



TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: AN OVERVIEW OF OUR WORK

**THE REVIEW ON
ANTIMICROBIAL RESISTANCE**

CHAIRER BY JIM O'NEILL

MARCH 2016

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INTRODUCTION

The Review on Antimicrobial Resistance (AMR) was commissioned by the UK Prime Minister, and is hosted by the Wellcome Trust. It is tasked with recommending, by the summer of 2016, a comprehensive package of actions to tackle the growing problems of drug resistance globally, across all types of antimicrobial drugs. In the meantime, it is publishing a series of papers looking at individual aspects of the wider AMR problem.

This paper provides a brief summary of the Review's work to date, collating the executive summaries from the eight thematic publications. Thus far the Review has analysed the scale of the problem of AMR if action is not taken; looked at early solutions the world can take to reduce resistance; recommended solutions to make the drug and diagnostic markets function better; examined the need to reduce antibiotic use in agriculture and antibiotic waste dispersing into the environment, looked at the potential impact of vaccines and other alternative approaches and finally, explored the importance of infection prevention and control, and surveillance in the fight against increasing drug-resistance.

Going forward, the Review will now publish its recommendations in mid- May. Further information on the papers and the work of the Review is available on our website, www.amr-review.org.

ANTIMICROBIAL RESISTANCE: TACKLING A CRISIS FOR THE HEALTH AND WEALTH OF NATIONS

December 2014

Antimicrobial resistance (AMR) kills around 50,000 people a year in the US and Europe, and is estimated to kill more than 700,000 people globally. However, what is most terrifying about drug-resistant infectious diseases is not the pain and suffering that they cause today, but what is likely to happen in the future as rates of resistance rise. In order to quantify this threat, the AMR Review asked two teams of economic modellers (KPMG and RAND Europe) to estimate what the world might look like in 2050 if action was not taken to tackle resistance.

Both teams examined a set of six pathogens (*E. coli*, *Staphylococcus aureus*, *K. pneumoniae*, tuberculosis (TB), malaria and, HIV), and modelled a series of scenarios of increasing levels of drug resistance and rising rates of infection between 2015 and 2050, based on consultation with experts to identify upper and lower bounds for likely future scenarios. The AMR Review report then considered the outputs of their central and most likely scenarios. In KPMG's case, this modelled resistance rates rising to 40 percent, and a doubling of rates of hospital acquired infections for *Staphylococcus Aureus*, *K. pneumoniae*, and *E. coli*. RAND's scenario looked at what would happen if resistance rates for all six pathogens rose to 100 percent over the next decade.

Both studies produced startling results. Even under relatively conservative assumptions of how growing resistance would impact population health, they suggested that without global action to reduce AMR, an additional 10 million people would die every year from drug-resistant infections by 2050. That is more than currently die from cancer and eight times more people than die from road accidents.

These deaths and illnesses were then fed into the researchers' predictive macroeconomic models, which found that if resistance is not addressed, the world will produce around eight trillion USD a less a year by 2050, and a cumulative 100 trillion USD would be wiped off the world's production over the next 35 years.

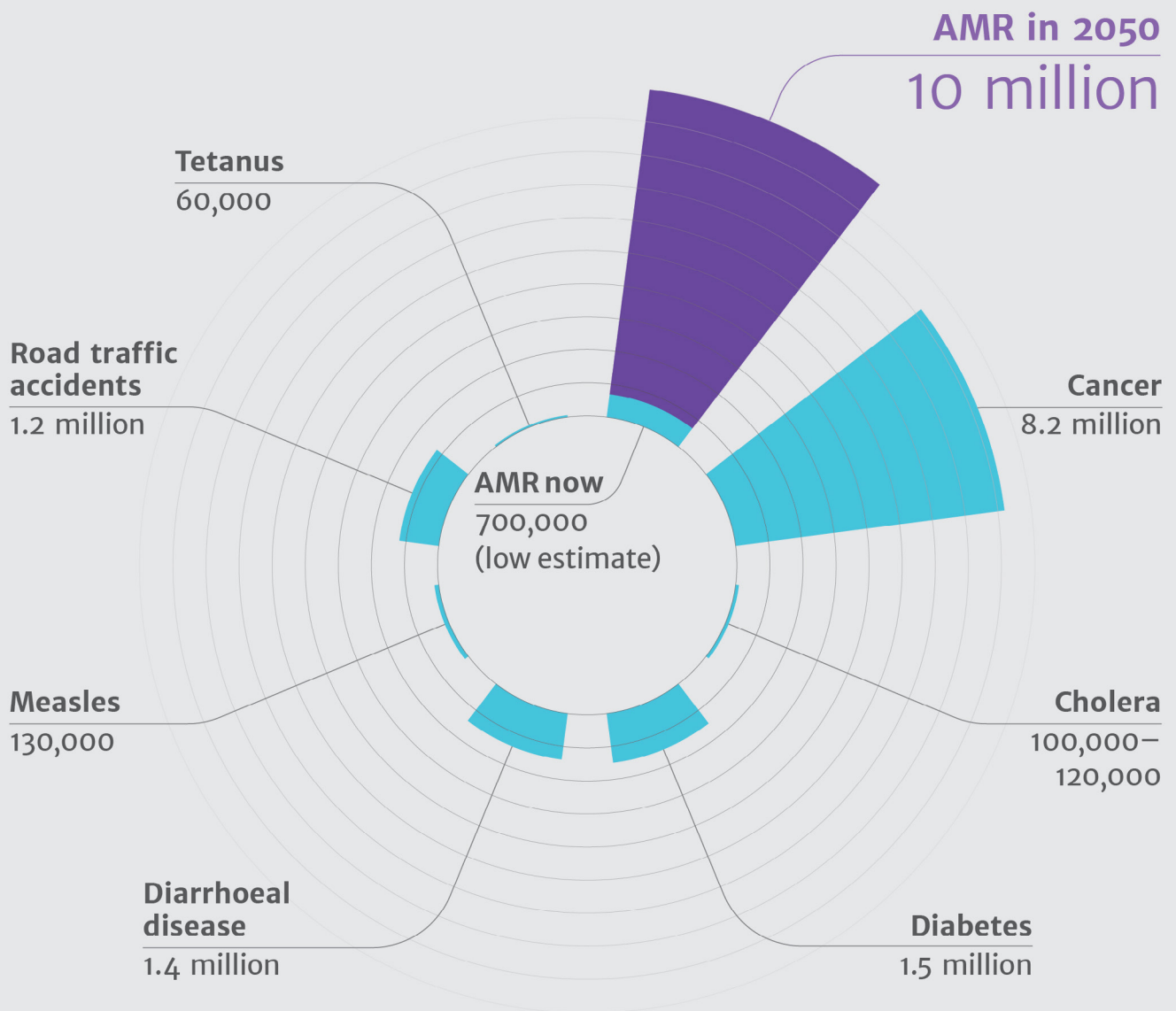
Despite the scale of this economic burden, it takes into account only the effects of lost economic output resulting from greater rates of death and illness. The research did not take into account increased healthcare costs associated with drug-resistant infections, or secondary effects, such as a reduction in joint replacement surgery, difficulty treating cancer, and the greater risk from caesarean sections. They also did not look at the higher mortality rate that would occur in areas such as gut surgery, which would become far more dangerous in a world where resistant infections were common, as this was too difficult to

model. Because of these assumptions we believe the estimates made by KPMG and RAND are likely to be conservative estimates of the true threat of AMR.

There were geographical differences in where the burden of AMR would land. The studies found that whilst the worst impact from rising drug resistance would be seen in Africa and Asia, wealthier parts of the world, such as Europe and North America would suffer greatly too, with the death toll in these countries rising steeply to more than 10 times the current figure of 50,000 a year.

By setting out the full magnitude of the potential human and economic costs of rising drug resistance, this paper demonstrates that there is a clear global imperative to take this threat seriously and start finding solutions, not least as action taken now could dramatically reduce both the enormous financial and human impact of resistant infections in the future.

Deaths attributable to AMR every year compared to other major causes of death



Sources

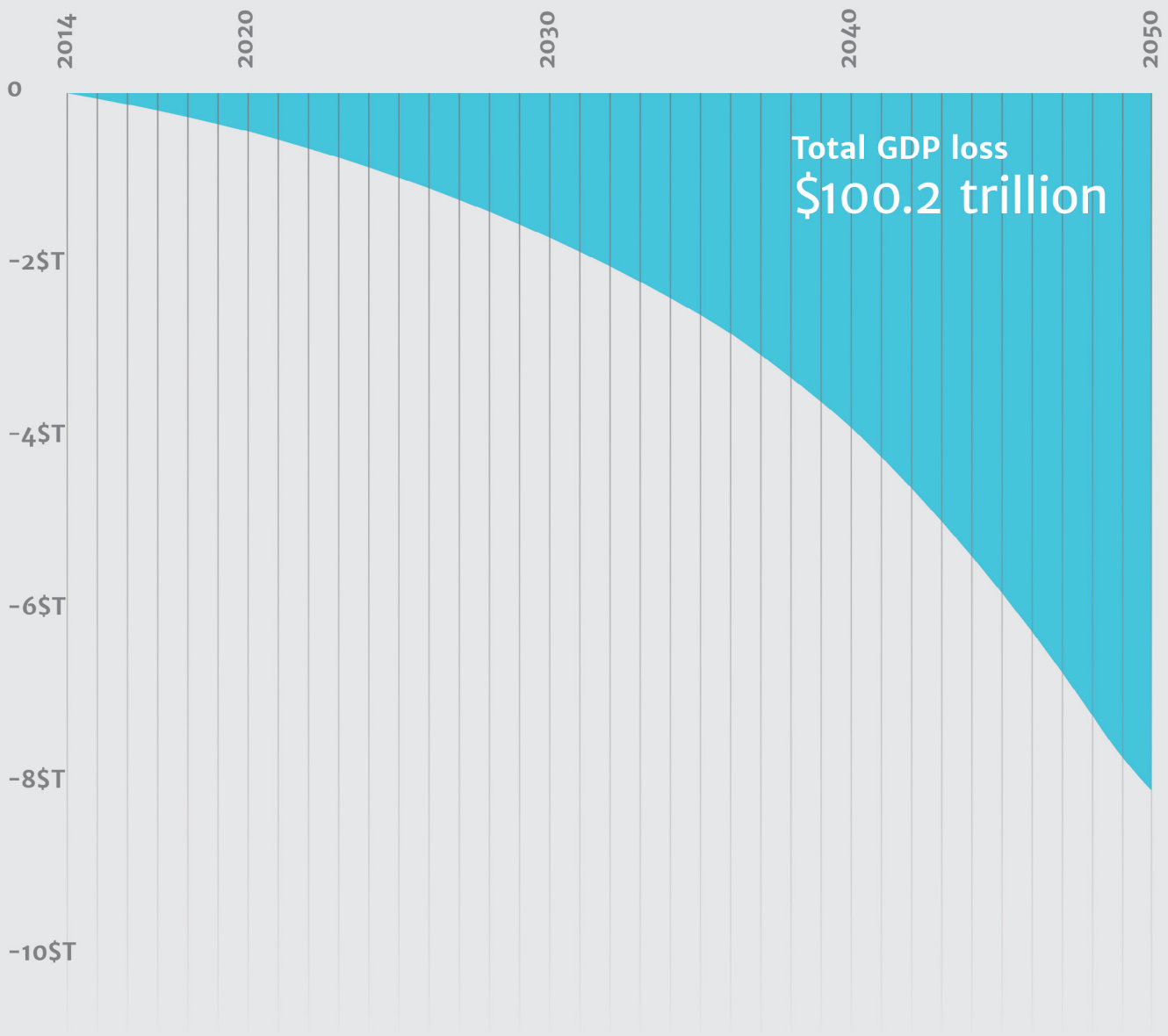
Diabetes
Cancer
Cholera
Diarrhoeal disease

www.who.int/mediacentre/factsheets/fs312/en/
www.who.int/mediacentre/factsheets/fs297/en/
www.who.int/mediacentre/factsheets/fs107/en/
www.sciencedirect.com/science/article/pii/S0140673612617280

