more years after a product reaches market, and may (in some instances) need to be staggered over a longer period.

- **There should be strings attached for recipients of the payouts**. A key quid pro quo for receiving a lump sum payment should be a broad commitment to continued development post-approval and responsible sale and marketing of the product. Central to this would be commitments to ensuring global, affordable access to the product – either directly or through licensing arrangements such as the Medicines Patent Pool (MPP) – see box below. Such commitments could go further, for instance by barring recipient companies from giving out financial incentives to their own salesforce or clinicians, linked to the volume of the antibiotic sold. Recipients could also be asked to commit to supporting professional and public education, and efforts to monitor use and resistance. The ability to 'claw back' all or part of a market entry reward in circumstances where there are egregious breaches of such conditions should be part of the award process.

- **Leaving control in the hands of the developer brings significant advantages**. From a public health purist's perspective, a 'buyout' model, whereby a commercial antibiotic developer cedes control of their new product to a global public body, might be optimal for stewardship and access. However, such an approach brings with it significant delivery risks, not least as commercial operators possess substantial advantages over bureaucratic entities to oversee complex global pharmaceutical supply chains.

- **This should be administered at a global level**. The pharmaceutical industry is global, with R&D conducted in all corners of the world and the demand for antibiotics coming from all regions. An intervention to deliver a stimulus to this market is therefore most efficient and effective if it is provided at a global level or by a critical mass of countries.

We believe this would provide the best of both worlds, encouraging the private sector to innovate while ensuring research priorities are aligned to public need. Such an approach will help stimulate the market for antibiotics, ensuring that there is better commercial reward for antibiotic development without relying on high prices or large sales volumes. By paying for successful end products, rather than subsidising antibiotic R&D directly, the problems of governments or bureaucracies being asked to 'pick winners' are avoided. Judgement about the scientific merits of a product remain with developers, who are best-placed to make such decisions. Companies will properly make decisions not to advance projects which are scientifically unpromising, but will no longer cancel antibiotic programmes that show scientific potential but are not looking promising commercially based on projected volume of sales during patent life.

> *"A key quid pro quo for receiving a lump sum payment should be a broad commitment to continued development post-approval and responsible sale and marketing of the product. Central to this would be commitments to ensuring global, affordable access to the product."*

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

Market Entry Rewards are not a one size fits all model

Market entry rewards should not be taken as a 'one size fits all' model. The 'de-linkage' model may be the best way of stimulating the market and supporting good stewardship for certain types of products, particularly broad-spectrum antibiotics that can be used in many situations. However, there may be certain types of products developed where patient populations are smaller and stewardship is less of a concern – particularly narrow-spectrum antibiotics. It is possible that these drugs can be purchased and made to be commercially attractive based on a different pricing model. This type of pricing model will become more realistic when there are rapid diagnostics that can quickly establish the need for a patient to use a more tailored and higher priced product, which is not the case yet. Work in the industry is on-going already to consider such new models, whereby new narrow-spectrum antibiotics would be reimbursed at a higher price only if they are confirmed to have been required and have been effective against a resistant pathogen.

Depending on the anticipated volume of patients expected to need these products and on their price, this model may work to both reward the developer commercially and ensure good stewardship of new drugs. However, the question of access to these medicines in health systems outside the richest countries will need to be considered.

The funding and administration of market entry rewards needs to be done at a supra-national level, with a sufficient critical mass of countries signing up to the funding structure and to a stewardship framework for the new drugs. Operating on this scale will mean that individual governments do not feel they are paying far in excess of their 'fair share', or that others use the new drugs excessively with no regard to conserving them for the future. A political agreement within the G20 group of countries would be an ideal forum in terms of countries represented and authority.

The market entry rewards system at the supra-national level will

Putting affordability and access at the heart of a solution

Across all parts of the world – but most frequently in low and middle-income countries, gaps in universal health coverage mean that affordability remains a pervasive barrier to patients receiving the medicines and care that they need. Antibiotics are no exception to this, and for many the lack of drugs for treatable infections will pose a more direct threat to their health than drug resistance. In India, for instance, more children die from a lack of antibiotics than from antibiotic-resistant bacterial infections[97].

It is therefore crucial that any package of action to address drug resistance and stimulate the development of antibiotics at a global level has considerations of access and affordability at its heart. This applies to existing antibiotics as much as to new ones: access needs to be improved whilst reducing excessive use.

The system of **market entry rewards** that we propose has clear potential to support improved affordable access to new antibiotics. Within reason, conditions can be applied to the payment of the reward – which could include the product developer making commitments to ensure supply of the product to low and middle-income countries at affordable prices. This might be via direct provision, or through licensing arrangements such as the Medicines Patent Pool (MPP), which has proven successful in working with patent-holders to lower barriers to access to life-saving drugs for conditions such as HIV/AIDS. Of course, efforts to improve access by such routes need to have improved antimicrobial stewardship at their core – something that, in low and middle-income settings, will require substantial assistance from multilateral bodies like the WHO, and global NGOs like MSF, as well as commitments from pharmaceutical companies themselves (including manufacturers of generic products.)

The Davos Declaration[98] included firm commitments from its signatory companies to improved, affordable global access to antibiotics. However, delivery against these commitments, and wider goals established as part of the development of a system of market entry rewards, will be complex and multifaceted, and would benefit from neutral and objective assessment. We note that the work of the **Access to Medicines Foundation**, and its Access to Medicines Index (ATMI) has been effective and widely-influential in shaping how global pharmaceutical companies approach questions of 'access' in low and middle-income settings. We believe that that there would be significant value in establishing an iteration of the ATMI specifically for antibiotics, to allow an objective assessment of progress and achievement against these important goals.

97 Laxminarayan R, Matsoso P, Pant S, Brower C, Barter D, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge, *Lancet*, 2015, 387, 168–175.

98 Industry Declaration, 2016, [Online], Available at: www.amr-review.org/industry-declaration

need to sit on top of and fit with existing national governments' and health systems' purchasing and supply arrangements – something we refer to in Chapter 5. Based on a global objective of developing about 15 new drugs a decade to keep on top of antibiotic and TB resistance, about four of which should have novel mechanisms of action, some narrow spectrum some broad, we have estimated that it will cost approximately 16 billion USD a decade to provide market entry rewards to these new drugs. We discuss in more detail how this could be funded in the next chapter.

Reducing obstacles to new drug development

As well as improving the market entry rewards for new antimicrobials there are steps governments can take to make it easier to bring new products to market.

Better global harmonisation of regulatory processes

With the exception of EU member states, 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 process that requires considerable money, expertise and manpower. Not achieving it hinders access for patients and reduces the addressable market size for companies. On the other hand oversimplification of the regulatory approvals process must not put patients' health at risk from new products.

Harmonising regulatory procedures can have a high impact in reducing costs and improving access. Significant steps forward have already been taken by the EMA, FDA and PMDA to ensure that their processes for new drug approval are more closely aligned. These efforts should continue and aim to go further – for instance to explore opportunities for mutual recognition of market approvals – with input from partner agencies in other parts of the world to achieve streamlined approval processes that work to benefit both patients and product developers.

A pragmatic approach to trial design

There are fundamental difficulties with running the large clinical trials needed to show that a new antibiotic – even one that clearly shows promise against drug-resistant infections – is statistically 'clinically superior' to established treatments. This is because in most patients with drug-susceptible strains of infection, a product being developed to treat drug-resistant strains will be no more effective than an existing treatment. On the flipside, the minority of patients with drug-resistant infections are difficult to find and enrol, and when establishing a control group it is unethical to give them established first-line treatments, where it is known these will not work. This makes proving 'superiority' in a large population difficult where drug resistance is not widespread. However, we cannot afford to wait until drug resistance is commonplace before undertaking trials on a new generation of products.

