Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations

The Review on Antimicrobial Resistance
Chaired by Jim O'Neill

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The Review

The UK Prime Minister announced a Review on Antimicrobial Resistance in July, calling for ideas to bring this growing threat under control. This is the Review team's first paper, where we demonstrate that there could be profound health and macroeconomic consequences for the world, especially in emerging economies, if antimicrobial resistance (AMR) is not tackled.

We believe that this crisis can be avoided. The cost of taking action can be small if we take the right steps soon. And the benefits will be large and long-lasting especially for emerging economies, including the so-called BRIC nations, who will need to make improved investments in their health infrastructure and build industries that leapfrog to the next generation of innovation.

Defining the specific steps needed is what our sponsors the UK Prime Minister and the Wellcome Trust set us off to do: by the summer of 2016, we will recommend a package of actions that we think should be agreed internationally. To do this, over the course of our Review we want to explore the following five themes, starting with this paper.

1. **The impact of antimicrobial resistance on the world's economy if the problem is not tackled.**

2. **How we can change our use of antimicrobial drugs to reduce the rise of resistance, including the game-changing potential of advances in genetics, genomics and computer science.**

3. **How we can boost the development of new antimicrobial drugs.**

4. **The potential for alternative therapies to disrupt the rise in resistance and how these new ideas can be boosted.**

5. **The need for coherent international action that spans drugs regulation, and drugs use across humans, animals and the environment.**

We approach our goals with a blank sheet of paper and open minds. We want to hear from bright and innovative minds across all countries and disciplines, starting with the hard-earned experience of physicians, healthcare workers and their patients.

What is antimicrobial resistance?

In 1928 a piece of mould fortuitously contaminated a petri dish in Alexander Fleming's Laboratory at St Mary's Hospital London, and he discovered that it produced a substance (penicillin) that killed the bacteria he was examining. Within 12 years Fleming and others had turned this finding into a wonder drug of its time, which could cure patients with bacterial infections. Further antibiotics were discovered and went on to revolutionise healthcare, becoming the bedrock of many of the greatest medical advances of the 20th century. Common yet frequently deadly illnesses such as pneumonia and tuberculosis (TB) could be treated effectively. A small cut no longer had the potential to be fatal if it became infected, and the dangers of routine surgery and childbirth were vastly reduced. More recently, advances in antiviral developments over the past 20 years have transformed HIV from a probable death sentence into a largely manageable lifelong condition.

But bacteria and other pathogens have always evolved so that they can resist the new drugs that medicine has used to combat them. Resistance has increasingly become a problem in recent years because the pace at which we are discovering novel antibiotics has slowed drastically, while antibiotic use is rising. And it is not just a problem confined to bacteria, but all microbes that have the potential to mutate and render our drugs ineffective. The great strides forward made over the past few decades to manage malaria and HIV could be reversed, with these diseases once again spiralling out of control.

AMR threatens many of the most important medical advances we have made, and this report will go on to quantify the costs that society will face if action is not taken.

The problem today

The damaging effects of antimicrobial resistance (AMR) are already manifesting themselves across the world. Antimicrobial-resistant infections currently claim at least 50,000 lives each year across Europe and the US alone, with many hundreds of thousands more dying in other areas of the world. But reliable estimates of the true burden are scarce.

There is considerable variation globally in the patterns of AMR, with different countries often experiencing different major problems. Despite this and in contrast to some health issues, AMR is a problem that should concern every country irrespective of its level of income.

For instance, in 15 European countries more than 10% of bloodstream *Staphylococcus aureus* infections are caused by methicillin-resistant strains (MRSA), with several of these countries seeing resistance rates closer to 50%.[1]

1. European Centre for Disease Prevention and Control Antimicrobial Resistance Interactive Database (EARS-NET) data for 2013.

Although in modern, well-funded healthcare systems, obtaining access to second and third-line treatments may often not be an issue, mortality rates for patients with infections caused by resistant bacteria are significantly higher, as are their costs of treatment. And we are seeing in parts of Europe an increasing number of patients in intensive care units, haematology units and transplant units who have pan-resistant infections, meaning there is no effective treatment available.