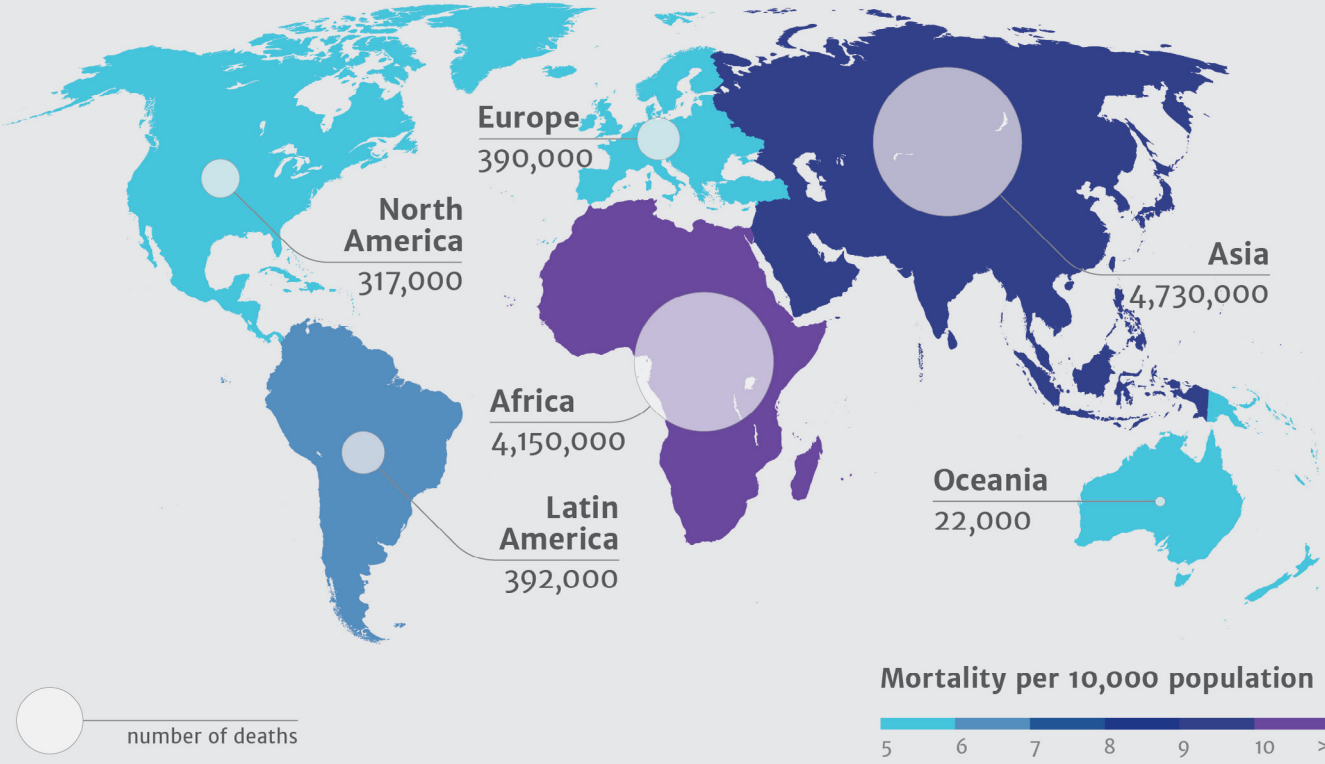
Measles
Road traffic accidents
Tetanus

www.sciencedirect.com/science/article/pii/S0140673612617280
www.who.int/mediacentre/factsheets/fs358/en/
www.sciencedirect.com/science/article/pii/S0140673612617280

AMR's impact on World GDP in trillions of USD



Deaths attributable to AMR every year by 2050



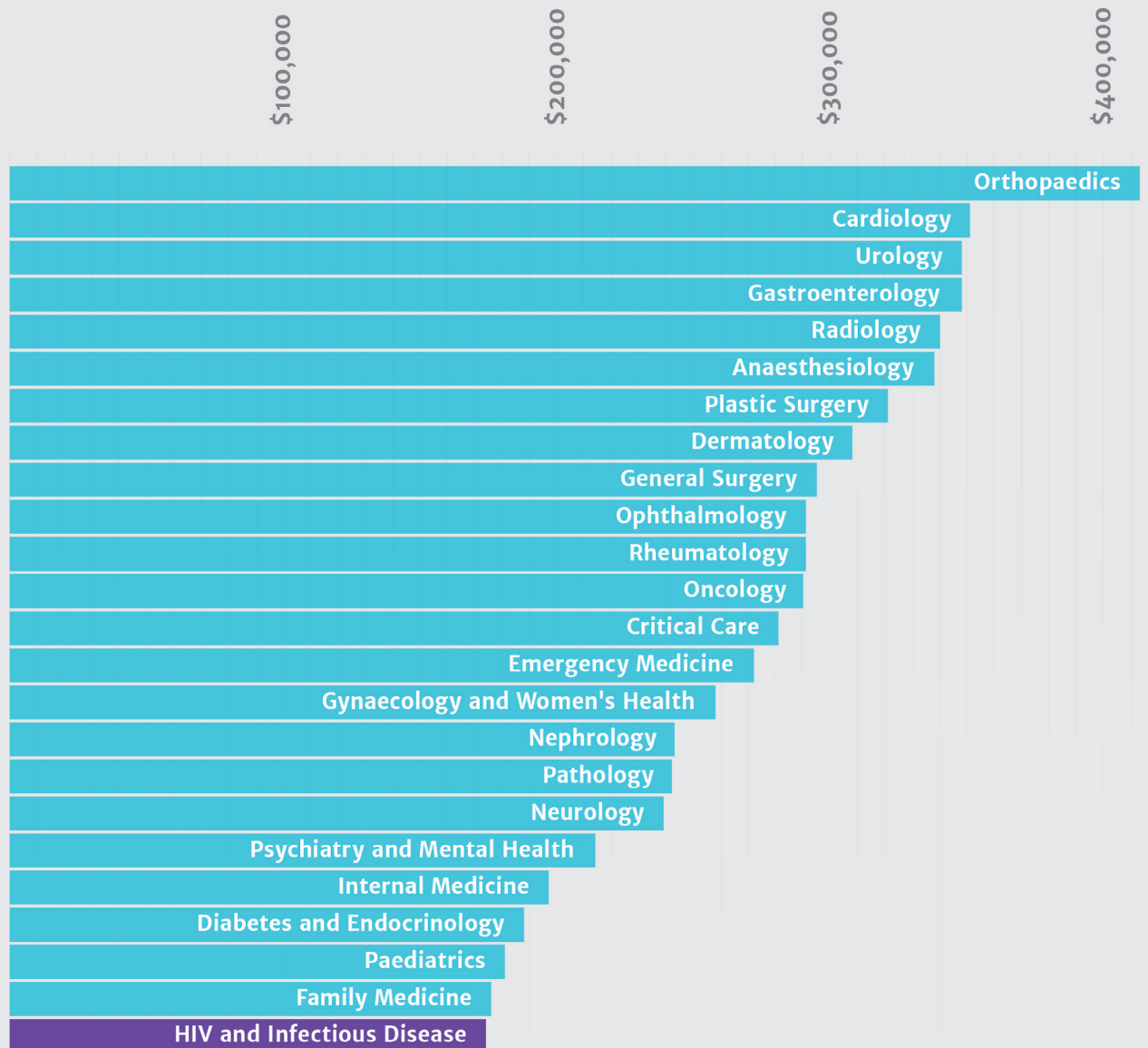
TACKLING A GLOBAL HEALTH CRISIS: INITIAL STEPS

February 2015

There are several areas where we think that action can be taken without delay and these areas form the basis of this paper. These ideas will not be news to people versed in the issues raised by AMR. The reason for stressing them here is to highlight and catalyse action on each area, without waiting for an overall package to be agreed. These five specific steps for action are:

- 1. Increase early science funding to tackle AMR:** established funders must address this however, in addition an 'AMR innovation fund' would act as an early research grant maker for blue sky science, and as a non-profit incubator for ideas that are more mature. Too many good ideas are not being pursued for lack of funding.
 - 2. Make existing drugs go further:** a systematic programme of re-examining existing antibiotics could test whether changing the dosing or combining them with other agents or other antimicrobials could slow down the spread of drug resistance and treat 'resistant infections' more effectively.
 - 3. Support the development and use of relevant diagnostic technologies:** if we had the right diagnostics, more patients would receive the right antibiotic to treat their infection, and fewer antibiotics would be prescribed unnecessarily.
 - 4. Invest in the people who will solve the problem:** many companies have retreated from antibiotic discovery in recent decades. It is crucial to train the next generation of doctors, scientists, microbiologists, pharmacologists, medicinal chemists and biochemists, as well as economists, social scientists and vets, among others. They will need to find novel approaches and therapies for microbial diseases, whilst maintaining a connected and global outlook.
 - 5. Modernise the way surveillance of drug resistance is done and used globally:** a more joined up and digital global approach is needed, using the latest advances in molecular testing and informatics, to improve access to real time global-scale surveillance information.
-

Doctors' annual pay for working on Infectious Disease and HIV compared to other medical fields in the US (2012)



SECURING NEW DRUGS FOR FUTURE GENERATIONS: THE PIPELINE OF ANTIBIOTICS

May 2015

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

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

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

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

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

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

new antibiotics in large quantities – a key factor in contributing to the development and spread of resistance.

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

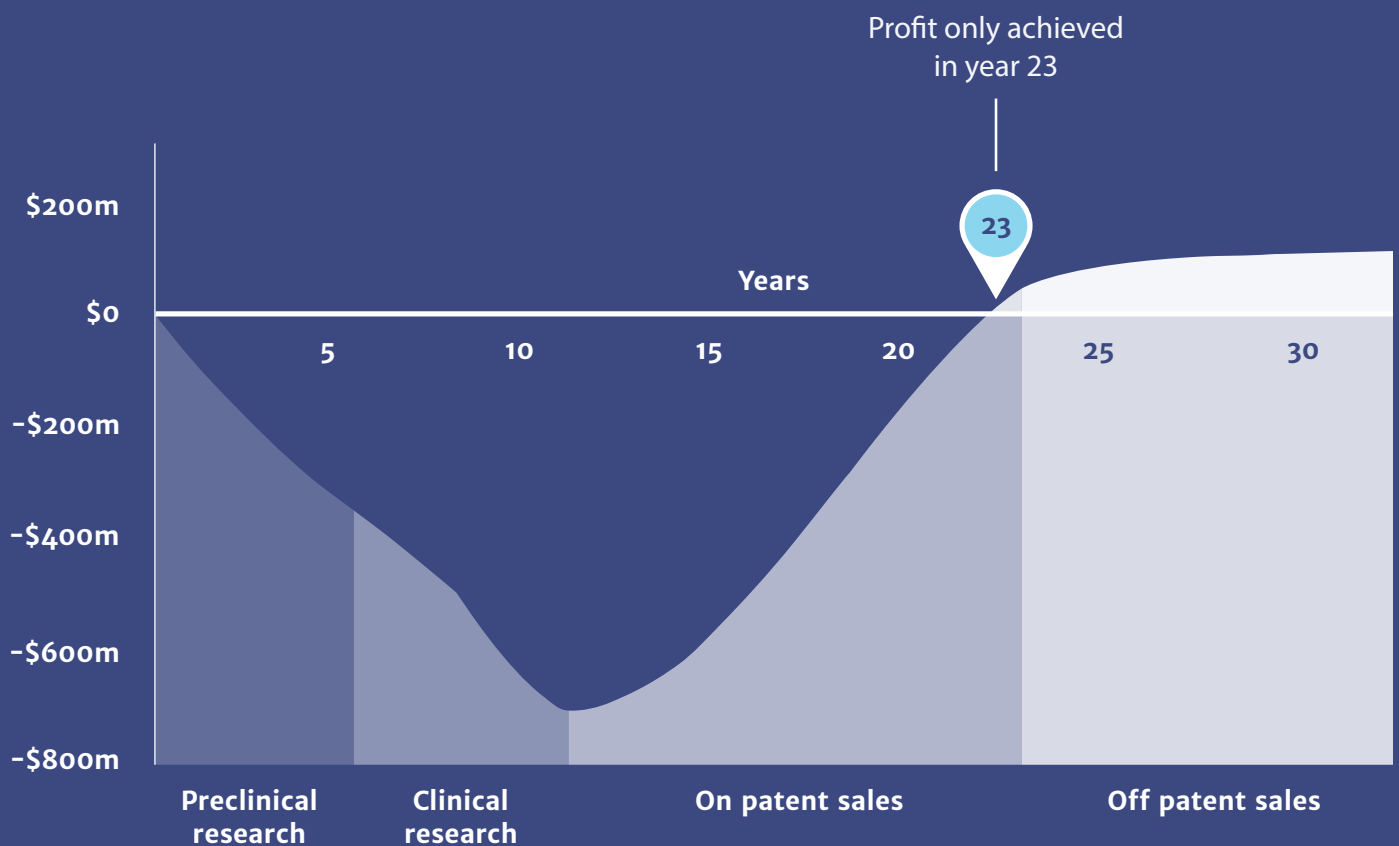
Finally, there are ways to further reduce barriers to drug development by lowering costs, improving the efficiency of research, and lowering global regulatory barriers wherever possible without compromising patients’ safety. Much has already been done in this space but we should continue to explore ways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