There are similar issues for alternative therapies, particularly for those products intended to be taken with antibiotics to increase their efficacy and/or reduce the resistance that may arise from their use. The former characteristic may be perceived as only incremental whilst the latter may not be factored into decision-making by regulatory bodies and payers at all, despite the benefits that accrue to wider society.

Over the past decade, there has been a greater move towards non-inferiority trials, where new drugs can be shown to be as good as old drugs in broad populations. Additional research is then done on either animals or smaller groups of patients with multi-drug resistant infections to establish that the drug is effective in these groups. As rapid diagnostics improve, it should become easier to identify these smaller groups of patients.

There is an understandable worry these trials will not provide enough data for doctors and patients to know if the drug will work successfully against the resistant pathogens, which could affect registration and reimbursement. For this reason, research should be undertaken now into whether animal models or small trials in narrower populations are able to provide adequate information. Furthermore, companies and health technology assessment agencies must consider how to establish fair assessments of value for money and cost-effectiveness for new products approved via adapted non-inferiority trial processes.

Establish clinical trial networks for antibiotics

At present, every time a researcher wants to run a large trial for a new antibiotic they need to enlist as many as 50 different hospitals to take part and train them in the protocol of how to run it. These sites are normally widely dispersed across a country or region to allow sufficient coverage and maximise the chances of identifying suitable patients in sufficient numbers. Because of this process it takes six to nine months to get a trial up and running; but once the trial is finished, this network of hospitals disbands and the enlistment and training process starts again for the next researcher. This can be slow and cumbersome.

Creating a sustainable clinical trial network for infectious disease research – emulating successful approaches in other fields – has the potential to speed up the trial process significantly, and reduce the costs of it. By some estimates, by sharing 'control arms' between trials, the overall size of each trial could be reduced by more than 40 percent[99]. A similar approach could be adopted for new vaccine and alternative candidates.

Recognising that we are still far off achieving this in practice, it is worth noting the potential additional benefits to regulators of having all trials undertaken using the same protocol and so reducing 'bio-creep'. This is the risk that sequential, non-inferiority comparisons of agents (A vs. B, then B vs. C, then C vs. D etc.) could lead to a situation in which each new product demonstrates non-inferiority when efficacy is in fact progressively declining. The use of a consistent, gold-standard comparator in a given network would alleviate this concern for regulators, potentially helping us to improve further the role and information gained from non-inferiority trials.

Another important benefit from coordinating clinical trials for new antimicrobials better internationally would be the opportunities for these to reach large populations of patients in low and middle-income countries. This supports the development of products that address the particular needs of these populations, as well as developing the capabilities and expertise of local clinicians, healthcare facilities, and companies, whilst also reducing the costs of trials.

Much work remains to be done in this space to turn aspirations into practical steps.

Antifungals

In many ways the obstacles facing antifungals are the same as those for antibiotics, though the problem might not yet be as bad. For this reason we have not focused heavily on antifungals because the blueprint that was created for antimicrobials more broadly applies very well. Here we outline what we believe are the priority areas that need to be dealt with in antifungals.

- **Agriculture:** Most crops are treated with fungicides, many with triazoles, which are similar to human triazole antifungals. We do not believe you can take away these products en masse, without endangering global food security. However some of the areas where these products are used most extensively are in the production of luxury items such as flowers and wine, which are not critical to food security. In these products, limits or bans might make sense, though there could be economic repercussions. There needs to be greater research into where triazole antifungals are overused, how this use can be minimised and whether their use is really necessary in particular areas. Further to this, we think that new classes of antimicrobials should not be used in farming, unless essential to particular major crops.

- **Environment:** Like antibiotics there is a problem with factories dumping active pharmaceutical ingredients or antifungals into the environment, and like antibiotics this needs to stop. Similar regulations should therefore be considered for antifungals as we have discussed for antibiotics.

- **Diagnostics:** Often fungal infections are mis-diagnosed as TB or other illnesses, meaning that necessary antifungal treatment is not given and unnecessary antibiotic therapy is given. Fungal disease diagnostics have improved greatly over the last two decades, but some are not available and there remains an excess reliance on culture, which is insensitive and slow. Greater use of rapid diagnostics would play a major role in reducing inappropriate antibiotic and ensuring appropriate antifungal use[100,101,102]. Surveillance of resistance also needs to be expanded both geographically and across populations. Furthermore, diagnostic reference capability needs to be enhanced and subsidised where appropriate in this area.

- **New drugs:** The early clinical development pipeline has grown substantially in the last three years[103] with eight compounds in early clinical development. If this healthier pipeline fails to translate into more new drugs, then governments should look at market entry rewards and early-stage funding for research.

99 McDonnell A, Rex JH, Goossens H, Bonten M, Fowler, V and Dane A., Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks, *Clinical Infectious Diseases*, 2016, Accepted.

100 Ben-Ami R, Olshtain-Pops K, Krieger M, Oren I, Bishara J, Dan M, et al., Antibiotic exposure as a risk factor for fluconazole-resistant Candida bloodstream infection, *Antimicrobial Agents and Chemotherapy*, 2012, 56, 5, 2518-23.

101 Martínez-Jiménez MC, Muñoz P, Valerio M, Vena A, Guinea J, Bouza E, Combination of *Candida* biomarkers in patients receiving empirical antifungal therapy in a Spanish tertiary hospital: a potential role in reducing the duration of treatment, *Journal of Antimcrobial Chemotherapy*, 2015, 70, 11, 3107-15.

102 López-Campos JL, Hartl S, Pozo-Rodriguez F, Roberts CM; European COPD Audit team, Antibiotic Prescription for COPD Exacerbations Admitted to Hospital: European COPD Audit, *PLoS One*, 2015, 23, 10, 4, e0124374.

103 Denning DW, Bromley MJ, How to bolster a sparse antifungal pipeline, *Science* 2015, 347, 1414-6.

Tuberculosis: a cornerstone of the global AMR challenge

Far from being only a threat for the future, drug resistance is a major challenge today in efforts to turn the tide on TB as a major global killer. TB is a bacterial infection which affects an estimated nine million people each year, a rate of incidence that has only been falling by 1.5 percent each year since 2000[104]. At this rate, the world is set to fail its sustainable development goal target to reduce TB deaths by 80 percent, agreed in the UN, by a wide margin. TB kills more people annually than any other infectious disease: 1.5 million die of TB every year, of whom 200,000 die of multi drug-resistant TB (MDR-TB)[105]. Even drug-susceptible strains of TB are inherently difficult to treat, requiring long courses (six months or more) of antibiotics administered in regimens that combine multiple antibiotics to reduce the chance that resistance develops. It is much more difficult to treat MDR-TB: even with more complex cocktails of drugs taken over two years, including eight months of daily injections. Many second-line drugs are toxic and have severe side effects. To complete a course of treatment for MDR-TB requires taking an astonishing 14,000 pills[106].

The terrible impact of drug resistance in TB threatens to become significantly worse in the future. Analysis undertaken by this Review showed that of the 10 million total deaths that might be associated with drug resistance each year by 2050, around a quarter will come from drug-resistant strains of TB[107]. Cases of extensively drug-resistant TB (XDR-TB), against which even established treatments for MDR-TB are ineffective, are already appearing in alarming numbers, raising the real prospect of totally drug-resistant strains of the disease becoming far more commonplace in future years.

The challenges of dealing with drug resistance are already deeply intertwined with the wider challenges of tackling TB and the global response to AMR is fundamentally incomplete if it does not directly address the particular issues of TB.

A combination of new treatments and better diagnostics could yield substantial global benefits

As with the wider challenges of tackling AMR, the greatest success in overcoming the challenges of TB will require both better diagnosis and better treatments. In order to best understand these benefits, the Review commissioned Dr Nimalan Arinaminpathy from Imperial College London[108] to examine the likely impact of new drugs and diagnostics for MDR-TB. This analysis used WHO estimates for annual TB incidence and prevalence for 219 countries worldwide between 2016 and 2026, and consultation with the Foundation for Innovative New Diagnostics (FIND), a non-profit organisation that aims to improve the development and delivery of diagnostic tests for poverty-related diseases like TB.