The threat of increasingly drug-resistant infections is no less severe in poorer countries. Emerging resistance to treatments for other diseases, such as TB, malaria and HIV, have enormous impacts in lower-income settings. The growing prevalence of drug-resistant strains of TB is well-documented: there were an estimated 480,000 new cases in 2013 – of which the majority went untreated.[2] The spread of resistant strains of malaria is similarly well-documented, and the development of resistance to antiretroviral therapy for HIV is closely monitored.

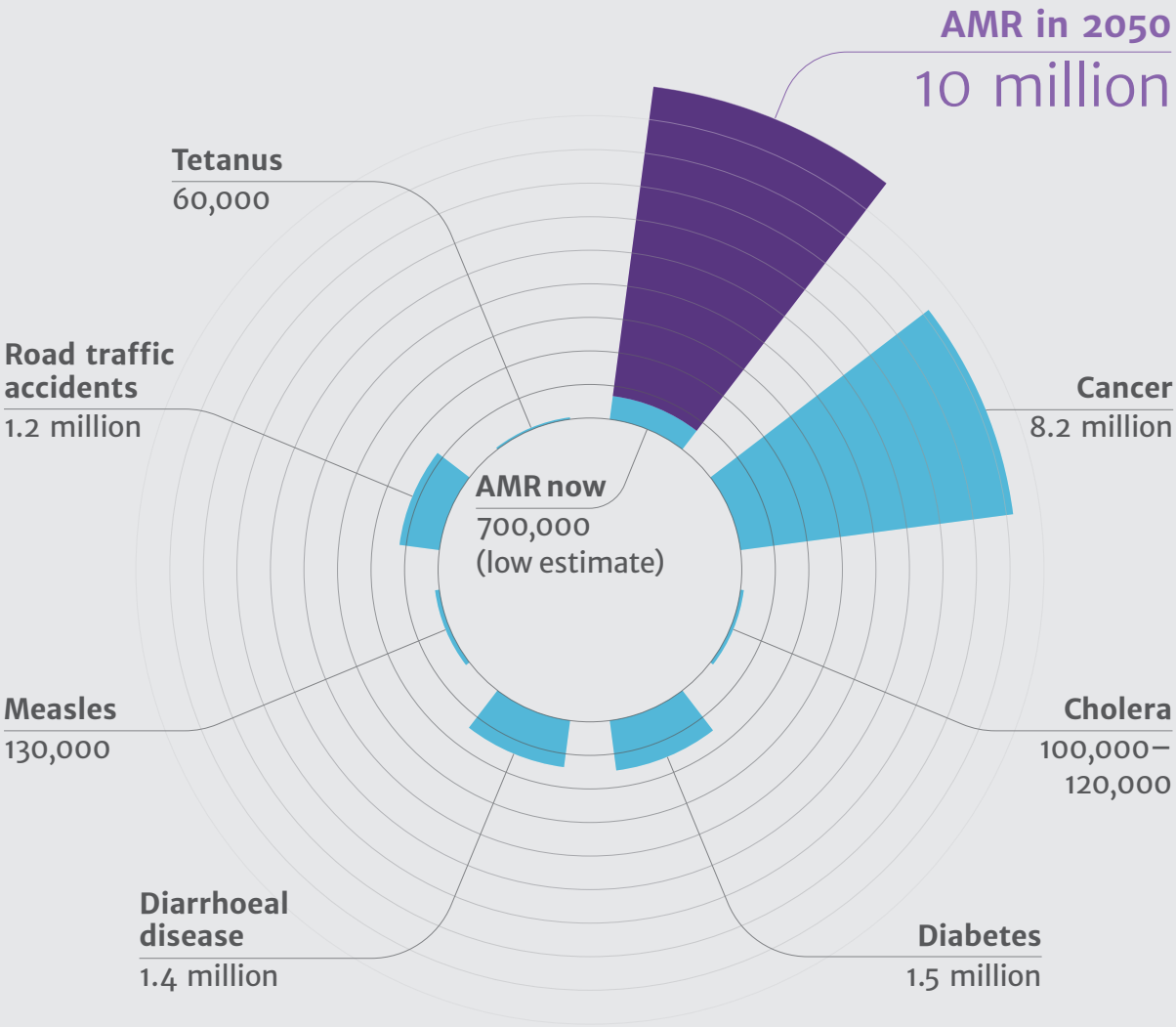
The variation in the AMR problems of individual countries is linked to huge differences in how heavily they use antimicrobial drugs. Global consumption of antibiotics in human medicine rose by nearly 40% between 2000 and 2010, but this figure masks patterns of declining usage in some countries and rapid growth in others. The BRIC countries plus South Africa accounted for three quarters of this growth, while annual per-person consumption of antibiotics varies by more than a factor of 10 across all middle and high-income countries.[3]