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

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

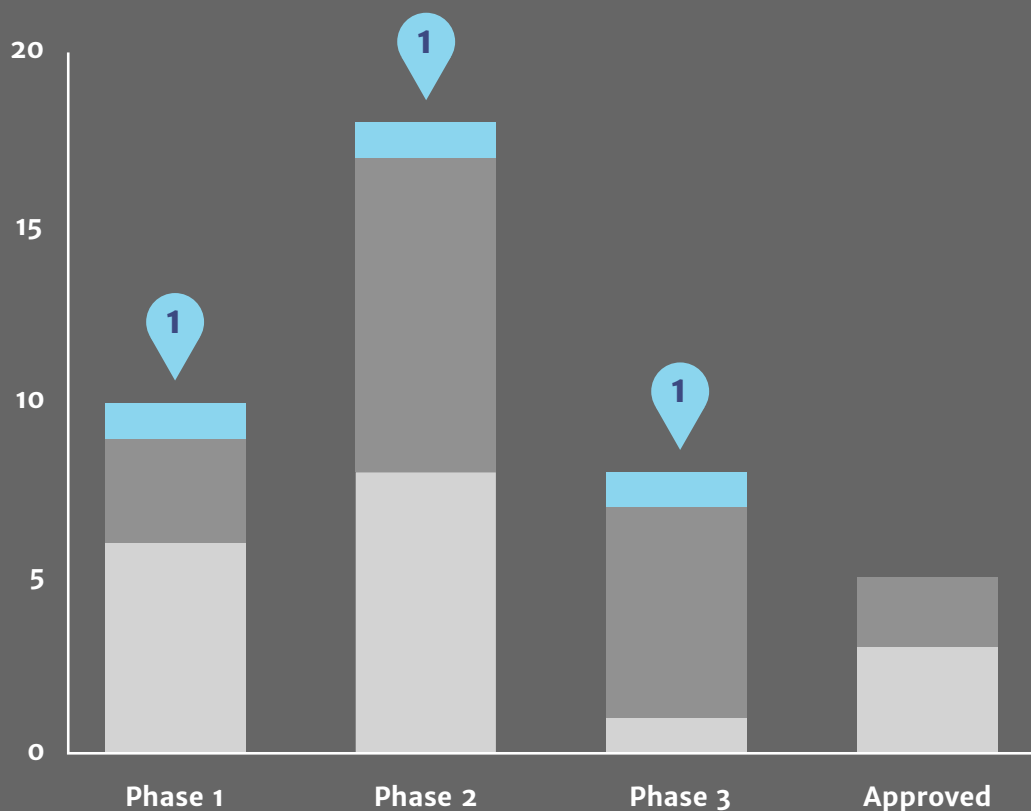
We look forward to working with governments, industry and other interested parties around the world over the next 12 months.

CUMULATIVE PROFITS FROM ANTIBIOTIC RESEARCH



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

ANTIBIOTICS IN THE PIPELINE OR RECENTLY LICENSED



High priority

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

Low priority

Does not meet the criteria for "clinically useful"

Medium priority

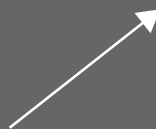
Targets at least one CDC 'Urgent' threat (Clostridium difficile, carbapenem-resistant Enterobacteriaceae or drug-resistant Neisseria gonorrhoea, but is not classed as a potential break through)

A PLAN TO OVERHAUL ANTIBIOTIC DISCOVERY

**Support a viable market
for the highest
priority antibiotics**

**Middle-stage
interventions
to catalyse
drug discovery**

**Better-funded
early-stage research**



RAPID DIAGNOSTICS: STOPPING UNNECESSARY USE OF ANTIBIOTICS

October 2015

At the heart of the global rise of drug-resistant infections, or AMR, there is a fundamental 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. In May 2015, we outlined specific proposals to address this supply problem, which have been echoed most recently by the governments of the G7 group of countries in October 2015.

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 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.

Take, for instance, a modern health system such as that in the US. Looking at adult patients visiting the doctor to treat respiratory problems, a study found that more than two-thirds of courses of antibiotics were likely to have been inappropriately prescribed for conditions that were not infections at all, or infections caused by viruses – for which an antibiotic would do nothing. That amounts to 27 million courses of antibiotics wasted a year in just one set of indications, in the United States alone.

Another worrying example is when patients are given powerful antibiotics that should ideally be kept in reserve, just in case their infection is caused by a drug-resistant strain that would not be cured by older medicines. This is seen for example in the treatment of gonorrhoea, where the world's 'last line' treatment is given on a precautionary basis to almost all patients, even though 70–80 percent of cases in the UK would be expected to respond to older, abandoned 'first line' treatments. As a result, cases of multi drug-resistant gonorrhoea are increasing, for which treatment options are severely limited – presenting the very real risk that untreatable cases will emerge.

Stewardship programmes to change the prescribing habits of doctors and the expectations of patients can go some way

towards addressing the issues of overuse. Countries like Sweden and The Netherlands have shown how it is possible to keep antibiotic use low with current technology. More recently other countries like China and Brazil have made progress in reducing over-the-counter sales of antibiotics in large urban centres.

But to solve the problem of unnecessary use, and to get the right drug to the right patient at the right time, regulation and stewardship programmes will not be enough: we need new rapid diagnostics too. The world needs a step change in the way that technology is incorporated into the decision-making process around antibiotic use – whether that be in the home, the pharmacy, a doctor's surgery or hospital.

The vast majority of antibiotic prescriptions are made outside the hospital setting, either by doctors without using a diagnostic tool, or in some cases by pharmacists or self-medicating patients buying antibiotics over-the-counter. When doctors 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 is a process that has remained basically unchanged in decades: most of these tests will be 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 for 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.

Empirical decision-making will often result in the patient getting the treatment that they need, and quickly – but it is also a major driver of the problems of unnecessary antibiotic use. Furthermore, as the prevalence of resistant infections rises, so too do the chances that the choice of treatment will prove to be wrong.

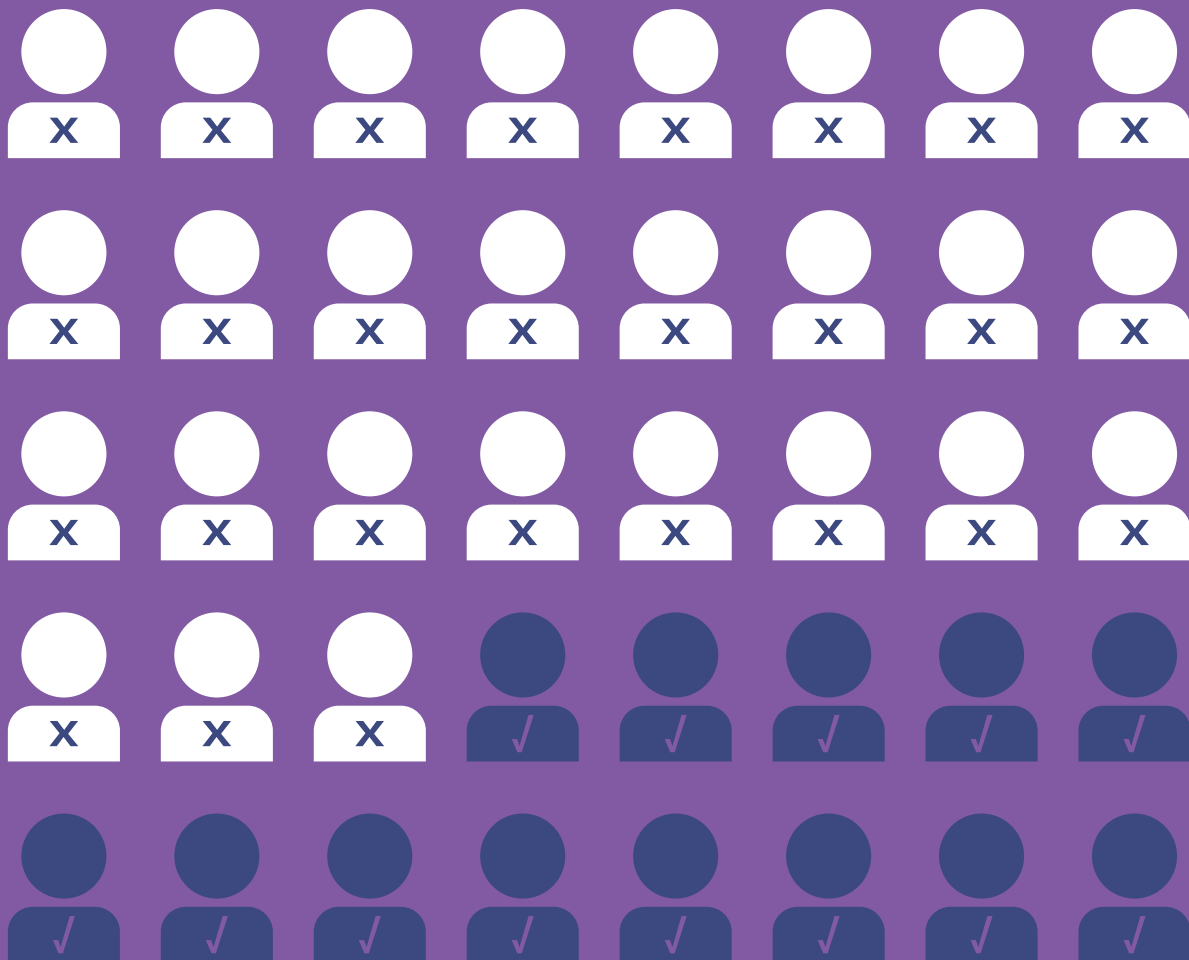
This needs to change totally if we are to tackle our chronic over-consumption of antibiotics. Rapid diagnostic tools for bacterial infections, which allow doctors to identify the nature of an infection in minutes instead of hours or days, have the potential to transform the diagnosis and treatment process from an empirical one to a precise one. What seems to the lay person

RAPID DIAGNOSTICS WOULD REDUCE UNNECESSARY PRESCRIPTION

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

27m
get antibiotics unnecessarily

13m
who need antibiotics get them



to be a simple question like distinguishing between a viral and a bacterial infection has proved a very difficult technical challenge, with no perfect tool to answer it rapidly and conclusively to date. Yet this is what is needed to make a dent in the very large number of antibiotic prescriptions given mistakenly for viral infections. More refined tests, able to identify the strain of bacterial infection and the antibiotics to which it is resistant or susceptible, will allow more precise prescribing of narrow spectrum antibiotics. This in turn reduces our dependence on broad-spectrum products, slowing the development of resistance and improving the treatment that patients receive.