As a baseline scenario, the health outcomes for those with MDR-TB were estimated to remain the same as at present with a mortality rate of around 50 percent, and treatment times of almost two years. The impact of HIV-TB co-infection in Africa (a common and highly damaging problem in regions where the prevalence of both diseases is high) was factored into the outcome model by using UNAIDS projections of the future HIV burden and coverage of antiretroviral therapy.

As a proxy for the impact of a new treatment regimen, it was assumed that people who were known to have MDR-TB (using existing diagnostics) could be treated as effectively as patients with usually drug-sensitive TB. Under this scenario, the incidence and mortality of MDR-TB would fall as people are cured more quickly, thus reducing their period of infectiousness.

To model the impact of new diagnostic technology, we looked at a scenario – based partially on advice from FIND[109] – where next generation sequencing technology (currently up to five years away from reaching the market) could rapidly identify up to 200 different mutations of the TB bacterium, and within these quickly diagnose MDR-TB cases. This would allow patients with MDR-TB to be identified rapidly, started on the most appropriate treatments, and managed so as to reduce the likelihood that they spread their infection. This is in contrast to current tests which have difficulty in distinguishing between MDR–TB and drug-sensitive TB patients at the point of diagnosis.

This modelling found that the advent of a better treatment regimen for MDR-TB would by itself quickly start to save a large number of lives, with more than 20,000 deaths being averted every year within three years of the new treatment's introduction – an 11 percent decrease in MDR-TB mortality. The introduction

104 WHO, Tuberculosis Factsheet, Online, Available at: http://www.who.int/mediacentre/factsheets/fs104/en/.

105 WHO, Tuberculosis Factsheet, Online, Available at: http://www.who.int/mediacentre/factsheets/fs104/en/

106 TB Alliance, Inadequate Treatment, Online, Available at: http://www.tballiance.org/why-new-tb-drugs/inadequate-treatment.

107 Review on AMR, *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*, 2014.

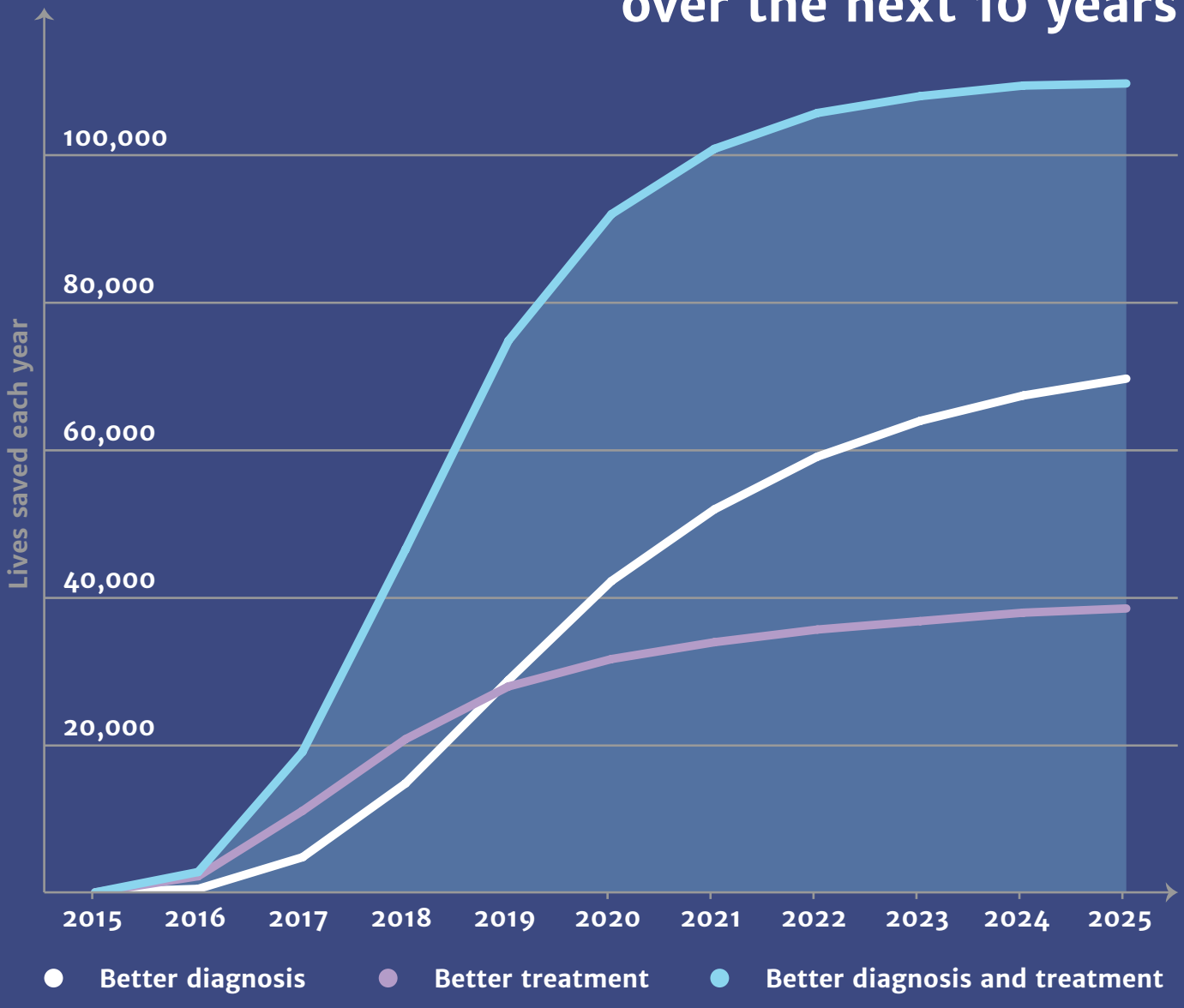
108 Arinaminpathy N, 2016, Avaliable online on Review website: www.amr-review.org

109 Denkinger C, FIND, Available on Review website: www.amr-review.org.

BETTER DIAGNOSTICS AND TREATMENTS FOR TB COULD SAVE NUMEROUS LIVES

Better diagnostics and treatment for tuberculosis could together save more lives than either could alone.

770,000
lives could be saved over the next 10 years



Source: Arinaminpathy N, 2016, Avaliable online on Review website: www.amr-review.org.

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of a new diagnostic (with no new treatment regimen) has a less immediate impact, but has a greater impact on transmission rates and therefore a more significant effect than a new treatment alone over time. After six years, a new treatment by itself would reduce deaths from TB by 34,000 each year, whilst the introduction of just the new diagnostic would be saving 52,000 lives. This represents a decrease in MDR-TB deaths of 18 and 29 percent respectively.

Most impressively, the results showed that the combined impact of introducing both a new diagnostic and a new treatment regimen would save 100,000 lives annually after six years, reducing death rates by 56 percent against their current trend. Over a decade, 770,000 lives would be saved by the combined interventions, underlining how significant a breakthrough the advent of new TB treatments and diagnostics could be.

TB drug development represents particular challenges

This modelling, and the rising burden of MDR-TB, together underline the pressing need for a strong pipeline of new treatments. This development pipeline is inextricably linked with that for antibiotics, as drugs for treating TB will by and large originate from the same processes by which antibiotics for use against other bacterial infections would be discovered. In common with wider antibiotic development efforts, the TB drug development field suffers from a prolonged period of dis-investment by commercial product developers, other than a few exceptions, leaving a perilously thin pipeline of products under development. There is a critical need to take action to reverse this and support the development of new and more effective TB treatment regimens, alongside better TB diagnostics and the continued search for new TB vaccines.

