Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Tackling a global health crisis: initial steps

The Review on Antimicrobial Resistance
Chaired by Jim O'Neill
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1. Executive summary

In December we published our first report[1] showing that infections caused by drug-resistant pathogens are one of the biggest health problems the world faces today. Bacteria and other pathogens have always evolved to resist the new drugs that modern medicine uses to combat them. But in recent years the rise in drug resistance has been a particular worry, especially the emergence of antibiotic-resistant *superbugs*. Unless action is taken to address this huge global issue, our conservative estimate is that it will cost the world an additional 10 million lives a year by 2050, more than the number of people currently dying from cancer annually. It will also have a cumulative cost of 100 trillion USD, more than one and a half times annual world GDP today, or roughly the equivalent to losing the UK economy from global output every year.

We now turn our attention to how this problem can be tackled. This paper is the first in a series that works towards global and sustainable solutions. There are many angles to the problem that we will need more time to consider. In particular, the focus of our next paper, due to be published in the spring, will be how to stimulate the market for companies to invest in and develop new antimicrobials and diagnostics, which is not fully addressed here. There we will assess potential 'push' and 'pull' incentives to encourage the development of new antimicrobial drugs, and set out our proposals for action by policy makers. In later papers we will also focus on important issues such as the use of antibiotics in agriculture and potential alternatives to antimicrobials.

In the meantime, 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 antimicrobial resistance (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 but 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, but fewer antibiotics would be prescribed unnecessarily.

1. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. http://amr-review.org/publications

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.

We know that further action will be required to make antimicrobial development commercially attractive and sustainable over the long term. This is likely to involve changes to the current market for antimicrobials. In contrast, none of the actions above require a change to the current drugs market and yet they can all buy time and lay the groundwork for future discoveries.

The Review will cover these and additional issues in more detail in later publications, including the market failures surrounding the development of new antimicrobial drugs. In this process we will need to ensure that appropriate measures taken to counter AMR do not inadvertently disrupt economic progress in developing countries. Indeed, although the Review was commissioned by the UK Prime Minister, it has a global outlook and Margaret Chan, Director General of the World Health Organization (WHO) has shown support for its work: "The UK is demonstrating strong leadership in raising awareness about the global threat posed by antimicrobial resistance. Forming this Review is a crucial step towards ensuring that the world has effective medicines to combat infectious diseases. WHO will work closely with the Review and other key partners on this important initiative."

We will recommend a final package of actions to the UK Prime Minister and Governments across the world by the summer of 2016. Over the course of the Review, we have committed to explore the following themes:

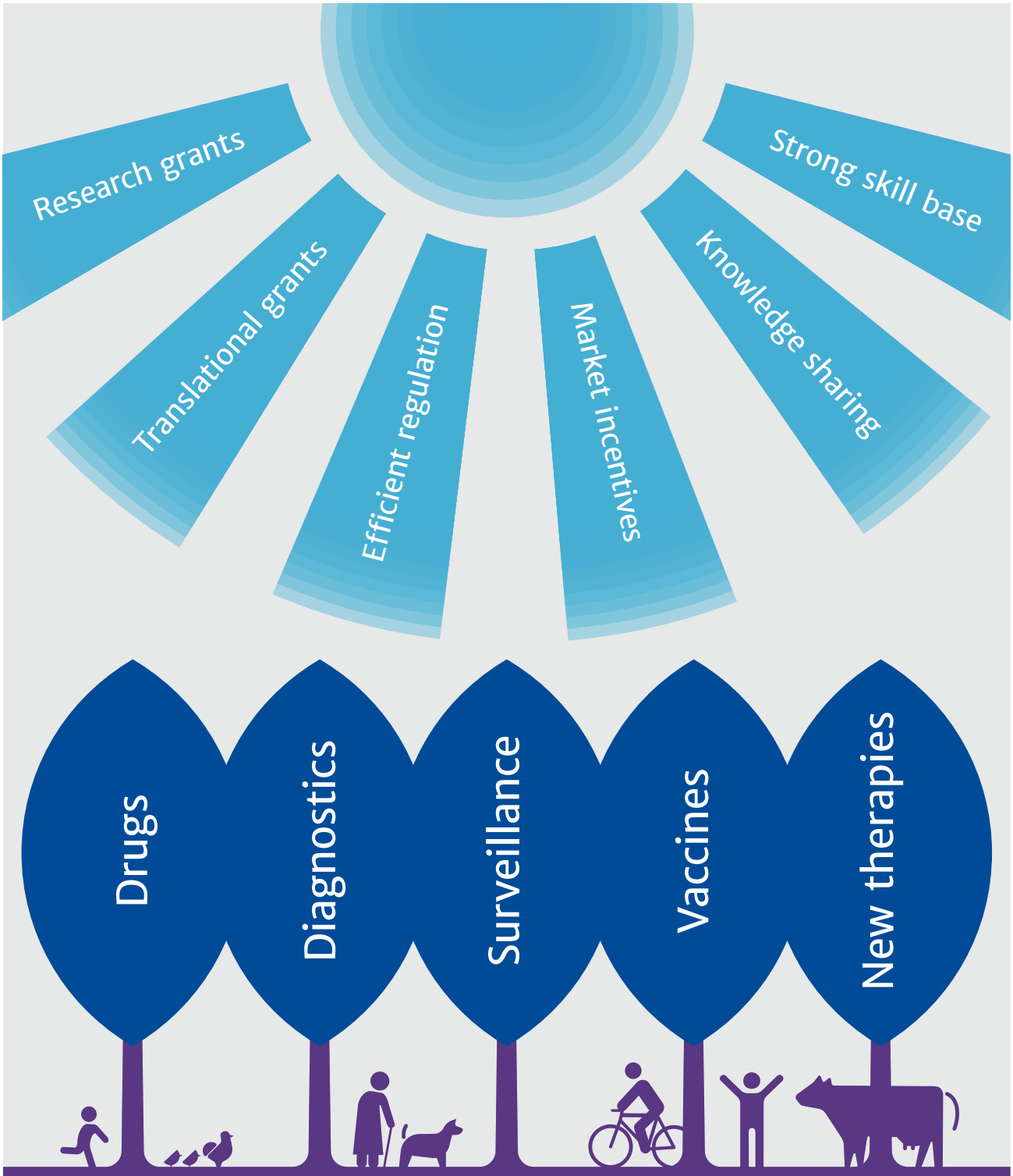
1. The impact of antimicrobial resistance on the world's economy if the problem is not tackled.