Any use of antimicrobials, however appropriate and conservative, contributes to the development of resistance, but widespread unnecessary and excessive use makes it worse. Overuse and misuse of antimicrobials is facilitated in many places by their availability over the counter and without prescription, but even where this is not the case prescribing practices vary hugely between (and often within) countries. Such issues are only made worse by large quantities of counterfeit and sub-standard antimicrobials permeating the pharmaceuticals markets in some regions.

As with all infectious diseases, the speed and volume of intercontinental travel today creates new opportunities for antimicrobial-resistant pathogens to be spread globally. Such mixing of different microbes, particularly bacteria, provides them with opportunities to share their genetic material with each other, creating new resistant strains at an unprecedented pace. No country can therefore successfully tackle AMR by acting in isolation.

2. World Health Organization ***Global Tuberculosis Report 2014***.
3. Van Boeckel, T P et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. ***The Lancet Infectious Diseases*** 2014; 14(8): 742–750.

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



Sources

Diabetes	www.who.int/mediacentre/factsheets/fs312/en/
Cancer	www.who.int/mediacentre/factsheets/fs297/en/
Cholera	www.who.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.who.int/mediacentre/factsheets/fs358/en/
Tetanus	www.sciencedirect.com/science/article/pii/S0140673612617280

The economic cost of drug-resistant infections

For doctors and for those who have experienced first-hand the anxiety of an infection that is drug-resistant, as a patient or when caring for a loved one, there is little need to prove the importance of tackling AMR.

However for the majority of people, including in leading policy and business circles around the globe, the threat of drug resistance might seem a distant and abstract risk, if it is known at all.

To bridge that gap between global perceptions of how bad the problem is today and how bad it is likely to become if the current trend is not altered, we have estimated the global economic cost of antimicrobial drug resistance by 2050. Given the severe lack of data, the studies we commissioned are necessarily based on high-level scenarios of what is likely to happen. They are a broad brush estimate, not certain forecasts.

The results show a considerable human and economic cost. Initial research, looking only at part of the impact of AMR, shows that a continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2% to 3.5% in Gross Domestic Product (GDP). It would cost the world up to 100 trillion USD.

We commissioned two multidisciplinary research teams from RAND Europe and KPMG each to provide their own high-level assessments of the future impact of AMR, based on scenarios for rising drug resistance and economic growth to 2050. Both research teams estimated how an increase in resistance would affect the labour force through mortality and morbidity, and what this would mean for overall economic production. Their results project that if resistance is left unchecked, the loss of world output will get bigger through time, so by 2050, the world will be producing between 2% and 3.5% less than it otherwise would. Furthermore, 10 million more people would be expected to die every year than would be the case if resistance was kept to today's level.

However, these studies only estimate part of the impact of AMR, for two main reasons.

First, the studies looked only at a subset of drug-resistant bacteria and public health issues, because of the lack of readily available data for this initial research.

Bacteria that already show concerning resistance levels	Broader public health issues for which resistance is a concern
Klebsiella pneumonia	HIV
Escherichia coli (E. coli)	Tuberculosis (TB)
Staphylococcus aureus	Malaria

It is worth noting that the three bacteria were selected from a larger group of seven that the World Health Organization (WHO) has highlighted as being key AMR concerns.

Second, the research was commissioned to understand the economic cost of AMR, interpreted strictly as its impact on global GDP. Other issues, such as social and healthcare costs, were not considered. If AMR continues to grow as a major problem in the world it will have enormous consequences for how we deliver healthcare.