Although the TB market shares some key characteristics with that for antibiotics, it represents a distinct challenge on account of two factors:

1. **Products need to be developed as combinations.** TB treatments must be delivered as combination therapies – usually using three or more antibiotics together – to prevent the development of resistance during prolonged treatment. The complex interaction of medicines means that the individual drugs making up these regimens should ideally be developed as combinations from early on during clinical testing, rather than once they are finished and licensed single products. This poses technical as well as commercial challenges. Furthermore, a new treatment should preferably be composed of multiple new products, rather than new products combined with those already in use which may hasten the development of resistance and offer limited value for the treatment of MDR-TB.

2. **The low incomes of most TB sufferers limit commercial potential.** Unlike conventional antibiotics, where the size of the market for new drugs is the key commercial challenge, the addressable market for a new TB regimen is huge. However, although not exclusively confined to low and middle-income countries, the greatest burden of TB falls on the poorest parts of the world, meaning that the principal purchasers of TB products will often be public or philanthropic donors.

These features are specific to TB drugs and need to guide what interventions are chosen to stimulate the development of new TB treatments. More detailed thinking than this Review can offer needs to be done to design the detailed mechanisms. At a high level it is clear that TB drug development needs sustained 'push' funding especially for early clinical work and better market 'pull mechanisms' to incentivise developers.

The world needs to sustain grant funding for TB research

In the absence of an effectively functioning market for new TB products, much R&D in this space is given vital support by the work of non-profit product development partnerships such as the TB Alliance, Aeras and other organisations looking to develop a new TB vaccine. The Bill and Melinda Gates Foundation's 'TB accelerator' is also becoming a critical tool to increase the number of promising molecules at an early stage of development. This type of funding needs to be sustained and increased where possible.

We also need much better 'pull' incentives to reward the development of TB treatments

In addition to traditional grant funding, there is a wide recognition that novel mechanisms are also needed to support the development of new TB treatments, including so-called 'pull' incentives that reward products for achieving market entry or important milestones along the drug development pipeline. Médecins Sans Frontières (MSF) in collaboration with other public health organisations, have developed a proposal referred to as the '3Ps', for 'Push, Pull, and Pool'. It uses a combination of milestone payments, R&D 'push' funding and pooling of intellectual property to overcome the key challenges of TB regimen development, by incentivising the early collaboration and open research needed to develop fixed dose combinations

(FDCs), and then ensure an affordable, quality-assured global supply of these through licensing mechanisms such as the MPP.

This type of proposal could do much on its own to reinvigorate the TB pipeline if it were funded fully, but further consideration should be given as to how it could be combined with a market entry reward for a new TB regimen as an additional 'pull' mechanism. Subject to further exploration, we believe that the system of market entry rewards that we propose for antibiotics can play an important role in 'supercharging' the current TB efforts, adding much-needed impetus to the work to bring TB product development from the early stage to the point where patients are treated. We view this as being possible in two ways:

- **Market entry rewards should be payable to the developer of a novel treatment regimen.** A new monotherapy for TB is of limited use in addressing global unmet need, and should therefore not be rewarded by a market entry reward in the same way that a conventional single antibiotic ought to be. However, offering an appropriate market entry reward for a complete regimen could provide extra impetus to regimen development efforts supported by initiatives like '3Ps' or others. In principle, market entry rewards should be offered to commercial and not-for-profit developers alike. When accruing to not-for-profit developers they can be reinvested in public heath oriented research.

- **Market Entry Rewards can also be designed to entice developers of antibiotics and alternative therapies for infections other than TB to make their product available at an early stage of development for testing as part of a TB regimen.** To do this, a premium could be awarded to product developers who have supported TB regimen development efforts by doing research themselves, making their antibiotic available for exploration for possible action against TB at an early stage, or making the product available for use in an FDC through the type of licensing arrangements proposed by the '3Ps' model.

Many details will no doubt need to be considered but the critical message here is that tackling TB and drug-resistant TB must be at the heart of any global action against AMR. The burden of TB is too great, and the need for new treatments too urgent, for it not to be a central consideration in the role and objectives of a global intervention to support antibiotic development.

Better interventions to deal with *E. coli*

Of the 10 million people whom it is predicted may die from drug-resistant infections each year by 2050, more than three million will lose their lives to one bacterial infection: drug-resistant *E. coli*. This would also account for more than 40 percent of the cumulative 100 trillion USD lost from world production over the next 35 years. But the problem of drug-resistant *E. coli* is already manifest: carbapenem-resistant *E. coli* more than doubled between 2008 and 2013 in the UK[110]. Recent evidence suggests that colistin, the only drug that works well against carbapenem-resistant infections, is also starting to fail. Despite this, when we analysed the pipeline for new drugs a year ago, only three drugs in the pipeline appeared to have the potential to be effective against 90 percent of carbapenem-resistant *E. coli* infections.

In order to examine the benefits of tackling drug-resistant *E. coli* we commissioned a piece of research from Professor Neil Ferguson and Dr Pierre Nouvelle, from the NIHR Health Protection Unit for Modelling Methodology at Imperial College London[111]. As their business as usual scenario, they examined what would happen if *E. coli* resistance in blood stream infections increased to the current level of *Klebsiella pneumoniae* (KP) over the next decade, as *K. pneumoniae* and *E. coli* are very similar and *K. pneumoniae* has seen huge increases in resistance over the past decade this seemed like a realistic estimate for what could happen.

Using the above assumption, their work estimated that, by 2026 40,000 extra people would die from *E. coli* infections annually in the EU alone, with an additional 1.7 million extra hospital days. Nouvellet and Ferguson then modelled the impact of a new diagnostic that could distinguish between susceptible and resistant infections. They estimated that a new diagnostic would save 6,000 lives and would reduce the number of hospital days by more than 300,000 every year. This is not only a huge decrease on the number of people who would otherwise die from resistant infections, but it is also likely to save health systems money in the long-term, even accounting for the cost of the diagnostics. They estimated that a new drug could save 7,300 lives. A new drug and diagnostic combined would save an estimated almost 15,000 lives and reduce hospital bed days by 650,000.

110 Public Health England (PHE) voluntary laboratory surveillance

111 Nouvellet P, Robotham J, Naylor N, Woodford N, Ferguson N, Potential impact of novel diagnostics and treatments on the burden of antibiotic resistant in *Escherichia coli*, BioRxiv, 2016.

4.

HOW TO PAY FOR IT: TACKLING AMR IS AFFORDABLE

So far we have discussed why and how the world needs to act to combat AMR. The investment needed to take action is dwarfed by the human and financial cost of inaction which is mounting already.

> *"The investment needed to take action is dwarfed by the human and financial cost of inaction which is mounting already."*

What is the cost of global action to address AMR?

Our broad estimate for the cost of taking global action on AMR is up to 40 billion USD over a decade.

Within this, we have estimated that it would cost about 16 billion USD to overhaul the antibiotics and TB R&D pipeline using new market incentives such as market entry rewards. Our costs are modelled on achieving 15 new antibiotics a decade, of which at least four would be breakthrough products targeting the bacterial species of greatest concern. We have also recommended setting up an AMR Global Innovation Fund endowed with two billion USD over five years.

It is more difficult to estimate the cost of supporting innovative new diagnostics and vaccines and then rolling them out, as the cost will depend very much on the type of products and size of population who need them. At this stage of our work and based on roll-out costs for other large public health programmes, we estimate that one to two billion USD a year to support take-up globally would make a very material difference in these areas.

Further economic analysis is needed urgently to understand the impact of reducing the unnecessary use of antibiotics in agriculture, whether that transition would impose a cost on the farming sector, how big this would be, how distributed, and for how long. So far most analysis has focused on high-income countries and therefore more analysis is needed of the impact in low and middle-income settings.