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 regulation and use of drugs (including antibiotics) across humans, animals and the environment.



Long term solutions to drug-resistant infections

2. Introduction

The best scientific breakthroughs often rely to some extent on serendipity as well as hard work. But we seem to be stacking the odds against ourselves in the fight against infectious diseases and the challenge of drug resistance.

The fact that commercial incentives to develop new antimicrobials are low compared to other fields is a well-established problem. Whereas antimicrobials once represented an attractive and highly profitable sector of the global pharmaceutical industry, a number of factors mean that they now tend to generate lower or even negative returns on investment compared to higher-priced or longer course treatments for cancer or chronic diseases.

This problem is not confined to the corporate world. It is also an issue in academia and in the governmental and charitable organisations that fund medical research. This is not surprising: as the global burden of infectious diseases reduced steadily during the 20th century, so did society's focus on efforts to combat them.

Unfortunately, time has shown that this was misjudged. The HIV/AIDS epidemic that started in the 1980s presented the world with one of its greatest ever health challenges, one that remains for many countries. The 'control' of HIV relies on drugs and behaviour change, but largely the former, and this is at risk in future decades. The global fight against malaria has been very successful, but the emergence of drug-resistant malaria strains is now raising alarm bells across South East Asia. And perhaps most worryingly for modern medicine, with the numbers of antibiotic-resistant bacteria rising across the globe, more and more doctors around the world are using last line of defence drugs, with no new antibiotics to replace the ones that are becoming ineffective, for example in the treatment of gonorrhoea.

Better awareness and strong leadership have already sparked change thanks to initiatives by the WHO, the European Commission and many individual countries, but further decisive action is needed urgently to turn these good intentions into results.

In this paper, first we highlight the undercurrents that make it difficult for the very good individuals working in this field to progress great science. In a nutshell, we think there is a problem of chronic under-investment in both the financial and human capital needed to tackle AMR.

Then we turn to five actions that we think can and should be considered immediately, without waiting for an exhaustive and definitive solution, or an international agreement, urgent and necessary though these long-term measures are.

3. We under-invest in the financial and human capital needed to tackle AMR

Adequate long term investment in research and development (R&D) is a prerequisite for the sustained medical innovations that have transformed how illnesses are diagnosed, managed and cured. Globally, the sums involved in maintaining this cycle of innovation are huge: more than 260 billion USD is spent each year[2] by private companies, governments and charitable or philanthropic organisations on healthcare R&D. This spending has historically been dominated by the US, Europe and Japan. But today the involvement of emerging economies is growing rapidly, with health research spending in China increasing by 17% annually in recent years.[3] AMR represents a truly global problem, so this emerging shift towards a more globalised landscape of research funding presents an opportunity to reflect the diverse needs and priorities of patients worldwide more adequately.

Whether this spending is guided by public policy, altruistic intent, or commercial benefit the distribution of funding for research activities at all stages of the development process is fundamental in determining the progress humanity makes against different categories of disease. In a survey conducted by this Review of researchers, funding organisations and private companies with an interest in AMR, 80% of respondents cited poor funding or economic incentive problems as the most difficult obstacle to creating new antibiotics.

Public and charitable funders invest relatively little in AMR

The late-middle part of the 20th century saw a shift in the collective focus of the medical community away from the threat of infectious diseases. This was driven in no small part by the belief – now shown to have been mistaken – that antibiotics, vaccines and enhanced public health had won the battle against infections which had been a significant cause of mortality and morbidity until the middle of the century. There was then a corresponding shift towards tackling chronic and non-communicable diseases, the burden of which has grown in recent decades, in large part due to increased life expectancy, but aided by the ability of antibiotics to fight infections. More than 80% of disability-adjusted life years (DALYs) lost in the developed world are now attributable to non-communicable diseases.[4] But this shift has left AMR, as well as many other areas of infectious disease research, chronically underfunded. Globally, our collective research priorities should reflect not simply the current burden of disease, but also a more far-sighted recognition of the future health challenges the world may face. In this respect, the Ebola crisis in West Africa presents us with a lesson of the costs of underestimating the threat that an infectious disease may pose and the impact that not being able to treat it may have.