Behind the scenes, 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.

We can be encouraged that some technology that could improve antibiotic use exists already, and more is within reach in a matter of years. But even where such technology is available, it is used too little; and where it is under development, the lack of viable commercial markets and reimbursement mechanisms for the end product means the innovation risks dying on the vine.

In this paper we set out policy interventions to support the development of game-changing new rapid diagnostics and their widespread adoption over the next five years, so that we can improve the business case for purchasing diagnostics, increase early stage funding, and subsidise uptake. These three interventions do not just consider the needs of the richest health systems, but instead seek to be useful to the largest number of patients, in the widest possible range of settings globally.

We do not underestimate the scale of the behaviour changes needed to alter long-established ways of using antibiotics. But we need new technology to support these new behaviours and a viable financial proposition to make that innovation happen. Even if it were possible, it would not be good enough to make the standard of antibiotic prescription in the BRICs reach a similar level to that of the United States. For material progress to happen over the next five years healthcare systems need to leapfrog to using rapid diagnostics wherever possible, before using an antibiotic.

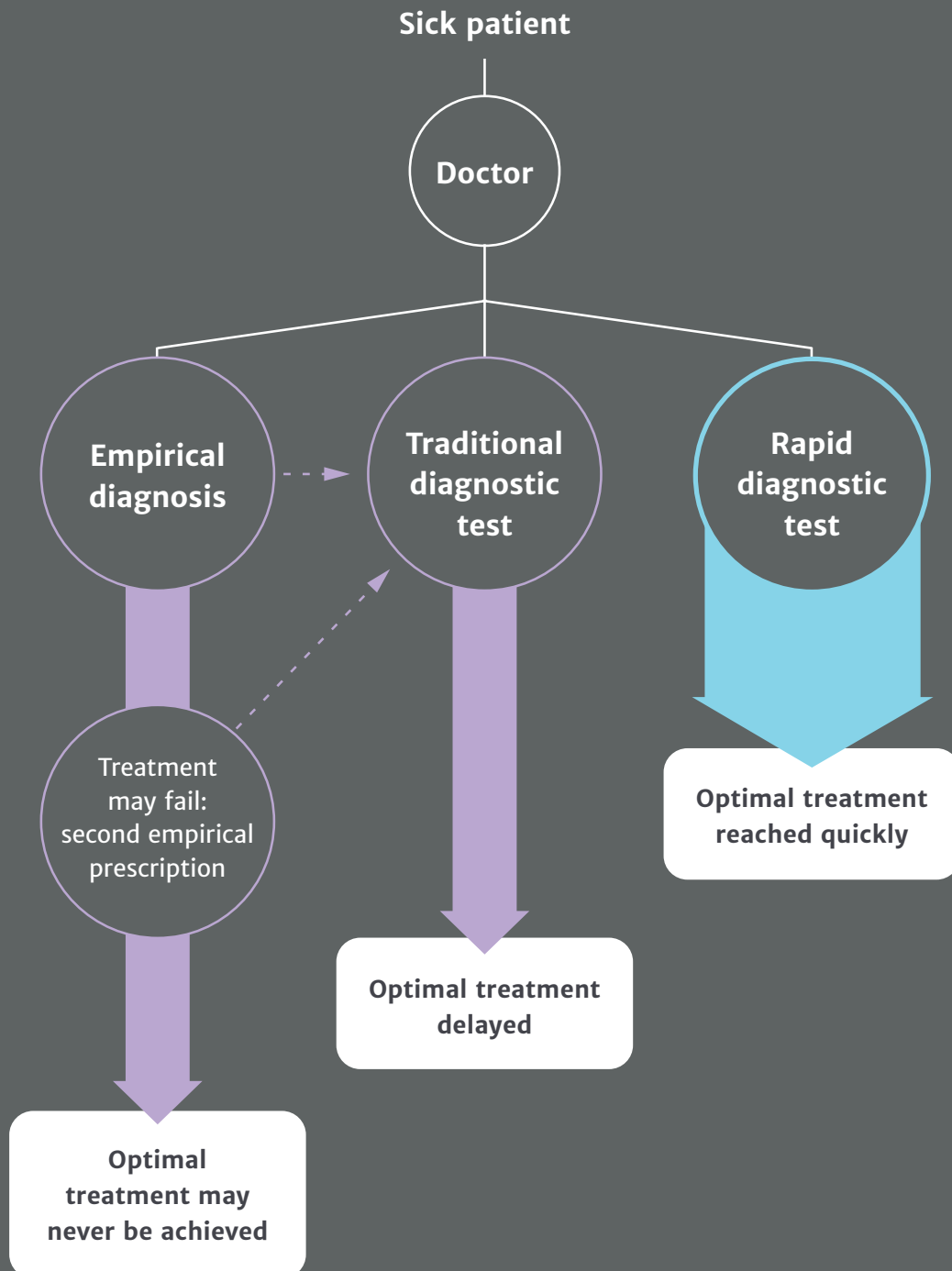
The Review made three recommendations for interventions in this paper.

1.

Diagnostic Market Stimulus pots to support a viable market for what is a classic ‘public good’

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 simply 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. Prize initiatives in the UK, 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, further and more sustained intervention is needed. To overcome this mismatch between the costs and benefits of diagnostics, we propose bold and globally-coordinated Diagnostic Market Stimulus pots (DMS), which would ensure a market-based revenue stream for developers of products that match a recognised area of need. DMS would not pre-judge which diagnostics are best, rather they would follow the success of actual products bought by healthcare providers, by topping up the payments to developers to make sure the commercial benefits and the needs of society are better aligned. We envisage this support would come from the same global payer we proposed in our last paper on incentivising new antibiotics, but that the funding needed would be on a scale far less than what is necessary to stimulate the antibiotic market. As such, it could be incorporated within the same 16 – 37 billion USD market intervention that we recommended in May. We envisage that as well as incentivising future innovation, this would also encourage the uptake of relevant products that are already being developed or that are available today. Based on these initial proposals, we will continue to work on how to structure an effective DMS.

NEW RAPID DIAGNOSTICS WOULD OPTIMISE TREATMENT



2.

Funding from a Global Innovation Fund for AMR to jump-start early innovation in the field of rapid diagnostics

There needs to be greater funding available to product developers to support early-stage R&D activities. Many developers are small or medium-sized companies, which may face difficulties in securing private investment given an uncertain market backdrop. We believe the Global Innovation Fund for AMR, of 2 billion USD over five years – described in our February 2015 paper – has a key role to play in supporting the early-stage development of rapid diagnostics. This support should not be limited, though, to developers of what we classically think of as a diagnostic test to improve antibiotic use. Rather, it should also seek to support other complementary innovative technologies that may guide prescription or improve use – such as advanced computer learning or artificial intelligence-based systems for use by clinicians during diagnosis, guiding them towards optimal treatments.

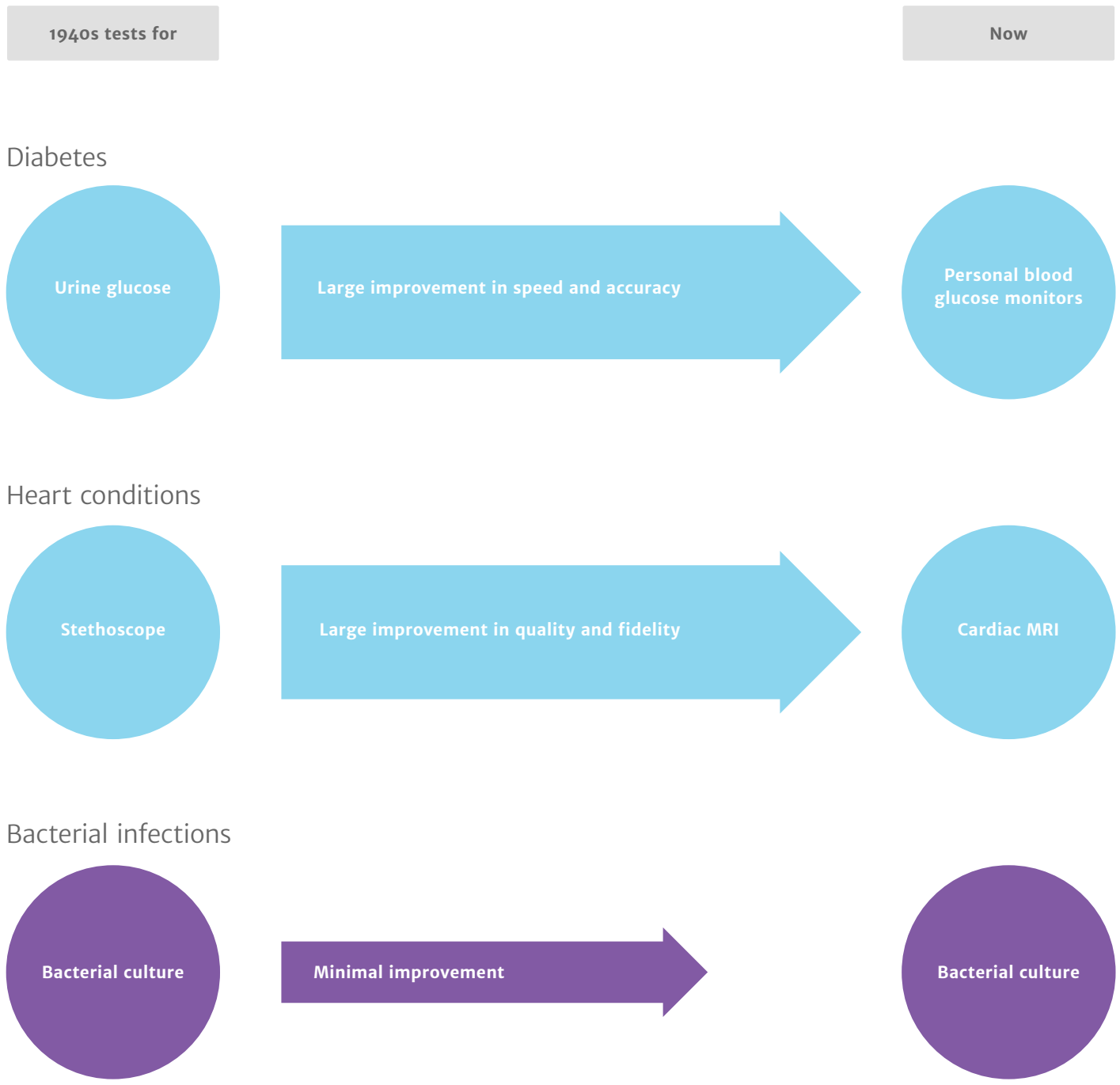
diagnostics represent. Only by doing this can we fundamentally and sustainably reduce our misuse and overuse of antibiotics. Incremental behaviour change alone will not have a big enough impact, and regulation can only go so far. Through targeted, measured interventions, on a global scale, we can ensure the use of rapid diagnostic tests that allow for a true “right patient, right antibiotic, right time” approach.

3.

Help build the long term economic case for rapid diagnostics as a public good in the fight against drug-resistant infections

For health systems to adopt a new technology, its clinical and cost-effectiveness must both be demonstrated using large, objective studies. The cost of doing this is usually borne by the company developing the technology. This can rise to tens of millions of USD, over and above the R&D costs, to build evidence from large randomised control trials. Given that rapid diagnostic tests for infectious diseases are a public good, with the benefits to society usually larger than the benefits to the individual patient or healthcare provider, there is a particular case for policy makers to support these trial processes. Health systems can play a crucial role in the evidence-building process, and in supporting the health economics studies that are together needed to demonstrate clinical and cost-effectiveness to regulators, purchasers and end users. If the world is serious about tackling the threat of drug-resistant infections, we need to fully embrace the step-change in technology that rapid point-of-care

BACTERIAL DIAGNOSTICS HAVE NOT KEPT UP WITH MEDICAL INNOVATION OVER THE LAST 70 YEARS



Source: Extracts adapted from Christensen C, Grossman J H, Hwang J. *The Innovator's Prescription: a Disruptive Solution for Healthcare*. 2009. McGraw Hill. New York.