Finally, we recommend interventions that are not specific to AMR but happen to help address drug resistance, such as good disease surveillance and better water and sanitation. These costs are part of normal investment to achieve good healthcare and so are not part of the package of global costs we describe here.

Estimated costs to be funded globally or pooled at a supra-national level over 10 years

INTERVENTION	COST	TIME PERIOD
Promote the development of new antimicrobials including making better use of existing ones	16 billion USD	Over 10 years
Global Innovation Fund supporting basic and non-commercial research in drugs, vaccines, diagnostics	2 billion USD	Over 5 years
Rolling out existing and new diagnostics and vaccines	1 to 2 billion USD	Per year
Global public awareness campaign	40 to 100 million USD (depends on size of campaign)	Per year
TOTAL	**UP TO 40 BILLION USD**	**PER DECADE**

Why some of these costs need to be pooled globally

Governments habitually fund, regulate or directly deliver public goods. Those are goods that we all rely on and use but that it is difficult to charge people for individually, such as the law and order provided by an effective police force or the navigational aid of a lighthouse. Since the 19th century, combatting infectious diseases has been considered a public good and a core objective of public policy.

Infectious disease and the rise of AMR is a global problem that cannot be addressed materially without a critical mass of countries coming together to implement consistent solutions. This is because drug-resistant infections spread very quickly; a person carrying resistant bacteria can fly across the world in a matter of hours. But when it comes to paying for the cost of new products, such as new antimicrobials, countries are incentivised to let others fund the research, creating a 'free-rider' problem. In the case of new antibiotics in particular this fear of 'free-riders' is made worse by the fact that potential funders are concerned that the antibiotics could be used excessively and 'wasted' by others very quickly.

There are other interventions that do not suffer from the 'free-riding' problem and can in principle be funded at the national level. This includes, for instance, new vaccine programmes or the uptake of rapid diagnostics.

All countries that can afford to will benefit from investing in these areas: there is not as strong a risk that others 'free-ride' on that investment. For instance, the benefit to the UK from having better vaccines, or to Japan from using more diagnostics, will in our view be greater than the cost imposed on them.

However, the consequences of these actions will benefit the whole world too. If antibiotic prescribing is improved through a diagnostic in one setting, the rest of the world benefits. For this reason, support at a supra-national or multilateral level should exist to provide access to diagnostics and vaccines in countries that could not afford it otherwise. Subject to further analysis that will need to be done in the coming months and years, this may also be true for moving away from relatively high antibiotic use in agriculture, or the cost of reducing pollution from factories. Even if out of pure self-interest, it may make sense for high-income countries to support these efforts in lower income settings.

The long-term cost of rising AMR is inevitably borne by governments and societies; by intervening now it can be reduced

The experience of Ebola is an unfortunate example of what can happen when investment is needed urgently due to an outbreak. Alarmed at the global health emergency that Ebola represented, the US Congress agreed an appropriation of 5.4 billion USD, although some of this money was later spent elsewhere. At least 20 percent (1.1 billion USD) was earmarked for the domestic response[112] to what remained a very limited direct threat to the US. It demonstrates the scale of funding that governments are willing to allocate when faced with an acute public health emergency.

This is because untreatable infectious diseases are both scary and expensive to deal with once there is an outbreak. When it comes to dealing with AMR, countries have three options in how they pay. First, they could wait until there is a problem and then try to get on top of it. As MRSA, Swine Flu, Ebola and other outbreaks have taught us, this is expensive both in lives and money. Second, they could recognise that prevention is better than cure and individually invest in the tools needed to stop resistance, in a patchwork or uncoordinated fashion. This has not succeeded so far, we think mainly because of the worry of 'free-riders' benefiting unfairly. Or third, by working together and paying for global public goods in a pooled way, countries could most efficiently and effectively work to avoid the type of large-scale outbreak of an untreatable infection that nobody wants to see.

There are several options for countries or regions to raise the funding required

Governments could reallocate existing funding and budgets, or create new ones to address AMR in a way that is less susceptible to political risk and changes in public budgeting priorities. We set out options under these two categories below. All have their merits, are workable and can be used in combination, meaning different countries may choose to fund the coordinated package of new global incentives in different ways.

As progress is made towards an agreement at the international

112 The Henry J Kaiser Foundation. *The U.S. Response to Ebola: Status of the FY2015 Emergency Ebola Appropriation*. December 2015, Online, Available at: https://kaiserfamilyfoundation.files.wordpress.com/2015/12/8809-02-the-u-s-response-to-ebola-status-of-the-fy2015-emergency-ebola-appropriation.pdf)

level, agreements between companies and healthcare system leaders to test new models for pricing, purchasing and distributing antibiotics at a national level will be useful to inform longer-term solutions that need to be agreed and rolled out in many countries for new medicines.

Using existing funding streams

1.

Allocate a very small percentage of G20 countries' existing healthcare spending to tackle AMR

We estimate that a package of three to four billion USD a year can materially reduce the impact of AMR including by stimulating innovation for new products and supporting the use of vaccines and diagnostics globally. This cost is exceptionally small in the context of aggregate G20 healthcare budgets, representing about 0.05 percent of the G20's total annual healthcare spending of seven trillion USD.

Governments can afford to cover the cost of addressing AMR out of their health and economic development budgets: committing funds to AMR now will reduce the amount it costs later when it develops into a bigger crisis, which will inevitably fall to governments. Most of the incentives we recommend are structured as 'payments for success' so they can be funded by building up investment progressively over many years, rather than requiring immediate and upfront public investment into projects that may or may not deliver results. Governments would only pay the reward once a new product would be available for patients to improve health, leaving most of the development risk with the innovators.

Governments could also explore with international financial institutions whether they could provide a financial guarantee that the market entry rewards for new antibiotics will be paid to successful developers according to an agreed framework. This would give important legal certainty to private investors that the money will be available and will be paid if and when the developers they are backing bring specified products to market.

2.

Reallocate a fraction of global funding from international institutions to AMR

International development organisations – those created in the aftermath of the Second World War as well as more recently established regional development institutions – were set up to support global economic development and poverty reduction, including the provision of global public goods such as infrastructure, education and health.

Tackling AMR fits comfortably within this mission: it is an investment that positively affects long-term economic development, by supporting better health outcomes and maintaining productivity in agriculture and food production. Moreover, it helps lay the foundations for countries to reach the UN SDGs.

We call on these organisations and their member states to consider how their funding could be used to correct the market failures that affect the supply of products that are global public goods such as antimicrobials, rapid diagnostics for AMR, vaccines or new alternative approaches.

International development institutions already provide substantial support in low and middle-income countries for strengthening health systems and addressing the burden of disease (for example from malaria, TB and HIV), and regarding maternal and child health. The progress made in improving global health outcomes through such support would be partially undone if drug resistance is allowed to rise. Supporting prevention and successful innovation that would be most needed and used by patients in lower-income countries could be a very good investment with a high return and limited scientific and financial risk given the timing of payments. The sums required are small relative to overall budgets and the lead time before payments are due is long.

These international institutions could also play a useful role, through their technical analysis, their ability to advise on mechanisms through which resources could be channelled, and through their convening power with the wide range of partners who would need to be involved.

Finally, global charitable foundations have a crucial role to play and the same type of approach may be relevant to some of their work on so-called diseases of poverty and neglected diseases.

Using new funding streams

Given the importance of insulating incentives for long-term innovation from short-term political risk, policymakers may want

to consider setting up new funding streams that will contribute to paying for action on AMR, particularly in relation to incentives for antibiotic development. Three options follow, which could operate as complements to the funding options described above.

1.

An antibiotic investment charge for pharmaceutical companies

Antibiotics allow other medicines and treatments to work. Most open surgery requires antibiotics to prevent or treat infections; whilst chronic conditions like cystic fibrosis or procedures that require or result in immunosuppression, such as organ transplants or chemotherapy for cancer, rely on the 'insurance' provided by effective antibiotics. This dependence across so many areas of medical practice is not a unique feature of antibiotics; analgesics and anaesthetics are similar. However, antibiotics have a second feature that the others do not share: they lose their effectiveness for everyone the more they are used.