The human impact of AMR is more than large enough on its own to justify a major intervention, to avert what threatens to be a devastating burden on the world's healthcare systems. However our economic results aim to show that this is an issue which transcends health policy. Even on a strictly macroeconomic basis it makes sense for governments to act now, working in coalition with the scientific community in industry and academia, as well as with philanthropic organisations, to tackle the rise in antimicrobial drug resistance.

Our research findings in more detail

The findings in this paper are based on two of the scenarios modelled by RAND Europe and KPMG. Further details of the two studies are set out in the box on the following page and the full papers are available on our website.

The two teams modelled an increase in AMR rates from where they are today, each using their own methodology, to understand the impact this would have on the world population and its economic output. Both studies were hampered by a lack of reliable data, in particular regarding bacterial infections, and as a consequence they most likely underestimate the true cost of AMR.

The studies estimate that, under the scenarios described below, 300 million people are expected to die prematurely because of drug resistance over the next 35 years and the world's GDP will be 2 to 3.5% lower than it otherwise would be in 2050. This means that between now and 2050 the world can expect to lose between 60 and 100 trillion USD worth of economic output if antimicrobial drug resistance is not tackled. This is equivalent to the loss of around one year's total global output over the period, and will create significant and widespread human suffering. Furthermore, in the nearer term we expect the world's GDP to be 0.5% smaller by 2020 and 1.4% smaller by 2030 with more than 100 million people having died prematurely.

The two studies also show a different economic impact for each of the drug-resistant infections they considered. *E. coli*, malaria and TB are the biggest drivers of the studies' results. Malaria resistance leads to the greatest numbers of fatalities, while *E. coli* is the largest detractor from GDP accounting for almost half the total economic impact in RAND's results. Because malaria and TB vary far more by region than *E. coli* in the studies, they are the largest drivers of differences between countries and regions.

RAND Europe and KPMG methodology

Scenarios

The RAND Europe scenario modelled what would happen if antimicrobial drug resistance rates rose to 100% after 15 years, with the number of cases of infection held constant. This was done across five of the bacteria and public health issues mentioned above, with the exception being malaria, for which mortality was modelled to increase in line with estimates of 1950 levels, this being just prior to the introduction of the first generation of modern malaria drugs. For calculating mortality and morbidity RAND Europe assumed that all drugs would fail, i.e. there would be 100% resistance to all antimicrobials across the relevant pathogens.

The KPMG scenario, again for all bacteria and public health issues except malaria, looked at what would happen if resistance rose by 40% from today's levels and the number of infections doubled as a result of people being infected for longer, leading to more transmission. For malaria, KPMG grouped countries into seven geographical areas and assumed that in malaria susceptible regions, every country with a low current incidence of malaria would see their infection rates rise to that region's (higher) average. For calculating mortality and morbidity, KPMG assumed that the established first-line treatment would fail, i.e. some antimicrobials would still be effective.

The effects of resistance in malaria were more difficult to forecast than for other pathogens, due to the more complex interactions at play between drug resistance and rates of incidence and transmission. For other pathogens, as resistance becomes worse, those regions or countries that are already badly affected continue to get worse. In contrast, regions that currently have malaria eradicated or under control are more vulnerable to increasing resistance, compared to those that already have high infection rates and have most likely reached a plateau point.

RAND Europe used historical data and KPMG used current regional data to try and estimate how anti-malarial resistance is likely to rise. These were considered as proxies in the absence of better data or forecasting tools; much more detailed and robust work will no doubt be done by academic researchers and clinicians in the future.

Mortality, morbidity and infection rates

For the mortality and morbidity of different pathogens KPMG used data based on current outcomes for patients with resistant infections. They looked at *Staphylococcus aureus* that was resistant to methicillin (MRSA), and at *E. coli* and *K. pneumoniae* strains that were resistant to third-generation cephalosporins. For TB they used the multi-drug resistance rates published in the WHO Tuberculosis database. HIV figures were taken from the WHO HIV

drug resistance report. RAND Europe used figures based on consultation with experts to assess how severe mortality and morbidity would be without any adequate antimicrobial drugs.