A PLAN TO OVERHAUL DIAGNOSTIC DEVELOPMENT

Barriers

Difficult to show
cost and clinical
effectiveness



**Fund and
facilitate
research**

Difficulty
raising capital



**Global
innovation
fund**



Diagnostics are more
expensive than empirical
prescribing



**Diagnostic
Market
Stimulus**

Solutions



SAFE, SECURE AND CONTROLLED: MANAGING THE SUPPLY CHAIN OF ANTIMICROBIALS

November 2015

The growth of unregulated internet sales of antibiotics, and manufacturers producing poor quality medicines, are two factors that risk fuelling the rise of drug-resistant superbugs, according to a new report published today. This short paper calls for global action by governments, regulators and internet companies around the world to clamp down on unlicensed internet sales of antibiotics, and to implement better monitoring of global drug quality, particularly in low and middle-income countries.

The excessive and unnecessary use of antibiotics is already widely recognised as a significant driver of the emergence of drug-resistant strains of common infections – as the increased exposure of bacteria to the drugs encourages the development of drug resistance, through a process of evolutionary natural selection. Although this is a problem even when antibiotics are prescribed by a doctor, it is exacerbated by patients self-medicating, without proper clinical direction – often using antibiotics purchased over-the-counter or, increasingly, via online pharmacies. Over-the-counter sales of antibiotics are illegal in most countries, with good enforcement of these rules in some parts of the world. However in practice the use of antibiotics without a prescription – usually bought over-the-counter – remains relatively commonplace in Southern and Eastern Europe and many low- and middle-income countries. But online pharmacies represent a new challenge for regulators. They are often based in countries where regulation is lax but they offer to ship prescription drugs anywhere in the world – so represent a problem for all countries. Even powerful, last-line antibiotics such as colistin can be found from online retailers willing to dispatch it to Europe without evidence of a doctor's prescription. This is the drug at the centre of fresh concern from public health authorities worldwide this week, after a novel form of resistance to colistin was found in bacterial infections in animals and humans by a team of Chinese scientists.

The report highlights the need for a concerted international effort to address the emerging risk of online sales, involving collaboration between medicines regulators, customs authorities, governments and internet companies to close the gaps in domestic and global regulatory mechanisms that allow illegal and unscrupulous online pharmacies to sell antibiotics without a prescription, and so to support dangerous and irresponsible self-medication. We also draw attention to the threat posed by poor quality antimicrobial medicines entering the global supply chain. These substandard drugs drive the development of resistance by delivering a dose of the active ingredient that is less than that

expected by the doctor or patient, exposing bacteria and other microbes to a sub-therapeutic dose that drives the development of drug resistance but without treating the infection properly. This leaves patients sick for longer, and creates perfect conditions for drug-resistant superbugs to develop and then spread.

The report calls for better monitoring of this problem within the supply chain for all antimicrobials. Monitoring mechanisms for substandard and counterfeit versions of some other types of antimicrobial drugs (particularly those for malaria) is relatively well established, but needs to be improved, and significant gaps remain in respect of antibiotics. This includes the identification of so-called 'tiered production' – whereby unscrupulous manufacturers produce drugs of lower quality for markets where regulatory oversight is known to be limited. Action is also required from industry to ensure that antibiotics are properly handled and stored along the full length of the supply chain so that they reach patients with no degradation in quality.

ANTIMICROBIALS IN AGRICULTURE AND THE ENVIRONMENT: REDUCING UNNECESSARY USE AND WASTE

December 2015

The precise quantity of antimicrobials used in food production globally is difficult to estimate, but the evidence suggests that it is at least as great as the amount used by humans. Indeed in some parts of the world antimicrobial use is far greater in animals than in humans; in the US, for instance, more than 70 percent of medically important antibiotics are used in animals.

The relative use in agriculture, without better policies, is likely to grow even more due to the rise of economic growth, wealth, and with these, food consumption of the emerging world. Consumption of antimicrobials by animals to produce meat products, in the BRICS countries (the major emerging economies of Brazil, Russia, India, China and South Africa) alone, for example, is set to double between 2010 and 2030.

Higher use of antibiotics drives increased drug resistance, as bacteria are exposed more often to the antibiotics used to treat them. This is also true for other medicines, such as antifungals.

The risks associated with the high use of antimicrobials are threefold. Firstly, it presents the risk that drug-resistant strains are passed on through direct contact between humans and animals (notably farmers). Secondly, these drug-resistant strains have the potential to be passed onto humans more generally through the food chain, i.e. when consumers prepare or eat the meat itself. Finally, there is a further indirect threat to human health as result of animal excretion. Both resistant bacteria, as well as significant volumes of antibiotics consumed, are then excreted by animals (with most of the active ingredient unmetabolised). This both releases resistant bacteria into the environment as well as causing the environment to be tainted with antibiotics, providing further opportunities for exposure to bacteria and creating additional selective pressure that leads to the development of drug resistance.

As in humans, the proper therapeutic¹ use of antibiotics in animals is essential for treating infection. It offers considerable benefits, both in terms of animal welfare and food production, though excessive and inappropriate use of antibiotics is undoubtedly a problem in many areas.

Much of the use of antibiotics in animals is not therapeutic however. Instead, significant volumes are used either

prophylactically amongst healthy animals, to stop the development of an infection within a flock or herd, or simply for growth promotion, to speed up the pace at which animals gain weight. Both uses are particularly prevalent in intensive agriculture, where animals are kept in confined conditions.

Although there is growing evidence to suggest that the use of antibiotics for growth promotion may only provide modest benefits to farmers in high-income countries – typically less than five percent – some argue that the impact of stopping their use for this purpose would be significant, particularly in lower income settings, and unjustified without clearer evidence of the extent of the threat to human health.

There is no doubt though that prolonged exposure to antibiotics creates ideal conditions for the cultivation of drug resistance; and there is evidence to show that this can increase the localised prevalence of antibiotic-resistant bacteria very significantly. In addition to assessing individual case studies, the Review has undertaken a literature review of 280 published, peer-reviewed research articles that address the issue of antibiotic use in agriculture. The outcomes of this literature review are discussed in more detail in this paper but of 139 academic studies the Review found, only seven (five percent) argued that there was not a link between antibiotic consumption in animals and resistance in humans, while 100 (72 percent) found evidence of a link. This suggests that antibiotic use in animals is a factor in promoting resistance in humans and provides enough justification for policy makers to aim to reduce global use in food production to a more optimal level.

As well as the volume used, the types of antibiotics that are used in food production must also be considered. Some last-resort antibiotics for humans are being used extensively in animals, with no replacements as of yet on the way. This problem was highlighted by a recent Chinese finding of a bacterial gene conferring resistance to colistin, a last-resort antibiotic for treating multidrug-resistant infections caused by Gram negative bacteria in humans, but which is also used extensively in livestock in some countries, including in Europe. This gene is particularly worrying as it can transfer easily from bacteria to bacteria, meaning it could spread quickly. The study also found this gene in 20 percent of the animals tested in the area and

1. In this paper the term 'therapeutic use' is used to describe treating an animal that already has an infection. Use to prevent an infection, is not covered by this term, and is referred to as 'prophylactic use'.

ANIMALS IN THE USA CONSUME MORE THAN TWICE AS MANY MEDICALLY IMPORTANT ANTIBIOTICS AS HUMANS



Source: 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% used in animals and 27.5% used in humans.

one percent of the people in the area, strongly indicating that the selection of this resistance was due to the use of colistin in animals and that this was capable of transferring to humans. This has brought home the huge threat posed by the use of important human antibiotics in agriculture.

As well as the risks created from humans and animals excreting antimicrobials into the environment, there is particular concern over the way that antimicrobials are manufactured, where pollution during the production phase can exacerbate this problem. During the manufacture of antimicrobials, destined for human or veterinary use, untreated waste products containing high levels of end products or active ingredients may be discharged into water courses. Some experts argue that this process is a particular risk for resistance because the concentrations of antimicrobials found in such scenarios can be many thousands, or even millions, of times higher than at sewage sites, for example. It only takes one occasion, in one setting, for resistance to emerge, and then we can only try to limit its spread. Therefore reducing 'hotspots' where the risk is greatest is very important.

This paper proposes three broad interventions to take bold global action to substantially reduce the use of antibiotics in agriculture and the quantities being dispersed into the environment:

1.

A global target to reduce antibiotic use in food production to an agreed level per kilogram of livestock and fish, along with restrictions on the use of antibiotics important for humans.

a. We need to reduce global levels of antibiotic use in agriculture, to an agreed limit for each country, but it should be for individual countries to decide how best to achieve this goal – a global target would make this possible. We believe an ambitious but achievable target for reducing antibiotic use in agriculture is needed, to reduce use over the next 10 years. There are countries that have advanced farming systems with very low levels of antibiotic use, particularly in Scandinavia. Denmark has combined low use with being one of the largest exporters of pork in the world. Reducing levels of use to that of Denmark for example, an average of less than 50 milligram (mg) of antibiotics used

a year per kilogram (kg) of livestock in the country, may be a good starting point for such a target. We think this would be feasible without harming the health of animals or the long-term productivity of farmers. This is based on our understanding of academic literature and case studies. The exact level of a target would, however, need to be discussed and tested by experts. Low and middle-income countries may need more time to achieve such a target, while many of these countries may already be below the threshold.

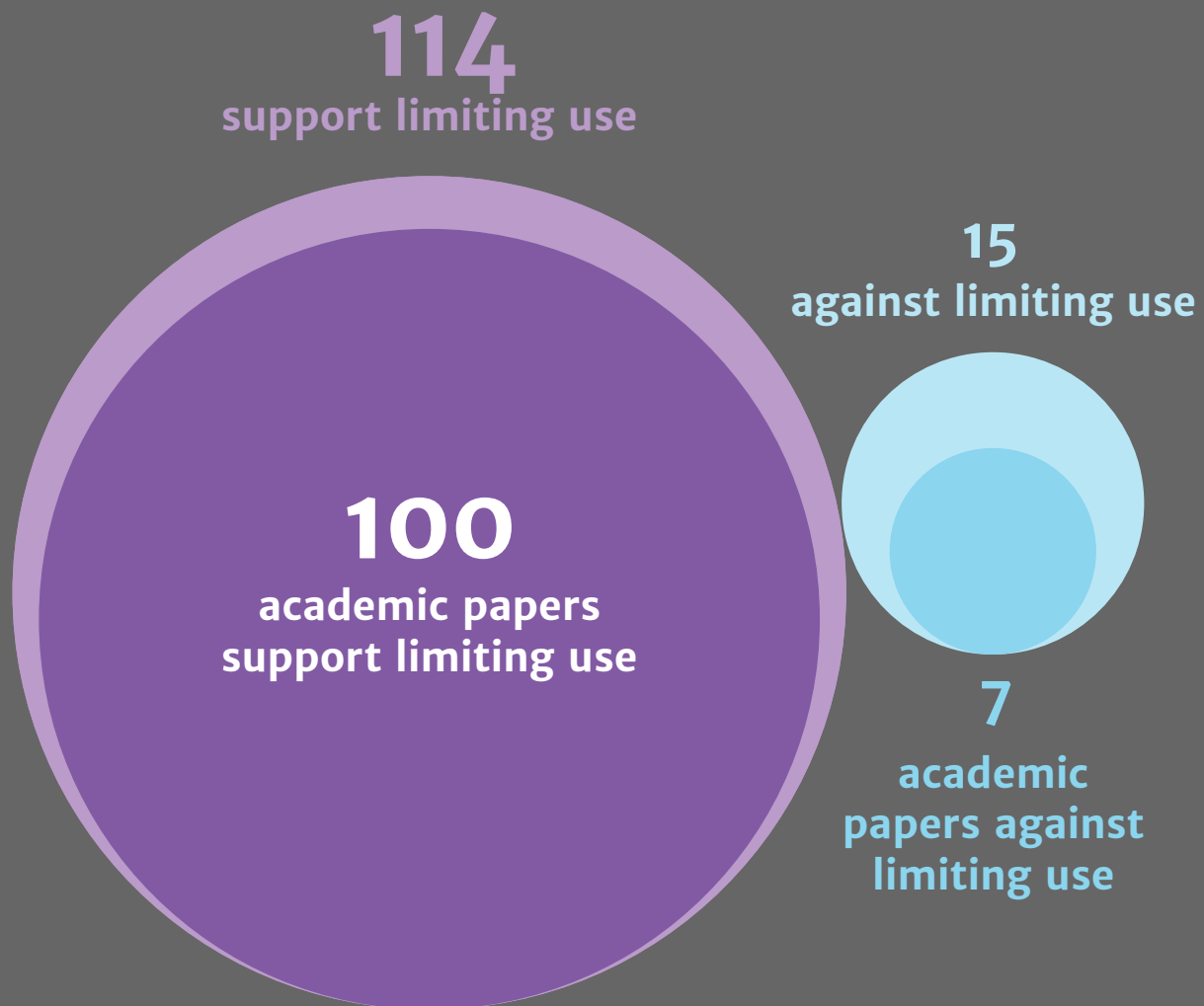
b. As well as reducing the quantity of use, the types of antibiotics used are also important. Currently many antibiotics that are important for humans are used in animals. We believe that countries need to come together and agree to restrict, or even ban, the use of antibiotics in animals that are important for humans.