2. Moses H, Matheson D H M, Cairns-Smith S, George B P, Palisch C, Dorsey E D. The anatomy of medical research: US and international comparisons. *Journal of the American Medical Association 2015*; 313(2): 174–189.
3. Ibid.
4. Global Burden of Disease study 2010

There are some encouraging signs among non-profit and government funders of money starting to flow again to support research related to AMR. Major charitable foundations such as the Wellcome Trust in the UK and the Bill & Melinda Gates Foundation in the US have begun to increase their focus on drug resistance within the areas they prioritise. In the UK, the Research Councils, together with other government funders, are working on a holistic approach to AMR research with a relatively small initial 25 million GBP investment. In addition, key initiatives such as the European Innovative Medicines Initiative (IMI) New Drugs For Bad Bugs project, and the Biomedical Advanced Research and Development Agency (BARDA) Broad Spectrum Antibiotics Programme in the US have between them invested nearly 650 million USD over the past five years directly into new antimicrobial discovery efforts in partnership with industry. Most recently, the White House has requested a sharp increase in funding from Congress, up to a total of 1.2 billion USD, to bolster US federal funding in 2016 to tackle AMR, including 650 million USD to extend the existing NIH and BARDA programmes of work. There are also promising moves towards improved coordination of AMR research funding, such as through the European Joint Programming Initiative on AMR (JPIAMR). However, significantly more can be done to ensure that research efforts transcend not just national borders but also boundaries between organisations and scientific specialties.

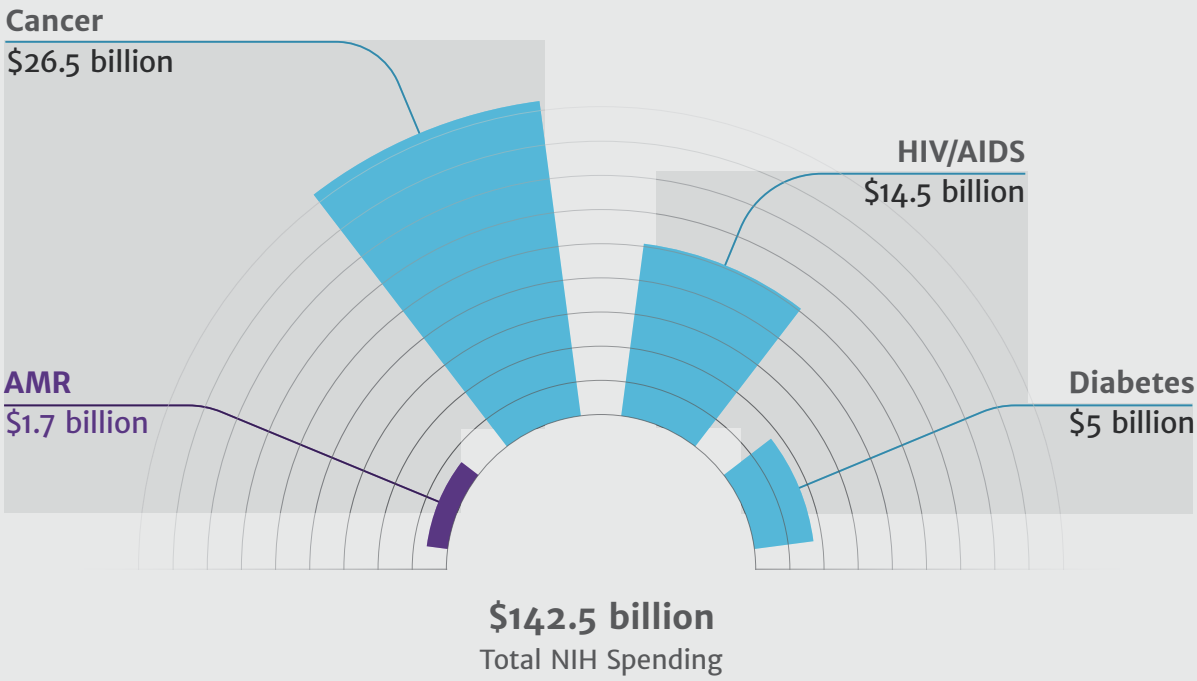
Given the scale and urgency of the problem, governments need to re-balance national R&D budgets further and faster to support high quality research on AMR.

To illustrate the point that governments invest relatively little in AMR, we have reviewed publicly available information for the US National Institute of Health (NIH), which is the world's largest single funder of health and biomedical R&D, with an annual budget of around 30 billion USD. Out of that total budget, NIH allocated around 341 million USD[5] annually on average, over the past five years, targeted at AMR. This money represents only 1.2% of the NIH's grant funding and is dwarfed by the 5.2 billion USD spent annually on cancer research in the same period, absorbing 18.6% of its total.

Reviewing the data for Europe was more difficult because there is currently no single source of data on spending on AMR-related research by public bodies in member states across Europe. But the picture we gathered by consulting experts and funders was that the absolute numbers allocated to AMR were smaller than in the United States, but that the proportion of spend allocated to AMR was broadly similar. In Europe, spending by member states is supplemented by funding from the European Commission. Over the course of the 2007–13 budget cycle a total of 560 million USD[6] has been directed towards AMR-related research, which represents 1.8% of all grant awards across relevant funding themes. These numbers stack up poorly to the amounts spent on diseases such as cancer and diabetes. A more comprehensive picture of funding in Europe is currently being prepared by the EU-wide JPIAMR.