To model incidence rates for infections today, RAND used data on the likelihood of contracting a hospital-acquired infection. They then used WHO data to calculate the average number of hospital stays in various countries and multiplied the two figures together to obtain an estimate for the number of hospital-acquired infections in each region. KPMG applied European in-hospital and community infection rates to the whole world in the absence of better available data. As RAND did not include infections acquired outside of hospital and KPMG used European figures that are lower than the world average, both of these analyses are likely to systematically underestimate true infection rates.

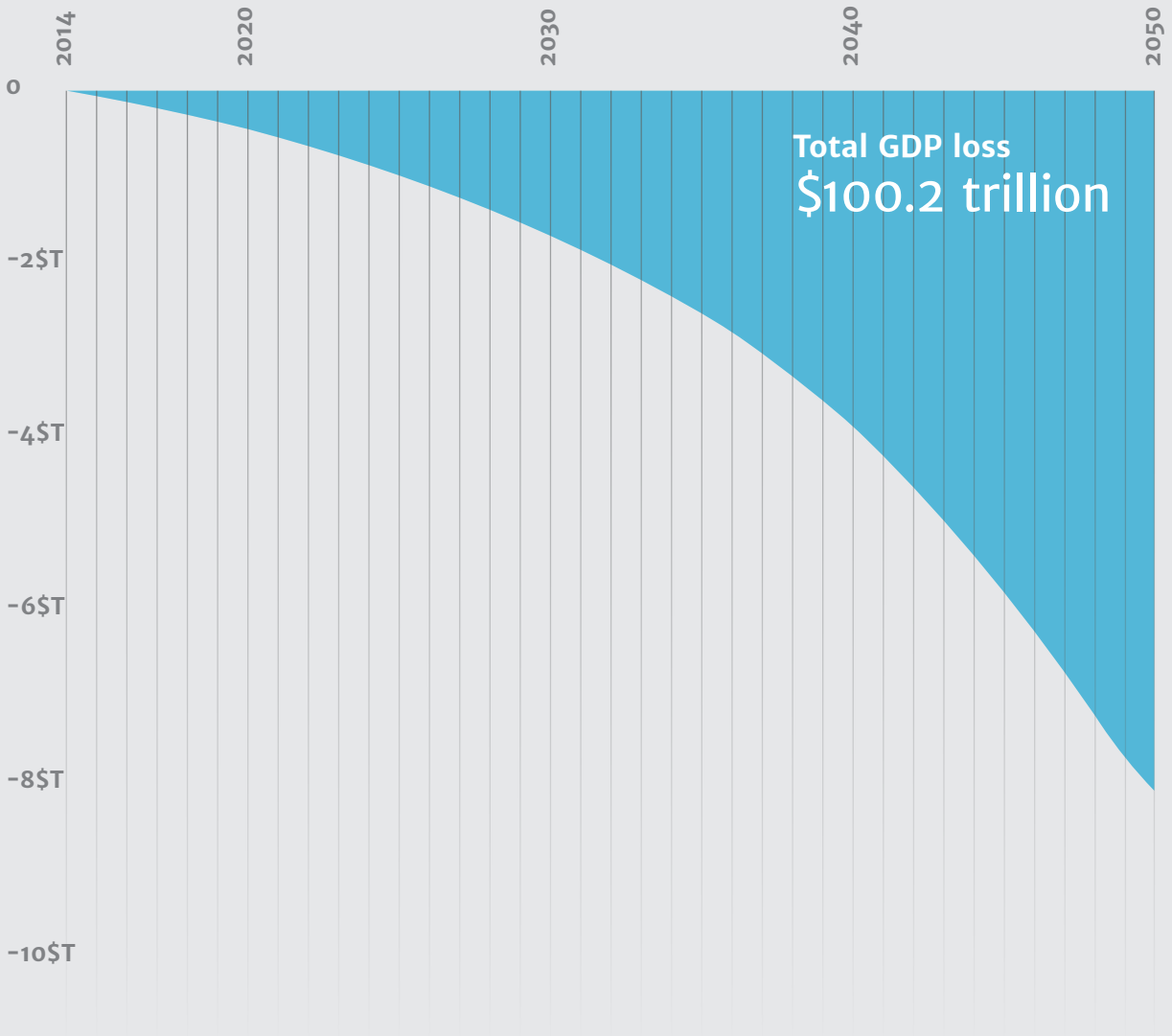
These approaches provided estimates of the mortality and morbidity (expressed in terms of time lost from the workplace due to illness), which were then applied to existing models of macroeconomic growth.