> *"Given the reliance of so many procedures and treatments on the availability of effective antibiotics, it makes sense that the pharmaceutical industry as a whole should help contribute to the development of new treatments."*

Given the reliance of so many procedures and treatments on the availability of effective antibiotics, it makes sense that the pharmaceutical industry as a whole could help contribute to the development of new treatments, to replenish the arsenal of products it depends. This might be achieved via a small charge on firms selling pharmaceutical and healthcare products or devices, which could be levied as a percentage of their sales and charged as a condition for accessing the health markets. This charge would be paid into a pooled fund used to pay for long-term incentives for new product development, such as market entry rewards to antibiotics of the highest global need.

This would ideally be agreed on a global level but could also function within large standalone markets, regions or groups of like-minded countries.

Such an approach, though, should recognise the contribution of those who are already undertaking work towards the development of products that help guard against the future threat of AMR. This is why we recommend incorporating the option that companies can either pay the charge, or demonstrate that they are investing the equivalent amount or more into R&D relevant to AMR. Such a system, which we are calling a 'pay or play' funding scheme, would give companies a strong incentive to resume, strengthen or start antimicrobial discovery projects. Combined with improved commercial rewards such as market entry rewards for example, this option has the potential to radically strengthen talent and stimulate R&D activities in the field.

Further consideration should be given to the detailed design and viability of such a 'play or pay' mechanism to ensure that it could be established in a way which is practical, fair and effective.

2.

A tax on antibiotics

Another option would be to create a tax on antibiotics[111]. Governments often use taxes that target particular products, to raise revenue and sometimes to influence consumption behaviours. For instance, petrol duties or tobacco taxes are widespread.

Taxes can have very different impacts depending on the local situation. Thus, we recommend consideration of this option at a country level, but not as a single global initiative.

In broad terms, notwithstanding country or regional differences, it is possible that the case for a hypothecated tax on animal use of antibiotics will look more compelling than one for human use. The idea here is that increasing the cost of antibiotics for animal use may discourage unnecessary use and encourage better animal stewardship practices, without compromising animal health or food security. Revenues raised could even be used to help farmers transition to farming systems that use lower levels of antibiotics, by improving infection prevention, or vaccine coverage. How to use a tax on antibiotics[113] used in animals will be a matter for each country; at a high level we would guard against a system where such a tax – paid by farmers – would be used solely to fund incentives for new antibiotic development for human use.

A tax on antibiotics used in humans could also be seen as a way to raise money while incentivising more positive individual behaviours. However, a tax is unlikely to be an effective lever of behaviour change in patients on an issue such as antibiotic consumption, not least as many (particularly in higher-income settings) are unlikely to be 'price sensitive'.

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113 Hollis A, Ahmed Z, Preserving antibiotics, rationally, *The New England Journal of Medicine*, 2013, 369, 2474-2476.

3.
Exchangeable 'vouchers' to reward new antibiotics

The idea of giving antibiotic developers exchangeable 'vouchers' as a reward for innovation is under discussion in the US in particular, drawing on previous examples elsewhere in drug development. There are two types of voucher being discussed.

The first is to give the successful antibiotic developer a 'priority review voucher' that can be applied to any drug awaiting FDA approval, as a way to go to the front of the regulatory queue and get approval faster. The recipient could either use it for its own drug, or sell it to another company. This idea is good in principle and would be of some help to incentivise antibiotic R&D. However, as more and more priority vouchers are awarded across priority healthcare areas, their relative benefits, and therefore value, diminish.

The second type of voucher being discussed would give an additional period of market exclusivity to the drug developer. Again, the recipient could use it for one of their own drugs or sell it to another company. This could represent a very large financial incentive, depending on how the scheme is designed. While far from perfect, these vouchers have the advantage of not requiring governments to raise money directly to fund market entry rewards, and may be politically more palatable. They enjoy popularity with many companies, especially those with profitable products nearing patent expiry, and would likely attract developers back into research for AMR. They are also a 'payment for success', similar in its logic to our proposed market entry rewards: the drug developer gets a payment only once a useful new drug has entered the market, leaving the scientific risk and the investment risk on the developer.

There are, though, two problems with these vouchers. Firstly, they push the cost of antibiotic development onto an arbitrary set of payers and patients (those who use the medicines on which the voucher is applied). Secondly, to deliver a similar incentive for new drugs, compared to market entry rewards, these vouchers would cost the healthcare system more in the long-term as they have to reward the innovative drug developer and provide an additional profit margin to the company selling the drug on which the voucher is applied.

Despite these drawbacks, they may be relevant in some jurisdictions, most likely the US, and there could be ways to mitigate some of their shortcomings. It is very promising that these design mitigations are already being discussed by companies and academics[114].

Three concluding thoughts on how to fund AMR interventions

Political leadership on the international stage is a more difficult constraint than the amount of money needed. Meetings of groups like the G20 and the UN General Assembly in September 2016 will be crucial in galvanising political consensus towards action at a global level.

Countries and regional blocks can consider mixing and matching how they fund the new incentives: as long as there is enough collective action to correct the worst of the market failures, how the money is raised and how some of the incentives are administered can be done at the local or regional level. Although a layer of globally-coordinated interventions are needed, not all countries need to adopt the same system of fundraising.

While governments discuss the shape of a new overarching international agreement and approach to antibiotics, national governments and companies should start implementing change and piloting new systems, building on the spirit and commitments in the Davos Declaration. The achievement of long-term goals in supporting the innovation that is so vital to the AMR challenge should not be at the expense of missed opportunities in the short and medium-term. This is particularly important for new pricing and stewardship agreements at country level for recently-launched antimicrobials and those coming onto market soon. Such arrangements can also serve as test beds for a wider global stewardship framework in the future.

> *"Different countries may choose to fund the coordinated package of new global incentives in different ways."*

114 Outterson K, McDonnell A, Funding antibiotic innovation with vouchers: Recommendations on how to strengthen a flawed incentive policy, *Health Affairs*, 2016, 35, 5.

5.

IDEAS FOR IMPLEMENTATION AND NEXT STEPS

We were commissioned to set out the costs of AMR and to recommend solutions to tackle this problem globally. These solutions must be grounded in the real world if they are to work and fit in with current national systems. We aim only to call for change and for international coordination when it is necessary for the solution to be effective.

A wholly new organisation may need to be created or an existing one could create a group focused on driving global solutions for AMR. We are conscious of the burden that establishing a new institution could create, and also of the global debate at present surrounding the role and function of key bodies within the global health architecture. Efforts should be made to consider in the first instance which existing institutions might be best placed to manage supra-national incentives for addressing AMR, rather than jumping to conclusions about the need for establishing a brand new body.

A supra-national entity will be needed to tackle AMR

At the very least, a supra-national entity is required to set the global priorities on AMR. For instance:

- Which are the pathogens for which we need new drugs, vaccines and diagnostics most urgently in human medicine?
- What is the picture for similar questions in veterinary medicine?
- What are good standards for securely sharing surveillance data globally?

This assessment of risks and priorities needs to be agreed based on global patterns of disease. This approach will ultimately deliver benefits to all. The needs and risks from drug resistance will change with time and will need to be reconsidered and updated. A lot of this can be done by strengthening or coordinating the work of existing institutions (including the WHO, the FAO, and the OIE) but it will need more power and focus than existing institutional arrangements to deliver clear and agreed priorities across sectors and across regions. It would benefit from having one organisation solely focused on delivering results in tackling AMR.