5. Figures are given in 2010 USD.
6. http://europa.eu/rapid/press-release_MEMO-13-996_en.htm

US National Institute for Health research spending 2010–2014



Source: National Institute for Health. Figures are in 2010 USD

Private and commercial investment is also insufficient

The value of overall health R&D spending by governments globally is only half that of funding from private organisations.[7] Much of the latter is from pharmaceutical companies, whose research efforts are also dominated by non-communicable diseases; 22 of the 25 indications with the greatest number of products under development are non-communicable and chronic conditions, with the remaining three indications being HIV/AIDS, hepatitis C, and influenza.[8]

Active clinical trials, as recorded by the World Health Organization International Clinical Trials Registry Platform, are similarly skewed towards non-communicable diseases, which outnumber those for communicable diseases by a ratio of nearly three to one. There are 67,000 clinical trials currently registered in non-communicable diseases, of which around two thirds are in cancer. There are only 23,000 clinical trials currently registered in infectious diseases, of which nearly half are in HIV/AIDS, TB and malaria. These trials will undoubtedly contribute to addressing some of the alarming challenges that we highlighted in our first paper of emerging resistance to treatments for these conditions. However, the number of trials looking at bacterial infections other than TB is minuscule in comparison: a mere 182,[9] or less than 1% of non-communicable clinical trials.

Unlike public funding, the significant change needed to increase focus on AMR-related research amongst private funders can only be achieved in the presence of a compelling commercial rationale. Patterns of R&D spending by private companies will ultimately respond most effectively to long-term market forces. But at the moment, the discovery and development of new antibiotics appears commercially unattractive in comparison to investment into treatments for cancer and chronic diseases, where prices are higher and treatment times longer. For private funding of antibiotic research and development to increase, markets need to adjust to ensure that the long term financial value attached to them is sufficient to incentivise a significant and sustained increase in research spending. Some of these changes will be down to governments, health providers and health regulators to bring about. We will focus the recommendations of our next paper on these questions, looking in particular at what so-called 'pull incentives' are needed. But the pharmaceutical sector will also need to adjust its research priorities independently of the action of governments, recognising that AMR left unaddressed is a risk to the viability of many other treatments, including cancer, diabetes and routine surgery.

7. Røttingen J-A, Regmi S, Eide M, Young A J, Viergever R F, Årdal C, et al. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? *The Lancet* 2013; 382: 1286–1307
8. Citeline Pharma R&D Annual Review, 2014
9. Data extracted from WHO International Clinical Trials Registry Platform website, http://apps.who.int/trialsearch/, accessed January 19th 2015

We also under-invest in the human capital needed to tackle AMR

AMR is a challenge with many facets and a global reach. Tackling it will require pulling together the efforts of the best basic and applied researchers including clinicians, infectious diseases specialists, microbiologists, 'omics experts and drug and medical technology developers, all in close collaboration with pharmacologists, public health professionals, big data experts, social scientists and vets, among others. We also need to make AMR a problem that both appeals to and is rewarding for specialists from other disciplines, including computer science, mathematics, and engineering and physical science.

We have observed the skills and capability picture for drug discovery and development across the relevant disciplines and career paths through our conversations with academics, government officials and companies. A story emerged that is not dissimilar to the funding shortage we describe above: we seem to be under-investing in the human capital needed to tackle AMR especially when considering it relative to other fields. We regularly meet many brilliant individuals working to make a difference to this global health problem but they are often working against the grain of their professional field and receiving less recognition for their work than they might do in other specialities.

The publicly available data we reviewed is consistent with these general observations. Some further details are set out below.

What is not surprising is that clinicians, researchers and the institutions employing them naturally follow the money, as illustrated by the successes of areas of research that are better funded in comparison, such as cancer or HIV/AIDS.

We are stacking the odds against winning the fight on AMR if we do not act now to make sure the next generation of high calibre cross-disciplinary professionals are being trained, supported and encouraged.

4. Five steps that can be taken now to tackle AMR

To people familiar with the challenge of AMR, none of the ideas below will come as a surprise. They are for the most part well-rehearsed within the medical community. The reason for highlighting them here, however, is to catalyse action and call on decision makers to deploy adequate resources now. Some have the potential to make a real difference within a small number of years. We know that further action will be needed to make the market for new antibiotics commercially attractive and sustainable over the long term, but none of the actions below requires a change in the current shape of the drugs market to be implemented. Equally no change to that market would make these actions redundant.

A. Set up a global AMR innovation fund to boost the number of early research ideas

Concerted action will be needed to drive investment in R&D focused on a new generation of drugs, using existing drugs better, improving diagnostics and finding alternatives to antibiotics. There is a shortage of investment in all stages of drug development in this field, and this is something that can only be rectified on a sustainable basis by ensuring that new antimicrobials are a commercially viable part of the global pharmaceuticals market: this will be the focus of our next paper.

However, there is also a pattern of under-investment in basic, early and mid-stage scientific research. It is this type of work – usually undertaken in academic settings or in partnership between academia or public health organisations and small and medium companies – that is the essential precursor for the type of breakthroughs we need in the field of drug resistance. It is this work that is sometimes picked up by larger companies who have the capability and experience to take drugs all the way to market.