2.

The rapid development of minimum standards to reduce antimicrobial manufacturing waste released into the environment.

This needs to be viewed as a straightforward issue of industrial pollution, and it is the responsibility of all actors in the supply chain to ensure that industrial waste is treated properly as a matter of good manufacturing practice. The risk of drug resistance must urgently become a key environmental consideration for all pharmaceutical companies, healthcare buyers and regulatory agencies everywhere. Failing to do this does most harm to the health of populations living near the manufacturing sites who are exposed to polluted water, and are paying the price of cheap antibiotics for the rest of the world. But in the long-term, we know that resistance spreads and these strains will in time likely become a global problem.

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 written by academics.

Source: Review's own analysis.

3.

Improved surveillance to monitor these problems, and progress against global targets.

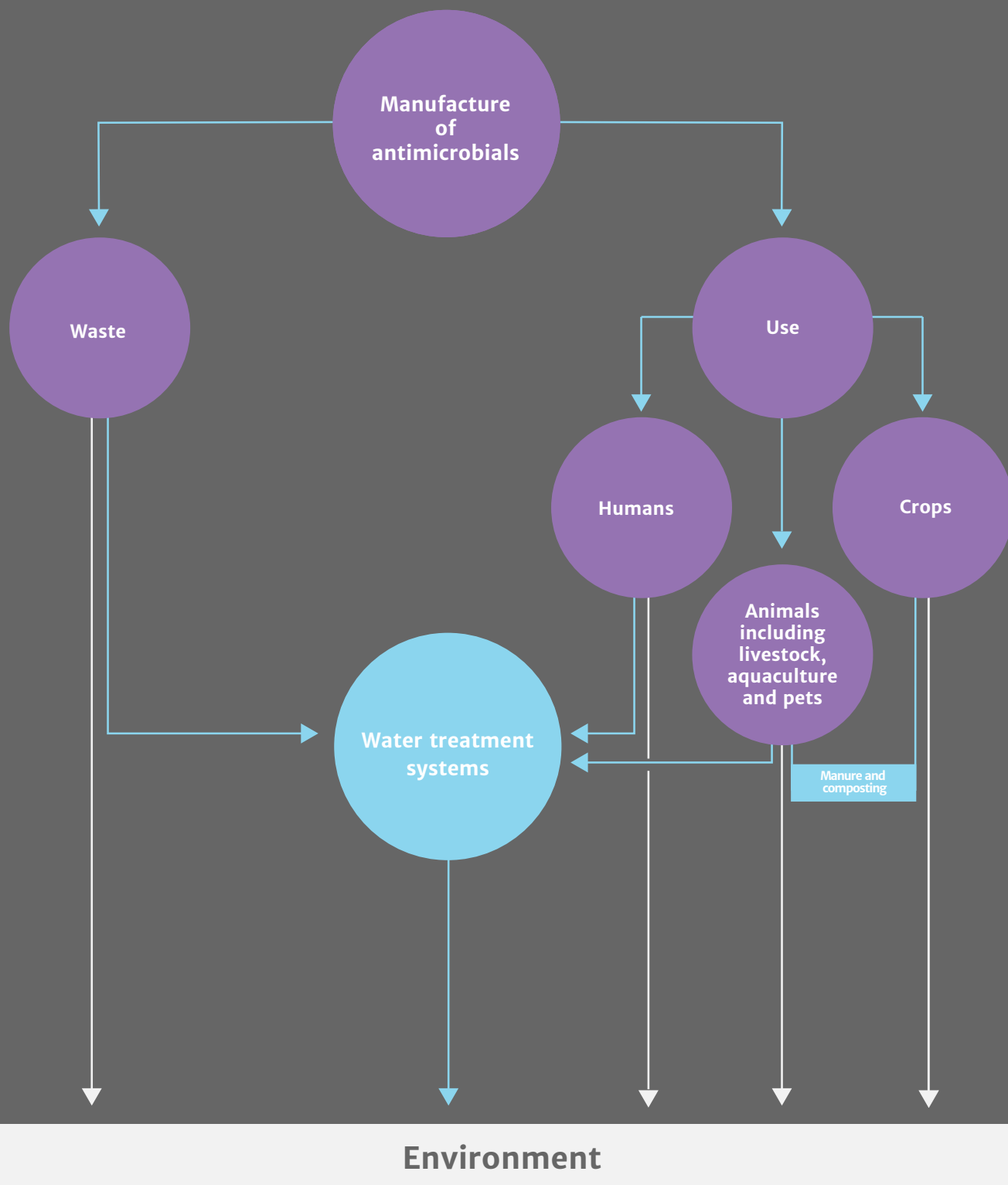
There remain too many knowledge gaps regarding patterns of antimicrobial use in agriculture and release during manufacturing, and what this means for resistance and, ultimately, human health. This needs to change if meaningful progress is to be made.

As with the human health aspects of AMR, these are complex issues that require concerted, coordinated action at an international level. Drug-resistant infections know no borders and do not respect barriers between industry, regulators and buyers, or between animals, humans and their wider environment. There are encouraging signs of some governments adopting a broad 'one health' approach to tackling the issue of resistance, but it is an approach that needs to be replicated by others.

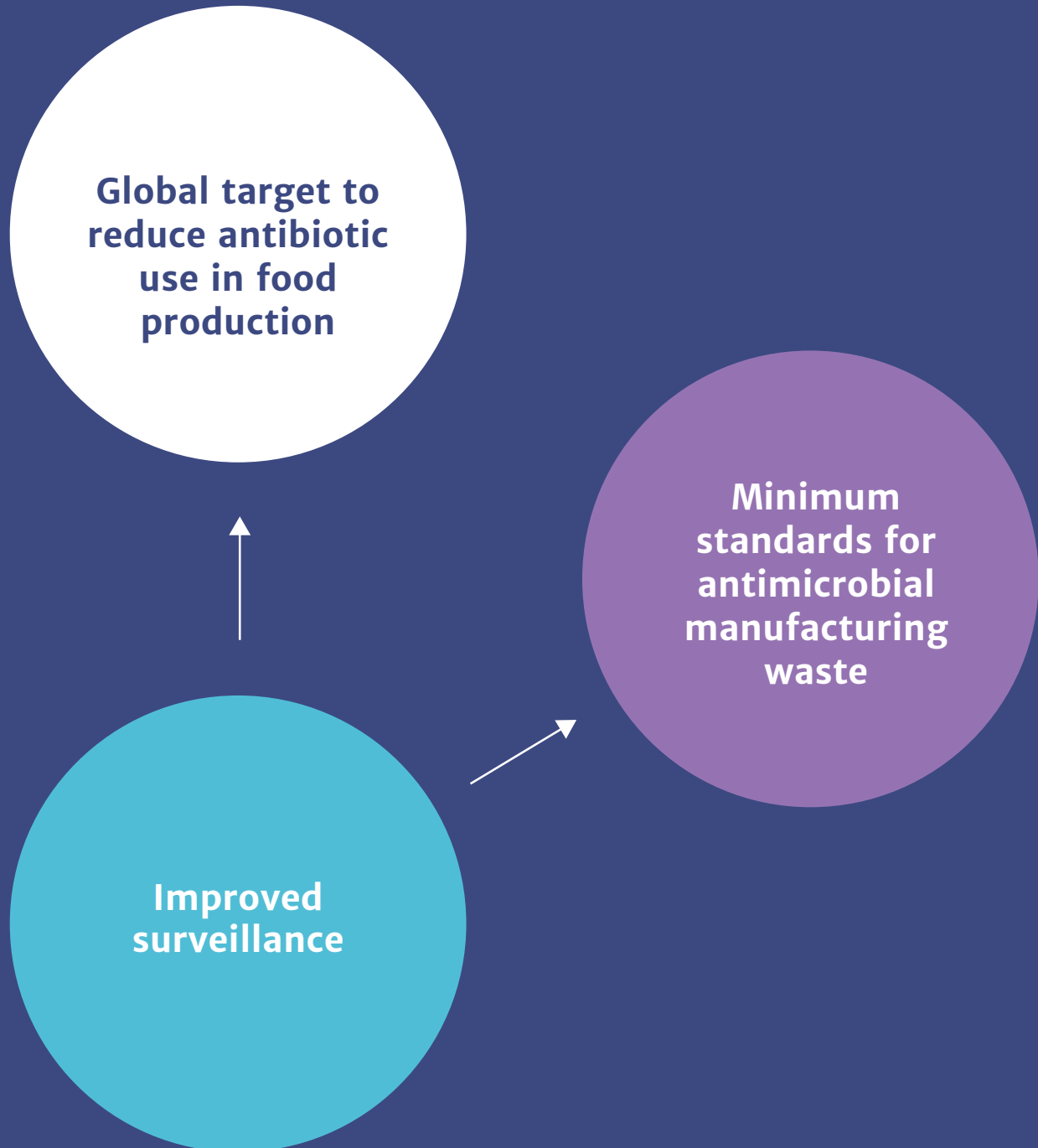
We believe that success can only be achieved by considering a full range of interventions:

- In agriculture, these should take into account the key drivers of the real or perceived need for antibiotics, whether for use as therapy, prophylaxis (prevention), or growth promotion. Interventions will no doubt include improvements in infection control, better animal husbandry practices, greater use of vaccines and the adoption of diagnostic devices to ensure better-targeted and more appropriate veterinary prescribing. In manufacturing, these should take into account the potential to prevent waste as well as to treat it.
 - This paper, though not prescriptive as to how countries should act, will focus primarily on the roles that fiscal measures (that is, taxation and subsidies) and regulation could play in reducing the risks associated with agricultural use of antimicrobials and environmental contamination.
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HOW ANTIMICROBIALS REACH THE ENVIRONMENT



A PLAN TO REDUCE DRUG RESISTANCE FROM FOOD AND PHARMACEUTICAL PRODUCTION



VACCINES AND ALTERNATIVE APPROACHES: REDUCING OUR DEPENDENCE ON ANTIMICROBIALS

February 2016

As the existing stock of antibiotics become less effective, because microbes evolve to resist them, we need to use those that we have more responsibly, in humans and animals, and ensure that we develop new ones. But even with increased investment, we have no guarantee that we will be able to find enough new antibiotics to tackle drug resistance in the long-term.

So we need to implement other strategies in parallel to support these efforts, including strategies that can prevent and treat infections better. This paper discusses the role of vaccines and other approaches and suggests that we are not moving anywhere near fast enough to develop them, recognise their potential value, and use them appropriately.

Vaccines prevent infections and so reduce the need to use antibiotics. This is true for vaccines that prevent bacterial infections, and it is also true for vaccines that prevent viral infections, such as the flu, which should not be treated with antibiotics but often are anyway. This may be for lack of rapid diagnostic tests to inform prescription or because patients buy them over the counter.