A supra-national entity operating on a model comparable to some recent successes in addressing market failures in public health (such as GAVI, the MPP, UNITAID, FIND or PATH) will also be needed to direct funding towards new incentives for innovation in antimicrobials (our proposal for market entry rewards), or where appropriate for new vaccines, diagnostics and alternative approaches. If governments agree to pool funds together into one entity, then that will need to play the role of a 'global payer'.

The details of how this could be set up should be explored in discussions between governments, international development organisations, the biopharmaceutical industry and civil society. There are several models that can be used, which entail varying degrees of integration across countries in how the incentives are funded. What is certain is that a critical mass of countries will be required for the new incentives to have sufficient market impact and to stimulate the private investment and innovation needed to address AMR. We would expect that the funds for those interventions would be raised from a subset of the world's richest economies, such as the G20.

It will be crucial that the buy-in to this global system is very wide and includes the most populated countries. An integral part of the global body's role would be to ensure that the products it supports are accessible in all parts of the world to those who need them, without unaffordability becoming a barrier to doing so in lower-income settings.

In return, all countries who benefit from the work of the global payer – regardless of their contribution – need to commit to wider efforts to tackle rising drug resistance, including taking national action to ensure the better use of antimicrobials and diagnostics in all settings.

Alongside the existing work of bodies like the WHO, the global payer can be an important lever in driving progress on these fronts.

Better national arrangements for purchasing antimicrobials will work alongside international action

In our proposed model for market entry rewards, product developers that receive funds from the supra-national payer would continue to access national markets in the normal way.

However, better purchasing arrangements that conserve

antimicrobials and do not incentivise unnecessary use are needed at the national level, for existing drugs and those entering the market soon. Discussions are already taking place between industry and a few governments to find a better balance to reward innovation while reducing the link between profitability and volume of sales. This work is very important. We need the leadership of a few 'early adopter' companies, regulators and healthcare buyers to find a different model to buy and distribute antibiotics within country health systems.

This work will inform the new stewardship framework that needs to be agreed globally with support from the WHO for existing and new drugs and that will underpin future international incentives. Even when such global incentives are in place, good national-level purchasing arrangements which balance innovation and stewardship, will continue to be essential. Such approaches could include insurance-type or subscription-based models, where health systems may pay for the availability of the antimicrobial, regardless of the volume actually used.

There is a golden opportunity this year to make substantial progress in key global forums

AMR is one of the biggest health threats that the world faces, with huge human and economic costs if we do not address it. Given the size and complexity of this threat it would be easy to think that solving it would be nigh on impossible. We strongly believe that this is not the case, and are confident that huge strides can be made this year, and beyond, to ensure we fix the supply and demand problems, and ensure the health of future generations.

WHO World Health Assembly

The World Health Assembly (WHA) will meet in Geneva shortly after the publication of this report. The WHO has taken an active and important role in driving forward proposals on AMR, and we hope that this continues in 2016 and beyond. We are looking forward to discussing our proposals with experts and policymakers in Geneva and hope that the WHA outcomes will feed into successful G20, G7 and UN agreements on AMR.

G7

The G7 is chaired by Japan this year and meets from 26-27th May. We noted the positive statement made for the need to tackle AMR in 2015[115] and hope that AMR will feature more strongly on the agenda this year. Calls to encourage not only innovation, but also to improve access and stewardship would provide useful groundwork for the wider G20 to take further action later this year.

G20

The G20 meets in September, chaired by China, and we feel that this group of countries is well placed to take forward the core solutions to support new innovation – including mechanisms to pool global funds to stimulate the development of antibiotics and diagnostics. It is vital that the market failures in the pipeline for new antibiotics are fixed, and that more successful products come to market. We also need to make much better use of the diagnostics that we currently have, as well as encouraging the next generation of products, something that a diagnostic market stimulus, providing top-up payments, could help to make happen. The G20 is well placed to develop and agree implementation of these ideas, keeping appropriate access as a core part of their design. We are hopeful that tangible progress will be made this year. Looking forward we see the G20 also playing a role in future years to drive forward progress to reduce unnecessary antibiotic use in agriculture, given that these countries currently account for around 80 percent of world meat production[116].

UN

The 194 member states of the UN also meet in September as part of its annual General Assembly, with AMR set to feature on its agenda for the first time in a High Level Meeting. There are a number of areas where we feel that a wide international agreement on AMR, with input from countries at all levels of income and development, is vital. This year we particularly hope the UN will focus on agreements to reduce unnecessary use of antibiotics in agriculture, improve global public awareness of AMR, and improve surveillance. Tackling these issues will be as important as stimulating new innovation in antibiotics and diagnostics, if we are to reach a long-term solution to AMR.

115 Leaders' Declaration, G7 Summit 7-8 June 2015, G7 Germany.

116 FAO data, FAOSTAT, 2016.

A world with working antimicrobials

We often take antimicrobials for granted, assuming that they will be there to protect us if we have an infection, as well as enabling us to have surgery. We all rely on them and for most of us a friend or family member has probably had their life saved by antimicrobials. Although the scenario where we do not take action is truly frightening, with over 10 million people dying every year by 2050 and a cumulative hit to the world economy of 100 trillion USD, it is sometimes hard to comprehend such large numbers. But these are not just large forecasted numbers; they represent the future for many individuals – all of us. Indeed, at least 700,000 people die every year already from drug-resistant infections. AMR is sometimes compared to a slow-motion car crash: sadly, it is one that has already started.

As shocking as these numbers are, it is well within our power to change this situation, and it makes complete economic sense, as well as being a moral necessity. What we need to do is to galvanise action, at the individual, organisational, state level and global level. At the individual level everyone can, and must, play their part in only taking antibiotics when they are needed and completing their course. At the organisational level, industry and NGOs need to make further progress on commitments, such as those made in the breakthrough Davos Declaration[117]. And at the state level, there needs to be more focus from across government departments. AMR has been seen as simply a health issue for far too long. It is also an economic and financial issue. We need all of these groups to come together to tackle it.

This process is already beginning and we are positive about the steps that have been made to tackle AMR in the last year. However the momentum must be maintained in 2016 and beyond to change the course of AMR, and give us all a brighter future.

“As shocking as these numbers are, it is well within our power to change this situation, and it makes complete economic sense, as well as being a moral necessity.”

117 Davos Declaration, Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance, 2016, [Online], Available at: http://amr-review.org/industry-declaration.

IF NOT TACKLED, RISING AMR COULD HAVE A DEVASTATING IMPACT

By 2050, the death toll could be a staggering

one person every three seconds

if AMR is not tackled now.

Source: Review's own analysis.

Review on Antimicrobial Resistance

SUMMARY LIST OF RECOMMENDATIONS

This represents a summary of the recommendations contained in this report.
The order in which these are presented reflects the structure of the report and not any kind of suggested prioritisation.