In the context of the total sums involved in medical R&D and drug discovery, this kind of research need not be expensive but it is rarely attractive to private investors as a commercial proposition. So funding for this basic, often blue sky, and translational science depends largely on resources from government and charitable organisations. Already there is progress in the way policy is being shaped. The draft global action plan published by the WHO; the coordinated strategy across the different parts of the US Government; the joint programming initiative between European research funders across Europe: these are all clear signs that policy makers are taking AMR seriously and aiming to mount a coordinated response. The immediate next step on the journey is for funders to allocate grants where they are most needed, with signs in the UK and elsewhere that funding bodies have already embarked on this.

We think an 'AMR Innovation Fund' dedicated to funding research on all aspects of AMR can help transform these efforts from intentions into results faster.

It will be important that the fund has wide eligibility for academic, public health and industry scientists and is global in its reach to support good ideas wherever they arise. We have shown in our first paper on the economic cost of AMR that emerging economies stand to lose the most from rising drug resistance. Ideas and solutions generated close to where these problems are most acute may be more fertile and tailored to the needs of those clinicians and health workers on the front line.

The details for how this fund would be set up and how it would allocate funds are very important and we will work through these ahead of our next paper. To do this we will continue our dialogue with governments, funders, regulators, researchers and companies, with the determination to build on what is working whilst keeping an open mind to why other things have not worked so far. During this process we are keen to foster partnerships between developed and developing countries in research and science, and enhanced monitoring of AMR through improved surveillance.

B. Make sure we are getting the most of out of existing drugs

When economists look at the challenge of AMR, they usually categorise issues between demand and supply. The availability of drugs is a supply side question, with the supply being made up of all the drugs that have been discovered already plus all the new drugs or new therapies that could be discovered in the future.

The comparison with fossil fuels often springs to mind: we seek to use our existing finite resources (oil and gas fields) more efficiently, and at the same time we look for new sources of power (solar, wind etc.).

When we asked what has been done to get more out of existing drugs, we were surprised by the answer when it came to antibiotics: not much has been done and certainly nothing systematic or comprehensive.

Not all the scientists we spoke to agreed on how we could make more efficient use of the existing arsenal of drugs. But on the whole they did agree that three avenues are worth trying and have not been exhaustively explored so far:

1. Is the dosing and length of treatment for most existing antibiotics consistent with the goal of minimising resistance?

2. Have we tested available antibiotics sufficiently in combination with other antibiotics or different agents to see if combinations could treat 'resistant infections' more effectively and/ or prevent increased resistance?

3. Do we know which old libraries and patent literature have been systematically mined, and how recently, and whether there are 'forgotten' compounds that could be put to use?

It is not clear whether large pharmaceutical companies with the ability to do this kind of applied research have done it. Nor is it clear whether universities, or public and charitable programmes have been funded to do it. We have come upon four

possible explanations. First, the path to commercial return is unclear because most of these old drugs are off patent and it could be difficult to patent a new combination or dose of said drugs. Second, this area could be seen as less exciting for many funding bodies and scientists than funding or undertaking work at the cutting edge of microbiology research into novel compounds. Third, it could be that the regulatory pathway for approval is too unclear or burdensome. Fourth, it can be surprisingly difficult to formulate combination products so that both drugs work effectively together.

We will consider this in detail in preparing our next paper. The reasons for the slow progress in this area will inform the recommendations we make for speeding it up. If it turns out that there are insufficient commercial incentives at play, it could be justified for governments to play a more direct role in procuring a programme of research, or change incentives to encourage others to do so. In the meantime, efforts in this area should be boosted and information shared on what has and has not been tried already.

C. Improve the use of diagnostics wherever they can make a difference

Another way to tackle AMR is to reduce the demand for drugs – the less antibiotics are used the slower resistance tends to build up. By improving the accuracy of prescribing, better diagnostics can help reduce our use of antibiotics when they are not needed.

Every time an antibiotic is used it gives advantage to bacteria that are resistant to it, and encourages others to become resistant. Therefore unnecessary prescribing or overtreatment increase the rate of resistance. For example, about 80% of gonorrhoea cases in the UK are caused by bacteria susceptible to penicillin and about 70% are susceptible to ciprofloxacin. However, health guidelines prescribe the use of more powerful antibiotics (ceftriaxone and azithromycin) as the standard treatment, because we cannot give a rapid, accurate diagnosis of infections that could be treated with penicillin or ciprofloxacin. If we could diagnose bacterial infections and resistance more quickly and accurately, even if only for certain types of infection, we could 'save' our most powerful antibiotics by using them only for cases resistant to other options. This would make our drugs last longer.

There has been recent recognition of this issue in the UK, US and Europe with the proposal of prizes to provide a 'pull incentive' to companies looking to develop new diagnostic devices. The 10 million GBP Longitude Prize 2014 is a welcome incentive, as was the September announcement by the US Government of its intent to launch a similar initiative, with prizes potentially in the region of 25 million USD, and the 1 million EUR European Horizon prize. However, it is generally agreed that they will not provide a total solution to this problem, and further action is needed to supplement that which has been taken already.

Earlier in this paper we set out a proposal for an "AMR innovation fund" to provide a 'push' incentive to generate early discoveries in academia and the labs of small companies. We do not think this should be limited to drug discovery, and therefore

ideas for new diagnostic tools should benefit from this fund, increasing funding opportunities for innovative ideas.