The pneumococcal conjugate vaccine gives an indication of the potential benefit of vaccines to combat drug resistance. The World Health Organization (WHO) estimates that *Streptococcus pneumoniae* kills over 800,000 children under five years of age worldwide every year – deaths that would be largely prevented by universal global coverage with the pneumococcal conjugate vaccine. A study in the Lancet estimated that such universal global coverage could also prevent 11.4 million days of antibiotic use per year in children younger than five. These children would otherwise be treated for pneumonia. We know there is a correlation between antibiotic use and resistance, so significantly cutting the need for antibiotics should have a large impact on resistance. The situation is similar for diarrhoeal disease, also a major cause of child mortality in developing countries and a driver of antibiotic use, both of which could be significantly improved by wider use of the rotavirus vaccine.

There are also many vaccines that we know would play a crucial role in tackling drug resistance but that are not on the market or even in early stages of development. The three “urgent” resistance threats highlighted by the US Centers for Disease Control and Prevention (CDC) are carbapenemase-producing bacteria (including *Klebsiella*, *E. coli*), gonorrhoea and *C. difficile*. There are no vaccines currently in use for any of them and too

few candidates in clinical trials. Vaccine development is a high risk endeavour, with high chances of failure, and often takes 10 years or more to complete, meaning we are a long way away from having them on the market. The same is true of tuberculosis (TB), and the worrying challenge of rising multidrug resistant TB. The WHO and others have also warned that the Sustainable Development Goal of eradicating TB by 2035 cannot be achieved unless new drugs, better diagnostics and improved vaccines are developed, and yet a new vaccine remains many years away and funding for TB vaccine research and development has declined in recent years.

Vaccines also have the potential to reduce the use of antibiotics in agriculture dramatically. In our last paper we highlighted the extensive antibiotic use in global agricultural systems, and our belief that there is enough evidence for the world to begin reducing this. Vaccines already play an important role in preventing disease in farm animals and aquaculture, but they are likely to have a greater role going forward as the pressure increases to optimise antibiotic use. Vaccines and other alternative approaches to reducing our dependence on antibiotics in food production should be explored urgently.

As well as vaccines, there are a number of alternative approaches that could have the potential to tackle AMR, including phage therapy, antibodies and probiotics. Some of these measures are preventative and some therapeutic. Some may also complement antibiotics by preventing the emergence, rise and dissemination of resistance; accompanying antibiotic use rather than replacing it. From a public health perspective these are all important ideas with clear benefits. The thinking must start now so that as such products mature and get closer to market, regulators and healthcare purchasers are well positioned to assess their value and make the best use of them.

VACCINES FOR BACTERIAL INFECTIONS IN THE PIPELINE

Of the groups of organisms classified by the CDC as 'urgent' antibiotic resistant threats, there are only five products in the pipeline, most in early stages, and none in use.

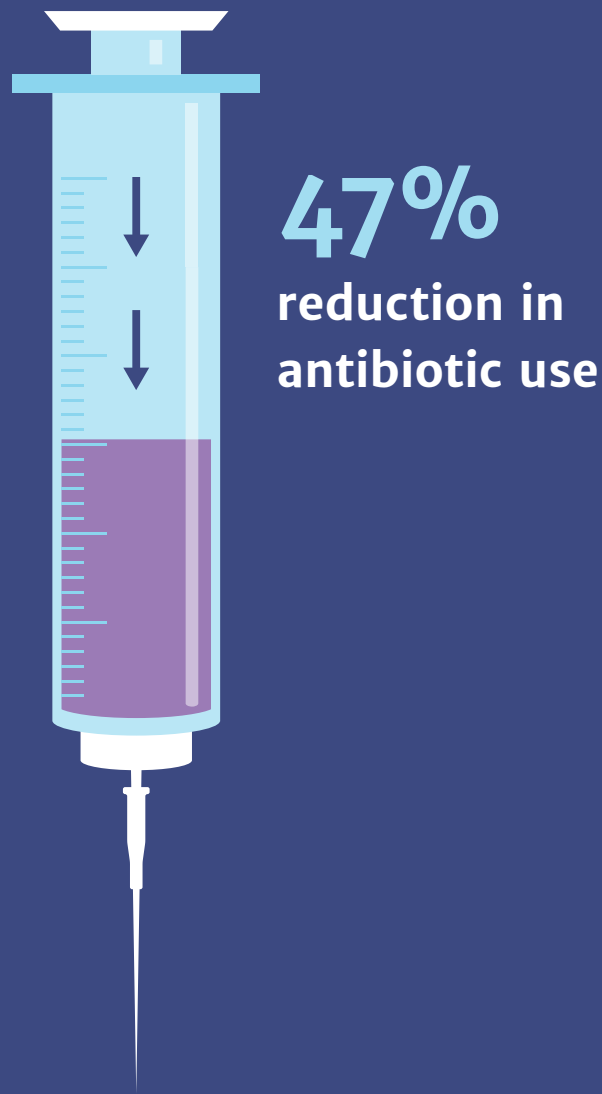
	Phase 1	Phase 2	Phase 3	In use
<i>Neisseria gonorrhoeae</i>	X	X	X	X
<i>Clostridium difficile</i>	X	2	1	X
<i>E. coli</i> *	2	X	X	X
<i>Klebsiella</i> *	X	X	X	X

**E.coli* and *Klebsiella* are included among Carbapenem-resistant Enterobacteria (CRE) in the CDC Urgent list, but are shown separately to show the pipeline for both organisms.

Source: Data from Cooke T, IDWeek 2015 Presentation, The role of vaccines in combating antimicrobial resistance: big opportunities and big challenges, updated 14th January 2016.

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*.



Source: 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.

Our recommendations in this paper follow a three-pronged approach:

1.

Use existing products more widely in humans and animals.

We need to act in the short term to increase the use of existing vaccines and improve delivery of these in both the community and hospitals, as well as in farming systems. This will involve providing financial support in some cases. For example, in low-income countries where Gavi, the Vaccine Alliance, UNICEF and others are making great headway towards better vaccine coverage. It is also relevant in some high and middle-income countries which lack universal coverage for large portions of the population and may be losing out on essential vaccinations. Thinking must also start now to improve the delivery of other alternatives to antibiotics.

2.

Renew impetus for early research.

We need renewed impetus in the science of vaccines and alternative approaches to make sure researchers in a wide range of fields and countries are looking for the solutions that will reduce our dependence on antibiotics and will help tackle drug resistance. To this end, we have previously proposed that a two billion USD five-year Global Innovation Fund should be set up. However, the funding need is large and diverse, and breakthroughs will require long-term sustained funding from philanthropic organisations, the public sector and companies.

3.

Sustain a viable market for needed products.

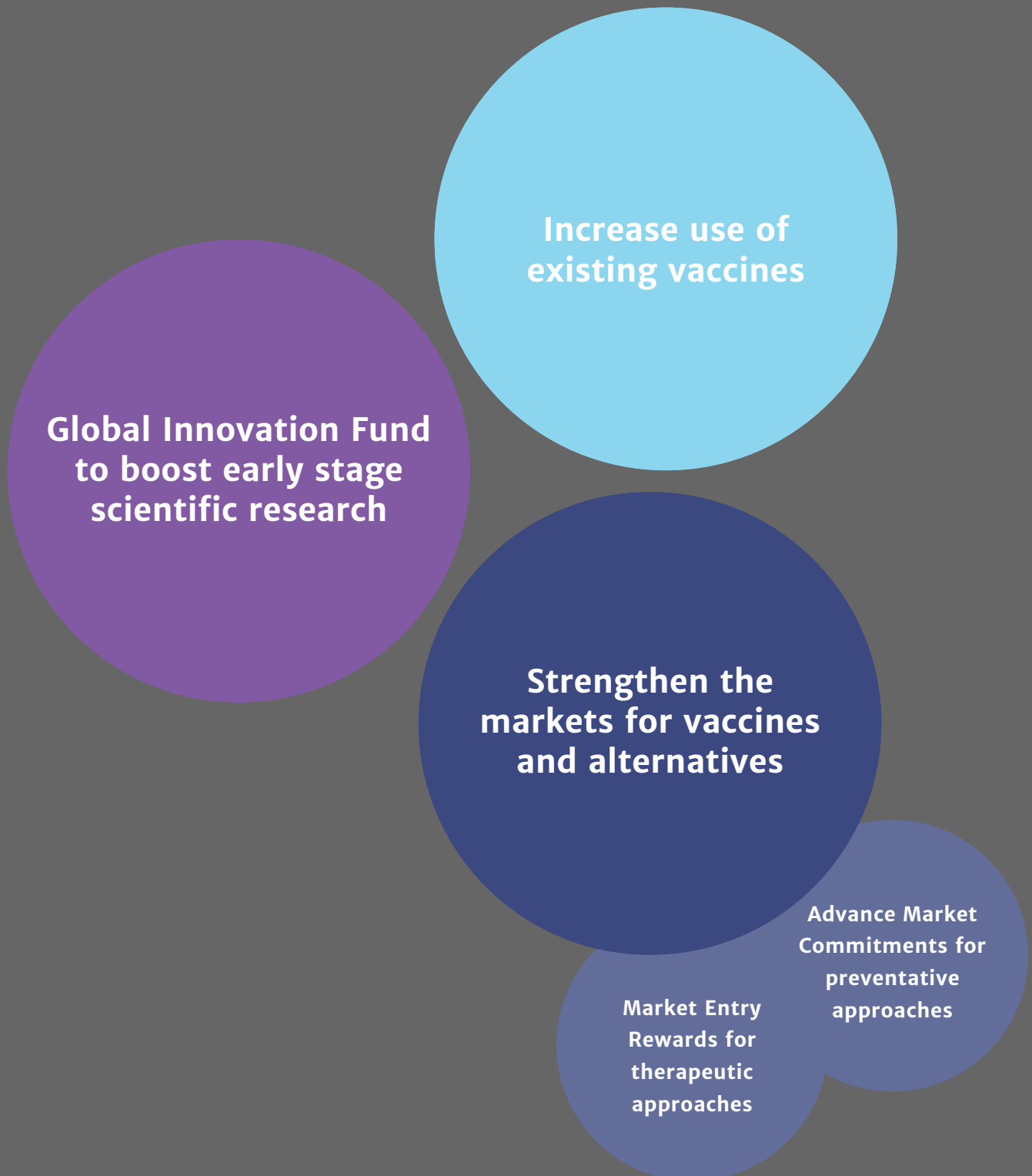
Specific measures must be considered in certain cases where research and development is not at the moment an attractive proposition for prospective vaccine and alternative developers.

Depending on the characteristics of the different products, possible interventions include Advance Market Commitments (AMCs) and market entry rewards. These are market interventions that only reward developers for successful products, rather than share in the risk of developing a range of products from an earlier stage. Some products are very profitable and may not need much or any public support at all. Others have different market failures, to different degrees, so it is important that the interventions are carefully tailored to each market and product. We have already set out similar proposals that we think can work for the development of new antibiotics and diagnostics, and we will consider the benefits of vaccines for combatting AMR further, alongside the costs of interventions that might be needed, in our final report.

We believe that these three proposals can have a significant impact on how vaccines and alternatives are developed and used to combat AMR, but they are part of a broader picture.

This year, 2016, is a critical year for action on the wider issue of drug-resistant infections, and both vaccines and alternative therapies have a crucial role to play as part of the strategy to tackle this threat. Internationally there will be focus on this issue at the World Health Assembly, the G7, G20 and UN General Assembly. The Review also welcomes the recent declaration by industry at Davos, where 85 companies, including vaccine developers, large pharmaceutical companies, diagnostic developers and biotechs, committed to further action to reduce drug resistance, increase research and improve access. This momentum for action from across the AMR landscape, from governments, NGOs and industry means this is a crucial time for the world to make significant progress – a moment that needs to be seized.