Both teams experienced significant problems with data collection because of the lack of consistent sources monitoring the number of bacterial infections globally. These problems were severe in OECD as well as non-OECD countries. This demonstrates the urgent need to improve the surveillance of infections, and the rising tide of drug-resistant infections. The Review will consider this issue in its future work.

Antimicrobial resistance will have a different impact in different parts of the world

Our results suggest that countries that already have high malaria, HIV or TB rates are likely to particularly suffer as resistance to current treatments increases. This is exacerbated by the fact that the regional variation is much greater for these three public health issues than for the three named bacteria studied. Particular countries at risk include India, Nigeria and Indonesia (malaria), and Russia (TB). In addition, if malaria and HIV drug resistance is not tackled, Africa as a continent will suffer greatly, and the debilitating impacts of HIV and TB co-morbidity already seen in many of the poorest parts of the world will likely get worse. Furthermore, drug-resistant malaria could constrain the economic progress achieved by some countries in Asia. It is also possible that the hard work China and Brazil have undertaken to almost eradicate malaria in the second half of the 20th century could be undermined if resistance is unchecked, and this could have a negative impact on their large export sectors. For countries in the OECD, the cumulative loss of economic output by 2050 will amount to between USD 20 and 35 trillion.

AMR's impact on World GDP
in trillions of USD



The secondary health effects of AMR: a return to the *dark age* of medicine?

Despite the staggering size of the figures set out above, they do not capture the full picture of what a world without antimicrobials would look like. One of the greatest worries about AMR is that modern health systems and treatments that rely heavily on antibiotics could be severely undermined. When most surgery is undertaken, patients are given prophylactic antibiotics to reduce the risk of bacterial infections. In a world where antibiotics do not work, this measure would become largely useless and surgery would become far more dangerous. Many procedures, such as hip operations, which currently allow people to live active lives for longer and may enable them to stay in the workforce, might become too risky to undertake.

Modern cancer treatments often suppress patients' immune systems, making them more susceptible to infections. Therefore without effective antibiotics to prevent or treat infection, chemotherapy would become a much riskier proposition.

Despite many medical professionals considering the secondary effects of AMR to be the greatest risk, there remain many unknowns, which have meant that few major studies have looked comprehensively at this impact. It is not clear how many more people will get infections when prophylactic antibiotics do not work, nor do we know how many people will opt to take on the risk and still have procedures. Therefore, instead of trying to work out exactly how much the economy would suffer because of these secondary health effects, we have sought to estimate the economic value that these procedures create for society. This gives a sense of what we might stand to lose if AMR rises, with the caveat that we cannot predict how much might actually be lost within this total. We hope that others looking at the impact of AMR will focus more on this area and can build on the initial broad-brush research that we have undertaken.

By way of illustration, we have considered four areas of high-volume medical intervention which have become entirely routine in many parts of the world but are dependent upon the availability of effective antibiotics to make them comparatively low-risk.

We estimate that caesarean sections contribute about 2% to world GDP. Joint replacements add about 0.65%, the vastly improved cancer drugs that have been created since the early 1970s add more than 0.75% and organ transplants add about 0.1%. These are just a small number of the areas in modern medicine that risk being undermined if we do not have effective antibiotics in the future. In aggregate they contribute almost 4% to the world's GDP, worth at least 120 trillion USD between now and 2050. While this total would not be completely lost, when this is combined with the other effects of AMR it shows that the world's economy could lose more than 7% of its GDP by 2050, or a total of 210 trillion USD over the next 35 years. These problems will not just affect high income countries where such surgery is already commonplace, but will also have serious and negative impacts on middle income countries that are expected to build universal health systems over the coming decades. While some of these procedures may continue in a world

with higher rates of resistance, there are many other procedures not captured here, including bowel surgery and bone marrow transplants, which would be undertaken less often, and whose economic impact we were unable to quantify.

Rising drug resistance would also have alarming secondary effects in terms of the safety of childbirth, including caesarean sections, with consequential increases in maternal and infant mortality. The 20th century saw childbirth in high income countries move from being something that carried significant risk to something that we take for granted as being safe: the world witnessed a 50-fold decrease in maternal deaths over the course of that century. Much of this progress could risk being undermined if AMR is allowed to continue rising significantly.