Beyond grants and prizes however, the most effective way to nurture innovation in this field will be to make sure that health providers are ready to take up appropriate diagnostic technologies. Health policy makers need to begin considering now how to establish clear incentives to promote the uptake and usage of point-of-care diagnostics once they are available. This is particularly important in settings where the costs of deploying new diagnostics will fall on individual providers, but the benefits accrue to health systems and society more broadly. They also need to consider how to encourage the behaviour change that will be needed to ensure that these devices are used appropriately when they come to market, and that the results are acted upon. These issues should be anticipated now; if they are not, and the route to market appears unworkable then development of these vital tools will be stifled.

We will be analysing the economic and healthcare financial management issues as they relate to diagnostics further in our next paper, including whether there is a need for further incentives to bring diagnostic tools to market and how this could best be done.

D. Attract and retain a high calibre skills base

Over the past months we heard recurring comments about the quality of the skills base involved in tackling AMR, including that AMR is failing to attract the new generation of researchers it needs in academia and public and commercial labs. There are also concerns about hospitals' recruitment of infectious disease doctors, with current skills and expertise dwindling due to retirements. This is compounded by the fact that large pharmaceutical companies and their research teams are withdrawing from the field, with a loss of institutional memory and experience hard earned through previous drug discovery programmes. Finally, AMR as a field is not attracting sufficient partnerships with professionals from other disciplines such as chemistry which are needed to solve the problem.

We tried to test these concerns against publicly available information where possible.

We found that data about: a) the employment and training of infectious disease clinicians in the United States, and b) the academic impact of publications relevant to the AMR field seem to corroborate some of the concerns about the AMR skills base.

First, looking at published data in the United States, we found that HIV and Infectious Disease doctors were the lowest paid among 25 medical professions examined in an annual compensation report for 2013.[10]

10. This is based on research undertaken by Medscape as part of their 2013 annual compensation report: http://www.medscape.com/features/slideshow/compensation/2013/public

We then found application data for 18 of the same 25 professions: infectious disease had the second lowest application rates. At 84 applicants for every 100 programme places it is one of only two specialities that receive fewer applications than there are places. Given the relatively lower pay combined with often longer hours and no prospect of complementing income through private practice, it is not hard to see why infectious disease has difficulty recruiting new doctors. This is also true in developing countries, and is particularly worrying because with rising resistance levels the need for infectious disease doctors is becoming greater.

We also found some evidence confirming a similar pattern for academic researchers. There is a view among AMR experts that the field has suffered poorer academic status historically in comparison with some other areas of medicine. Concerns include that:

1. AMR has been less favoured by funding bodies (though this is changing in some countries);

2. Industry-sponsored research is less favoured (e.g. by universities) than research funded by research councils etc.; and

3. The highest ranked specialist AMR journals are judged by some universities not to have sufficient impact for academic excellence assessments.

Microbiology journals form a relatively small field. For instance, there are five times more cancer publications than there are microbiology.[11]