1	**A massive global public awareness campaign**
1.1	With leadership from an appropriate global body, establish an internationally-coordinated public awareness campaign to improve public understanding of the problems of drug resistance and support positive behaviour change regarding antibiotic use. Whilst globally consistent in its overall message, this should be delivered at country or regional level, with the message and the medium (e.g. social media, broadcast advertising, celebrity endorsement) tailored to local and regional norms.
1.2	At a country level, establish robust regulations to prevent the sale of antibiotics and other antimicrobials 'over-the-counter' (OTC) without a prescription, and ensure that these are properly enforced. Such policies to be locally-tailored to recognise instances where OTC sales may be only means of accessing antimicrobials – but where this is the case, provision of proper, clinician-led access should be a priority.
1.3	Global organisations (including the WHO, INTERPOL and World Customs Organization) to ensure a robust and internationally-coordinated effort to prevent cross-border sales of antimicrobials over the internet without prescription. This should be supported by outright bans on non-prescription internet sales at country level.
2	**Improve hygiene and prevent the spread of infection**
2.1	Governments, insurers, regulators and other healthcare system leaders should embed infection prevention and control (IPC) as a top priority at all levels within healthcare systems, using defined healthcare-associated infection (HCAI) reduction goals as the basis for targets, incentives and other performance management measures.
2.2	Public and philanthropic funding bodies to support improvements in funding for studies that demonstrate the effectiveness and cost-effectiveness of novel IPC interventions in health and care settings, and measures to induce positive behaviour change by clinicians and other healthcare workers.
2.3	Governments of low and middle-income countries should ensure that the benefits of improved public health and reduced antimicrobial resistance are properly factored into investment decisions about improved access to water and sanitation infrastructure.
3	**Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment**
3.1	The G20 and UN, with input from the WHO, FAO and OIE, should lead urgent global efforts to improve the collection and use of surveillance data regarding the use of antibiotics in agriculture, and the emergence and spread of drug-resistant microbes amongst animals. This should be prioritised over the next two years to inform targets to reduce unnecessary use of antibiotics starting in 2018.
3.2	International institutions with the relevant experience should undertake now a detailed economic analysis of the transition costs associated with lowering the use of antibiotics in farming across different regions and countries – particularly those in low and middle-income settings, where less analysis has been done to date
3.3	The WHO, FAO and OIE should, as a matter of urgency, convene a global group of experts, working across the relevant regulatory bodies and international organisations, to agree a single, harmonised list of those antibiotics most critical to human health. This would help to inform those antibiotics that should be banned or restricted from use in agriculture.
3.4	Food producers and retailers to take steps should improve transparency for consumers regarding the use of antibiotics in the meat that we eat, to enable better informed decision-making by customers. As part of this we call on major producers, retailers and regulators to agree standards for 'responsible use', to be used as the basis for an internationally-recognised label, or used by existing certification bodies.

3.5	In 2018, defined targets should be established at the country level to reduce unnecessary use of antibiotics in agriculture. There will not be a one-size-fits-all target, but all countries need to play their part in reducing use. An international panel of experts will be needed to guide the design of these targets and help countries implement them, alongside support from the WHO, FAO and OIE. Our suggestions on how they could be formulated: targets could be set over 10 years, with milestones to ensure regular progress, for reductions in total agricultural usage of antibiotics. These could be defined on the basis of milligrams of antibiotic used per kilogram of meat or fish production, with consideration given to appropriate variation by species. 50 mg/kg would be a reasonable objective for many high-income countries, but each country will need to have and regularly review their own ambitious targets.
3.6	Global bodies/national governments and regulators should establish evidence-based, enforceable targets for maximum levels of antimicrobial active pharmaceutical ingredient (API) discharge associated with the manufacture of pharmaceutical products.
3.7	Pharmaceutical companies should improve monitoring of API emissions from directly-operated manufacturing facilities as well as those of third party suppliers, and support the installation of proper waste processing facilities to reduce or eliminate API discharge. Such efforts should be based in voluntary, transparent and auditable commitments, with a globally-consistent 'quality mark' applied to end products produced on 'environmentally responsible' basis.
4	**Improve global surveillance of drug resistance in humans and animals**
4.1	WHO to provide global leadership and coordination to efforts – supported from governments, regional organisations, and philanthropic organisations – to establish a global surveillance system to monitor the emergence and spread of drug-resistant infections.
4.2	National governments/regulators and globally-representative bodies to initiate work to incentivise and remove barriers to the safe, secure and appropriate sharing of data of use to global surveillance efforts between public and private organisations on a large scale, with a particular view to unleashing the potential of advances in 'big data', cloud computing and machine learning in the coming years.
5	**Promote new, rapid diagnostics to cut unnecessary use of antibiotics**
5.1	In high-income countries, governments, regulators and other health system leaders to support the uptake and use of rapid point-of-care diagnostics in primary and secondary care. Incentives should be considered in high-income countries to facilitate the mandatory use of such tests to support clinical decision-making, where they are available, or the use of up-to-date epidemiological data where they are not, by 2020.
5.2	In low and middle-income countries, the uptake and use of rapid point-of-care diagnostics to guide the use of antimicrobials should be supported via a globally-administered 'diagnostic market stimulus' system, providing a direct per unit subsidy to diagnostic test manufacturers upon evidence of their product's purchase or use.
6.	**Promote the development and use of vaccines and alternatives**
6.1	Promote the uptake and use of existing vaccines more widely in humans and animals to save lives and reduce unnecessary antibiotic use, including through the work of Gavi or by initiating comparable new initiatives.
6.2	Sustain a viable market for vaccines with the greatest potential in tackling drug resistance. Depending on the characteristics of the vaccines in question, this might be through 'pull' funding using a similar form to existing Advanced Market Commitments (to promote broad uptake in mid to large-sized populations), or as market entry rewards (to ensure availability for smaller populations at high risk).
6.3	Some alternatives aim to prevent infection, as vaccines do, others to replace antibiotics as treatment, and still others to make antibiotics more effective or reduce the likelihood of resistance arising by being taken alongside them. We believe that alternatives should be eligible for the same incentives as vaccines or antibiotics, where they fulfill the same role in combating AMR.

7.	**Improve the numbers, pay and recognition of people working in infectious disease**
7.1	Governments, healthcare system leaders and private actors (such as clinical professional bodies and academic institutions), should work together to expand funding and training opportunities to increase the number and capacity of healthcare workers on the frontline of fighting resistance, and of academic scientists working in the field. These efforts should extend to considering the pay, recognition and standing of professionals working in fields relevant to AMR within the healthcare, academic, and commercial communities.
8.	**Establish a Global Innovation Fund for early-stage and non-commercial research**
8.1	Governments, and public and philanthropic research funding organisations, to collaborate on a global basis to develop a Global Innovation Fund for R&D into new antimicrobials and other related products (including vaccines and diagnostics.) This fund should build on existing bilateral and multilateral arrangements for pooling and coordinating the spending of research funds, but do more to ensure that AMR-related research is properly funded and more proactively targeted towards neglected areas (e.g. re-purposing of older products.)
9.	**Better incentives to promote investment for new drugs and improving existing ones**
9.1	Institute a system of 'market entry rewards' to provide lump-sum payments to the successful developers of new antibiotics that meet a specified unmet medical need. In principle, this should be administered and funded on a supra-national basis, with support for global, affordable, and responsible access to antibiotics at its heart. Detailed work on the design and implementation of such a system should be picked up as a matter of urgency by the appropriate international partners.
9.2	Consider the role that such a system of market entry rewards can play in supporting the development of complete treatment regimens for tuberculosis (TB), as a means of 'supercharging' systems of support for TB product development.
9.3	Key regulatory agencies should work together to improve the global harmonisation of regulatory pathways for new antibiotics, and explore the possibilities for mutual recognition of regulatory approval across multiple jurisdictions.
9.4	Pharmaceutical companies, regulators and healthcare system leaders to work together to institute national and regional 'clinical trial networks' for antibiotics, to streamline the clinical trial process and reduce the costs and duration of antibiotic development.
10.	**Build a global coalition for real action – via the G20 and the UN**
10.1	The G20 group of countries should take leadership on defined aspects of the global response to AMR, particularly work to develop and implement new incentive models to support the development of new antibiotics, diagnostics and vaccines. This should be complementary to wider discussions on the global response to AMR as part of the UN General Assembly, and the continuing efforts of the WHO, FAO and OIE in their respective sectors.
10.2	Governments and relevant global bodies to initiate rapid work to consider in detail the global coordinated structures which would be required to oversee the development, implementation, and operation of global systems of financial support for antibiotic and diagnostic development and use.
10.3	Governments, industry and relevant global bodies should continue to work together to identify adequate and sustainable global, national and local funding mechanisms for raising the money required to finance a long-term global response to AMR. This should include the exploration of – amongst other options – mechanisms to raise revenue from new sources and on a hypothecated basis, for instance through modest and targeted levies on antibiotic use and/or on the global pharmaceutical, healthcare products, and medical device industries.

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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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