Finally, previous health scares such as SARS have shown that travel and trade can have a much bigger impact on the economy than the health costs assessed by this paper. The reaction is likely to be a growing aversion to travel in a world with dramatic and widespread AMR problems. If there is no effective treatment for malaria, for example, people from malaria-free countries may be unwilling to travel to malarial zones. This should be a major worry for all economies, particularly those reliant on tourism, foreign direct investment or global trade.

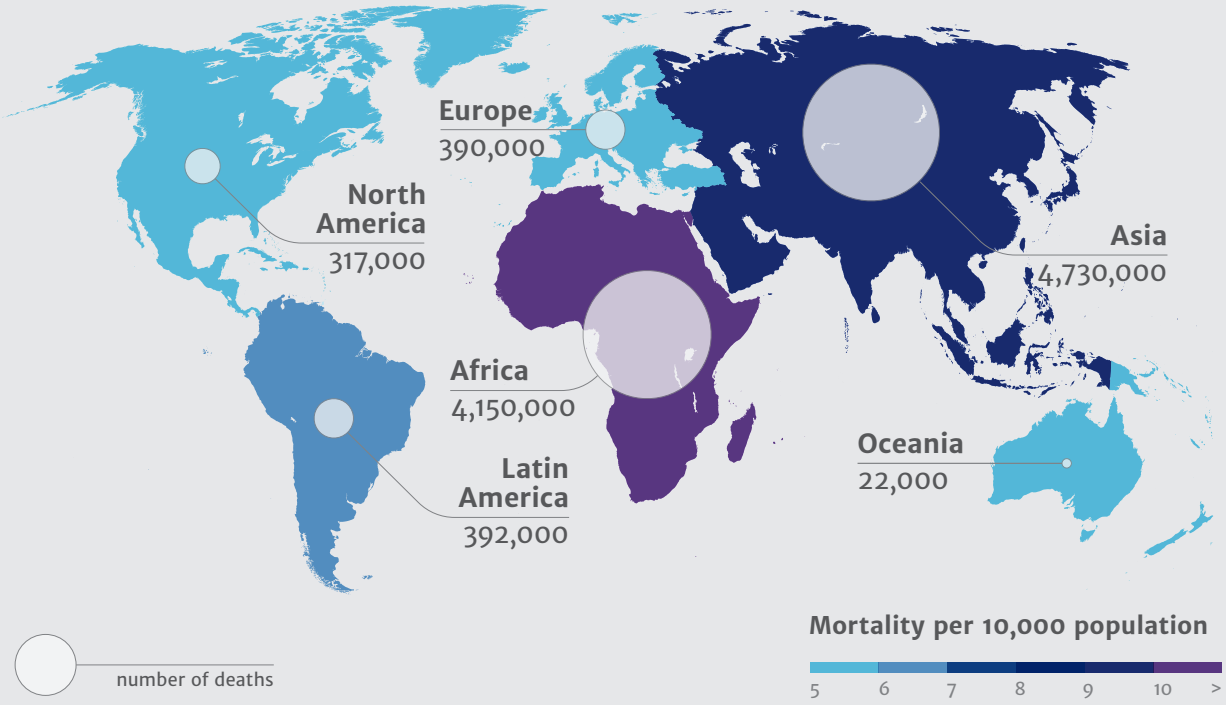
Left unchecked, the current trend in rising drug resistance is a crisis of global scale

The potential impacts outlined above demonstrate that it is vital that the world's healthcare systems are not undermined by resistance to antimicrobial drugs. What this paper has sought to show is that resistance is not just a major health worry, which will lead to millions more people dying every year, but that it is also an economic issue. Financially the cost of dealing with resistance is far smaller than not taking action. This is why we will seek to find the most effective ways for the world to combat resistance, and allow us to preserve some of the most precious medical resources the world has ever had.