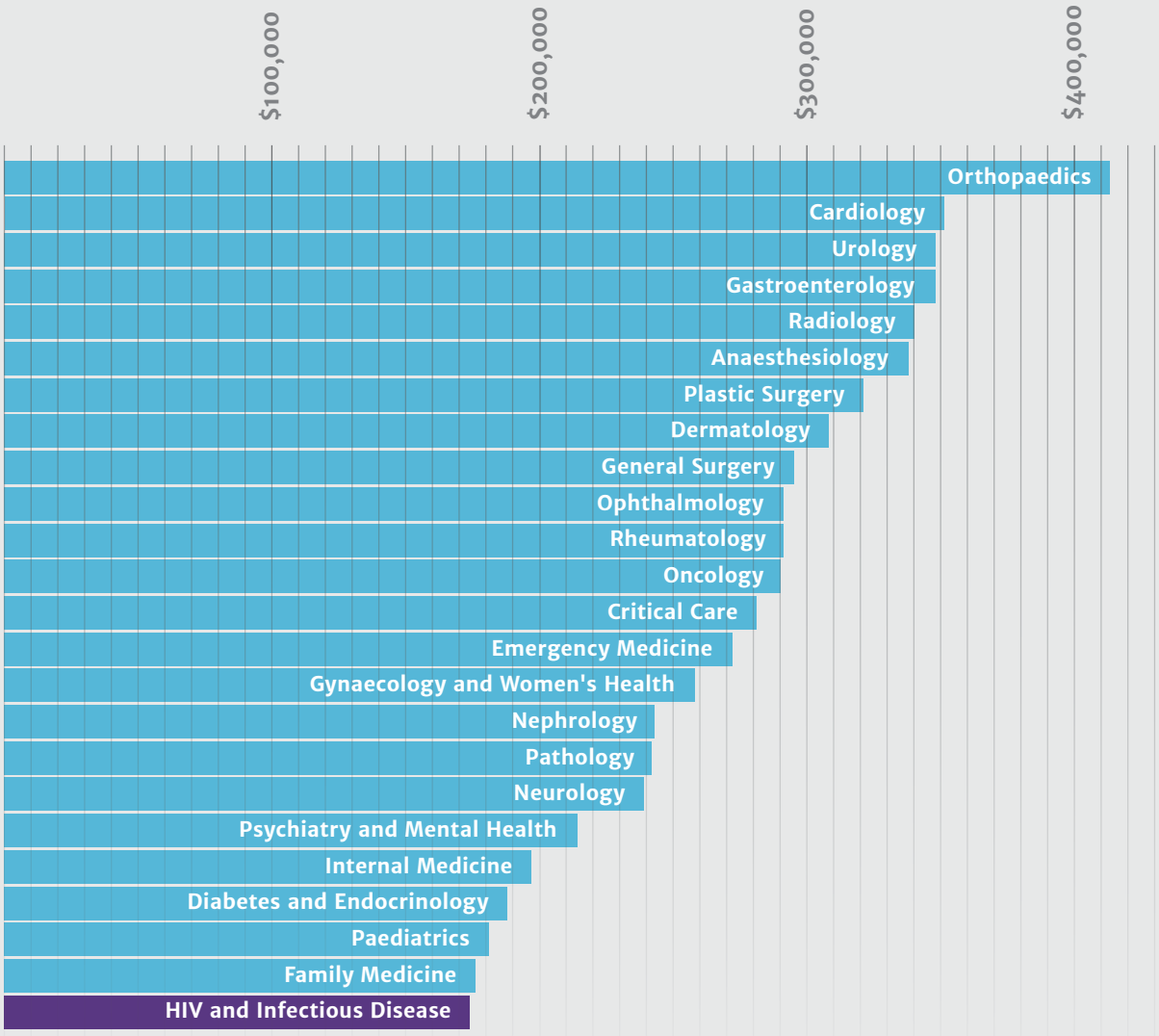
We then looked for ways to judge the impact of microbiology as a field, regardless of its size. Amongst the several different metrics used to assess the impact of a journal, the most common one is to look at the number of citations that the average article receives in its first two years after publication. While this is a test designed to test the impact of specific journals we used it to compare different fields in this case, to see how impact differed across disciplines. We found that microbiology journals do less well by this score than any other field we examined, and infectious disease is the second lowest. The average microbiology paper receives 2.7 citations in its first two years and an infectious disease paper receives just under 3, whereas cancer publications get 3.5 citations in this period, and immunology ones get almost 4. This is not due to microbiology's lower number of publications, as we only found a very small (0.05) non-statistically significant correlation between this measure of impact and number of publications.

Another widely used metric to judge an academic or journals' prestige is the "*h*-index". Using this metric again shows that microbiology is under-represented with no microbiology journals ranked in the top 30 medical journals in the world, while oncology, immunity, pharmacology, neurology and endocrinology all have at least two top 30 journals.

While these differences might not seem significant, the number of citations a researcher gets has a huge bearing on their academic career.

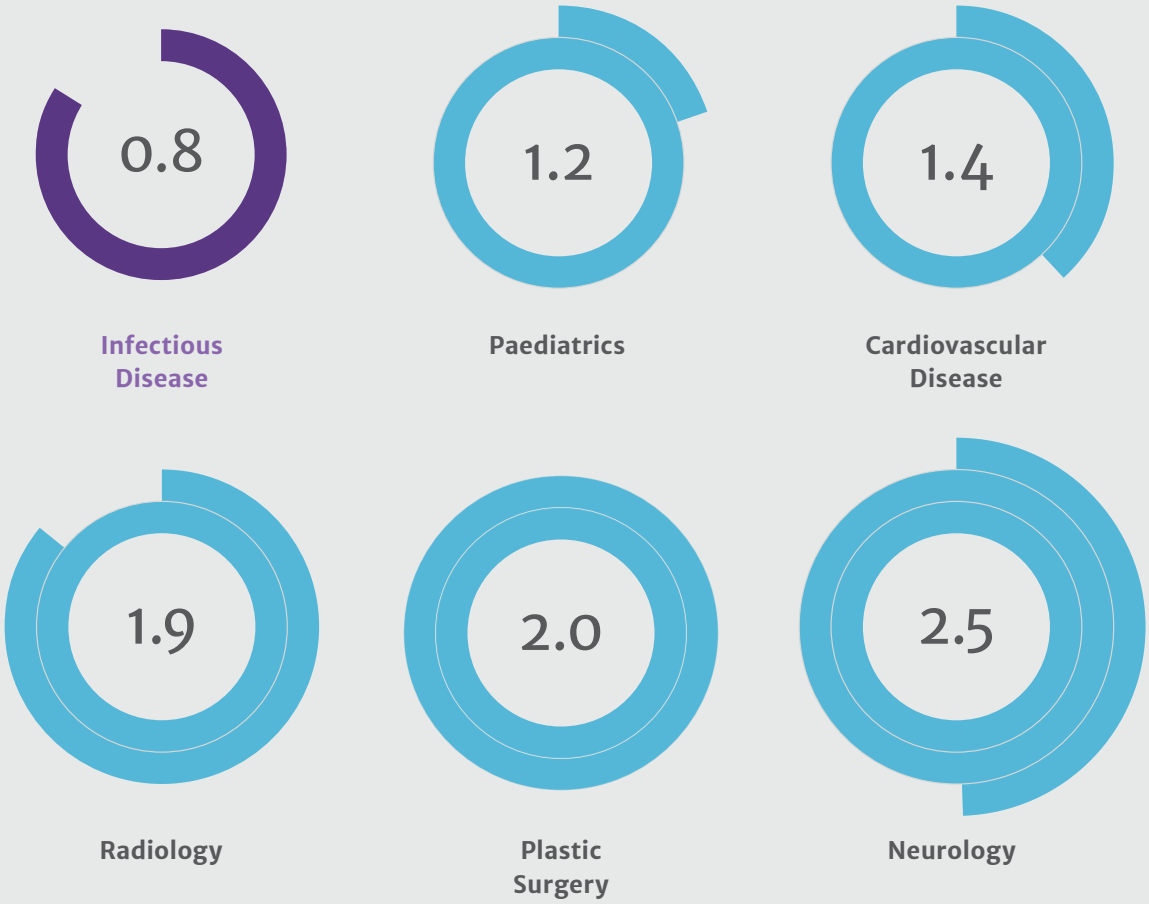
11. Figures based on www.scimagojr.com/journalrank.php data