A PLAN TO OVERHAUL THE VACCINE AND ALTERNATIVE MARKETS FOR AMR



INFECTION PREVENTION, CONTROL AND SURVEILLANCE: LIMITING THE DEVELOPMENT OF DRUG RESISTANCE

March 2016

Much of our previous work to address the alarming rise of drug-resistant infections has focussed on initiatives to re-invigorate the supply of new antimicrobial drugs. Success with coming up with new drugs will shift the 'supply curve' and solve the problem of antimicrobial resistance (AMR) for a period of time. However, as we have also articulated before, shifting (and specifically reducing) the demand curve for antimicrobials provides a permanent solution to AMR over the longer term.

In earlier reports, we have addressed this goal of lowering demand by looking at the role of new diagnostic technologies and vaccines in reducing the unnecessary consumption of antibiotics, and the need to reduce unnecessary use and dispersal of antibiotics in agriculture and the environment. We now turn to simpler but equally crucial interventions, to reduce demand for antibiotics by preventing infections occurring in the first place, and stopping them spreading when they do.

We face a rising global burden of new drug-resistant strains of bacteria, particularly amongst the most difficult-to-treat Gram-negative species such as *E. coli* and *Klebsiella pneumoniae*. In practice, bacteria will continue to evolve to develop resistance at a speed that is difficult to pin down but that we know is accelerating. Meanwhile, we will have to wait most likely at least another 10 years before new antibiotics may become available to treat patients with the worst superbugs, and likely even longer for vaccines and other alternative treatments to come through. In this light, interventions to prevent and monitor the development and spread of drug resistance are some of the most prudent actions we can possibly take.

Improving hygiene and sanitation was essential in the 19th century to counter a growing threat from infectious diseases to large urban populations. Two centuries later, this is still true.

First, we look at the role of clean water and effective sanitation to prevent the spread of infections in the community and ultimately reduce the development of drug resistance. Improved water and sanitation infrastructure, particularly in urban areas, has always played a crucial role as countries industrialise and develop economically. In the 19th century, governments and public health professionals had to tackle infectious diseases with no effective treatment options available to them. So prevention was their only recourse, and it

worked: in many places the greatest steps forward in tackling infectious diseases like cholera, plague or tuberculosis were made before we had access to modern healthcare and antimicrobials.

Today, however, the availability of antimicrobials has shifted the focus from prevention towards treatment. Many countries have skimped on investment in basic sanitation infrastructure, to the direct detriment of the health of their populations, and with the secondary effect of contributing to the rise of antibiotic-resistant diseases.

Using data published by the World Bank and the World Health Organization, 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.

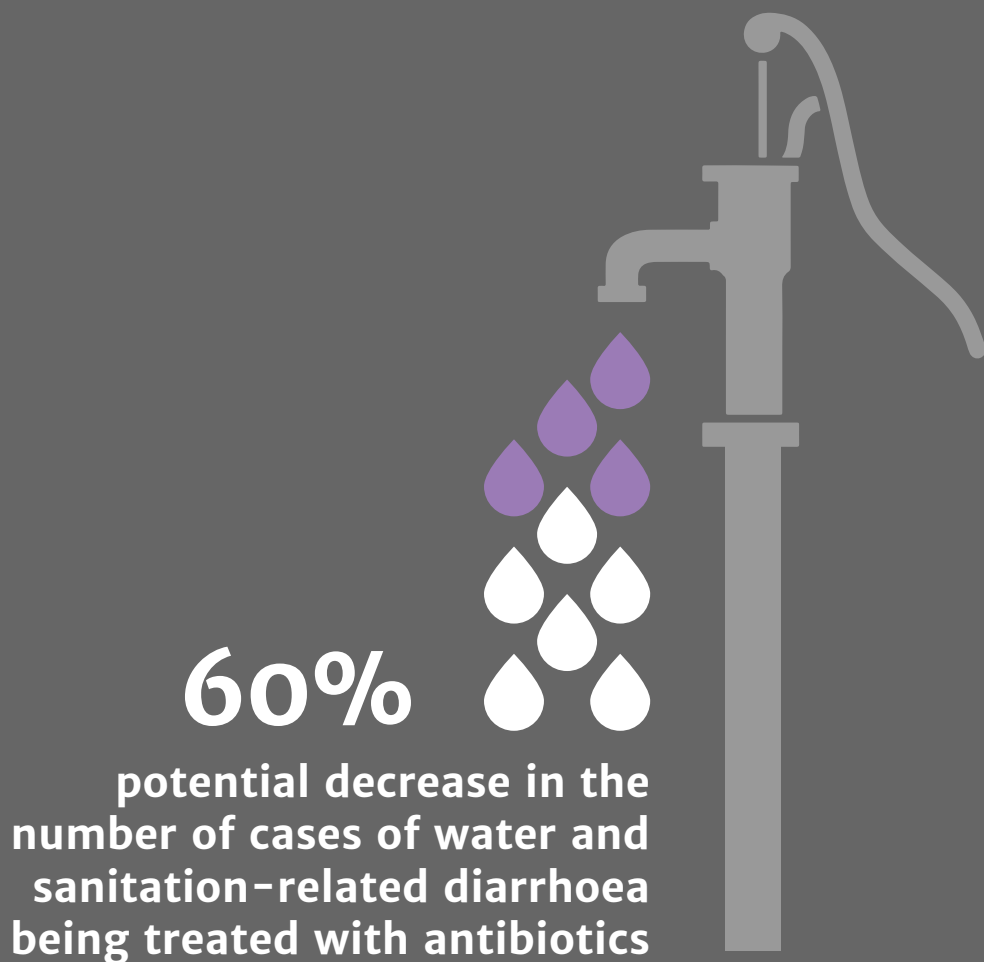
We also commissioned analysis that estimates that across four middle-income countries (Brazil, Indonesia, India and Nigeria), at least 494 million cases of diarrhoea are treated each year with antibiotics. But with universal access to improved water and sanitation in these four countries, the volume of antibiotics consumed to treat cases of diarrhoea caused by inadequate water supplies and sanitation could be reduced by at least 60 percent.

Second, we look at ways to prevent and control infections in health and care settings. When this goal is prioritised across health systems, the impact can be big. For example, in the NHS in England, the introduction of national reduction targets for methicillin-resistant *Staphylococcus aureus* (MRSA) was associated with a 56 percent decline in cases over a four-year period between 2004-8, with continued significant reductions in the following years.

Steps as simple and inexpensive for professionals as washing hands more, and following checklists, can make a material difference in the rates of infections arising in health and care settings. It may be easier said than done in practice, but there is no doubt that a system-wide focus needs to be placed on prevention if we are to tackle AMR.

BETTER WATER AND SANITATION REDUCES ANTIBIOTIC CONSUMPTION

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



HAND HYGIENE IN HOSPITALS IS VITAL BUT ADHERENCE IS LOW

A systematic review found that on average, adherence to handwashing practices by healthcare workers is only 40% - although self-reported rates are frequently near 100%.



Last, we need to continue improving our monitoring and understanding of the infectious disease burden globally, and ensure that the surveillance of drug-resistant infections is included in these systems. Efforts are underway to improve

surveillance in general and the monitoring of drug resistance specifically, with important work being led within the WHO, regional blocs, and philanthropic organisations 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 375 million USD Fleming Fund – the latter being a direct response to early recommendations made by this Review. Both of these initiatives, as well as a number of others, intend 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. This will deliver benefits for doctors and patients as much as it does for global and national policymakers. One particular challenge is to ensure that health systems, doctors and researchers are ready to 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 even less developed countries may be able to ‘leapfrog’ into using them to some extent. So questions about how data is owned, used and shared need to be answered now if the full potential of this information revolution is to be harnessed in our battle with drug-resistant infections.

We will return to these issues in our final report in May, where we will aim to outline our estimate of the likely global costs of implementing a coordinated global system of surveillance for drug resistance.

HOW SURVEILLANCE CAN IMPROVE HEALTH OUTCOMES

Globally

Provide early warnings of emerging threats and data to identify and act on long-term trends

Nationally

Guide policy and ensure appropriate and timely public health interventions

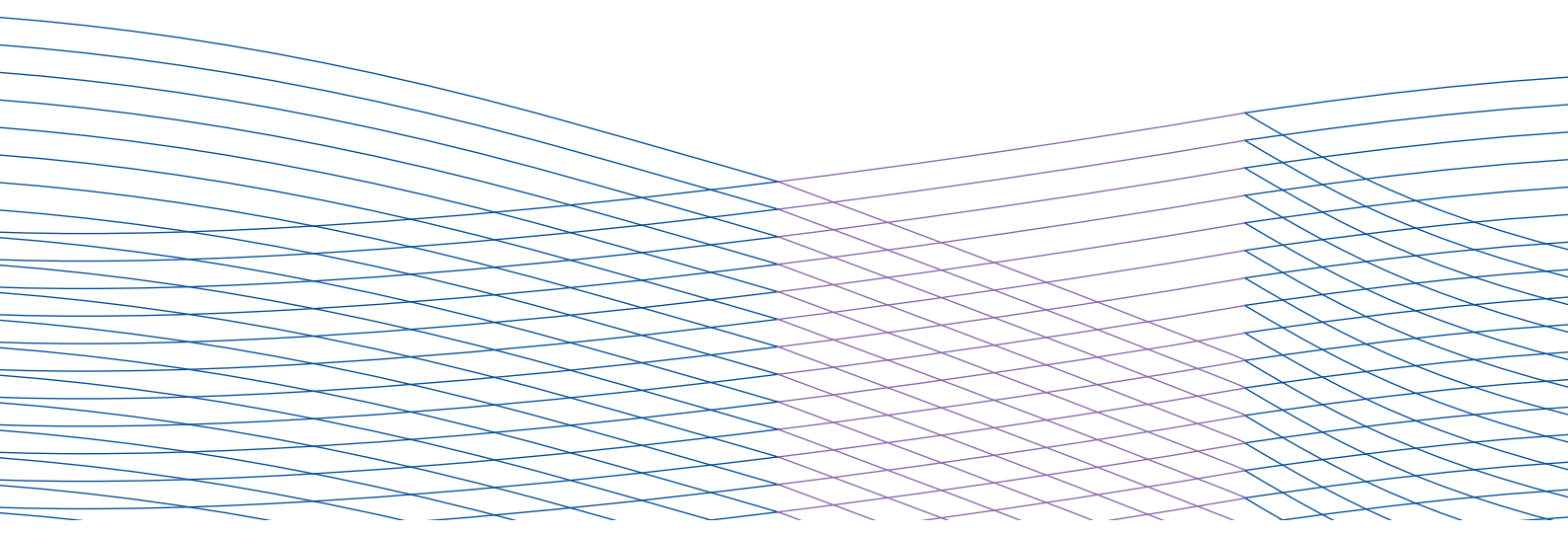
Locally

Allow healthcare professionals to make better informed clinical decisions to ensure better patient outcomes

WHAT COMES NEXT?

The problems being faced are difficult, and action will inevitably mean short-term economic costs, but the economic cost of inaction, which could mean a cumulative hit to the world economy of 100 trillion USD by 2050, dwarves these costs. This is not to mention the many millions of lives that will be lost if we do not curb resistance or find long-term solutions to producing, using and disposing of antimicrobials. We have already called for action at the G20 and UN General Assembly, to agree specific recommendations for action, and are pleased to see the international progress that is being made. The recent communiqués from the German G7 presidency and Turkish G20 presidency both highlighted this, naming AMR as one of the main health threats we face, and asking the 2016 G20 to continue to work towards solutions. It is particularly important that the G7 and G20 focus on solutions to ensure that there is sufficient private and public investment to increase the supply of useful products: in particular our proposals for how we can re-invigorate the weak pipeline of new antibiotics, or develop new rapid diagnostics that can better guide decisions to prescribe antibiotics and so cut our massive overuse. Agreement at this level is essential, and we hope that 2016 will be the year when specific actions are agreed, and implementation begins.

The Review will release its **final report** in mid-May, outlining its final recommendations on the steps the world needs to take to avert this growing problem, as well as giving a more detailed overview of the costs and benefits of action.



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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