Our research also underlines that acting quickly is crucial. The development of resistance is an evolutionary inevitability, even where antimicrobials are used properly and sparingly. However, the high level estimates we commissioned show just how important it is that we do everything we can both to slow the spread of resistance, and to ensure that we are able to mitigate its impact with effective new treatments to replace those that it renders obsolete. The value of a delay is potentially enormous: RAND Europe's study demonstrated that delaying the development of widespread resistance by just 10 years could save 65 trillion USD of the world's output between now and 2050. It is for this reason that the Review is looking so carefully at how to conserve the world's existing antibiotics and those developed in the future.

Infection rates are another important driver of the results. KPMG looked at what would happen if infection rates doubled and then stayed constant. This analysis

Deaths attributable to AMR every year by 2050



showed that an increase in infection rates alone could mean 150 million people dying prematurely and reduce world GDP by 55 trillion USD between now and 2050, just over half the total impact they estimate for AMR. This shows the importance of not just treating infections but also reducing and controlling them. This is why the Review will need to look at ways to improve hygiene and sanitation both in and outside hospitals, to break chains of transmission and stop people getting sick in the first place. Although enormously beneficial to society, the advent of antibiotics may to an extent have reduced the world's focus on fighting infections at their source, as treating them became much easier. This is a trend that needs to be considered carefully.

Already we see cause for optimism

While we are yet to estimate how much it would cost the world to solve the problem of AMR, there is no doubt that the returns will be many orders of magnitude greater for society than the investment.

Based on our initial conversations with policy makers, companies, researchers and clinicians, we already see some cause for optimism. While the problem is enormous, it can be solved if we collectively take the rights steps soon:

- **We have met a vibrant field of university researchers and biotech entrepreneurs teeming with ideas to solve this problem – from early stage development of new drugs, to vaccines and alternative therapies, such as antibodies. For each stage of the innovation cycle we will consider whether and what action can be taken to accelerate these bright ideas.**

- **There is an international governance framework with the WHO taking the lead to agree a global action plan to tackle AMR between 194 countries this spring. Ambitious philanthropic initiatives could emerge for antibiotics in the wake of the achievements and lessons from the work of the Bill & Melinda Gates Foundation and others on malaria and HIV/AIDS. Already there is cooperation at the highest level in the European Union, and between the EU and the United States for pushing more collaborative and innovative research for new antibiotics involving academics, clinicians and companies, large and small. We will work within these frameworks, as well as outside them, to identify the actions that can be implemented with the highest chance of success.**

- **Advances in genetics, genomics and computer science will likely change the way that infections and new types of resistance are diagnosed, detected and reported worldwide, so that we can fight back faster when bacteria evolve to resist drugs. These same technological advances will in the future deliver rapid diagnostic tools which will in time improve the way we use antibiotics, antimalarials, and HIV and TB drugs. Therefore, we will examine the market for new, quicker, point**

of care diagnostics and whether there are market failures or bottlenecks in development, just as we are for the antimicrobial drug pipeline.

- **Finally, tackling drug resistance is aligned with the growth objectives of low and middle-income economies. Sustained growth will be helped by investing in sanitation and basic health infrastructure that protect citizens from excessively high rates of infection. The industrial opportunities presented by drug and diagnostic innovations may help many of these same countries leapfrog to more effective technologies that support their long term economic success. In developing our recommendations, we will consider the economic priorities of all parts of the world inclusively and look for examples of novel, effective funding both within and outside healthcare.**

This crisis can be averted if the world takes action soon

This might be one of the world's biggest problems, but it does not need to be its hardest.

At the core of this Review is the conviction that we need to preserve and further support the huge progress in medicine and poverty alleviation that has taken place over the last 25 years. It would be unforgiveable if the great progress made in combatting infectious diseases could be threatened by the lack of new drugs that are within reach, or for lack of common sense investment in infrastructure that keeps us safe from avoidable infections.

Many issues relating to AMR are complex and inter-related. Coordinated action among many different countries is by nature more difficult to agree than individual initiatives, yet it is necessary: drug-resistant bacteria know no borders. We need coherent international action that spans drug regulation and antimicrobial drugs use across humans, animals and the environment – all matters that this Review will consider carefully. This is a looming global crisis, yet one which the world can avert if we take action soon.

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- Staff of the Wellcome Trust

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

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 the UK Government, but operates and speaks with full independence from both.

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

HM Government

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