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



Source: Medscape

Applicants per vacancy for US medical residencies and fellowships



Source: National Residency Matching Program 2014

There is certainly no one silver bullet for boosting such a diverse skills base. But there is an urgent need to recognise this problem and take action.

An idea may be to catalyse change by creating actual or virtual centres of AMR excellence that are connected internationally. These entities would need to connect expertise from across diverse disciplines and backgrounds, including universities, public health laboratories, and industrial partners. They would provide international research leadership to promote development and retention of professionals at each stage of the career path, from new PhD programmes to supporting experienced researchers with the skill sets appropriate to address all aspects of resistance. They could foster research programmes that encourage exchange of staff between academia, public health and industry, improving expertise in all aspects of AMR and antibiotic development. Programmes would extend from the basic science of target and drug discovery and resistance characterisation (including microbiology, biochemistry, chemistry, pharmacology, and 'omics'), through clinical trials and medico-legal/regulation issues to licensing and clinical use. Most importantly, these centres leading on AMR should be connected internationally.

E. Modernise the surveillance of drug resistance globally

In order to deal with AMR effectively over the long term we need to have better systematic global surveillance systems, to track the spread of both infectious diseases and resistance. This includes having data collected on a local, national, and international level. It is also critically important that we think about how to make better use of digital opportunities for gathering, analysing and acting on real-time data. The Review will look at this issue in more detail in later publications but we have already concluded that we need to:

1. Better use and share the data that we currently have available; and

2. Improve our collection of data, without imposing undue costs on health systems that cannot afford them.

Although some multinational surveillance systems exist, e.g. CDC and EARS-Net, no system offers adequate access to the most recent global data. Systems that do exist are fragmentary and are only able to provide data with limited granularity.

There are organisations that provide very useful information in an accessible format on infectious disease occurrences and outbreaks. However, when mapping AMR, they largely rely on data that are released into the public domain on a voluntary basis, e.g. by US hospitals. Again such data are sporadic, sometimes years out of date, and patchy, with some parts of the world having no data at all.

At a technical level, this challenge is in some respects linked to that of diagnostics. The more accurately and widely we are able to collect diagnostic laboratory data, the better our surveillance will be. However, access to the requisite laboratory technology to conduct tests is currently variable. The basic laboratory technology required for local data generation is in widespread use in the developed world, but deployment is uneven in the developing world. Increased access to laboratory

facilities, or simplified devices to enable testing in laboratories with limited resources or in hospitals, doctors' surgeries, or even pharmacies, would facilitate both better diagnosis and more comprehensive data generation. Because surveillance needs to be global to be truly effective, governments should consider now how it can be improved on an international level, including the infrastructure surrounding it.

Effective surveillance of AMR, and movements towards the digitalisation of surveillance, also raise data policy and data quality questions, which policy-makers ought to consider now. It is inevitable that in the future more data on AMR will become available increasingly quickly, and governments need to be ready to receive, store and share this data. They will need to address who controls this data, and ensure that they reach agreement on how to share their data in the most appropriate way, in order to manage it safely and effectively. The draft Global Action Plan proposed by the WHO is a strong foundation to this work – but decisive action including funding needs to happen now to turn intentions into results.

To summarise, there is a unique opportunity for innovations in computing and the use of data to unlock transformational change in how we approach global AMR surveillance. The risk otherwise is that the world either misses out on the potential of digital surveillance – or that the benefits are spread unequally and inefficiently.

5. The next steps

During the coming months we will continue work on all the themes we have outlined. In the meantime, we would like this paper to catalyse action to support five initial steps that can already be taken to tackle AMR.

We look forward to working with senior decision makers in governments, philanthropic agencies and industry who need to address the details of how to tackle the problem of AMR across its many facets. In the coming months we will be travelling to India and China to discuss antimicrobial resistance with policy makers and companies, to discuss their views on the most promising solutions.

The efforts to bring forward innovations in areas such as new therapies, diagnostic devices and surveillance techniques need to be international. With the right kind of cooperation between countries a lot can be done to upgrade and link up existing infrastructure, and help countries embrace new technology wherever feasible. This is why we think that the fight against antimicrobial resistance must be placed high on the G-20's agenda.

A solution to antimicrobial resistance need not be expensive. It is likely to cost the world much less than 0.1% of global GDP. Weighed against the alternative – 100 trillion USD in lost production by 2050 and ten million lives lost every year – it is clearly one of the wisest investments we could make.

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Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

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