Review on Antimicrobial Resistance
Tackling drug-resistant infections globally

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

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

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CONTENTS

EXECUTIVE SUMMARY

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 pneumonia*. 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.

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.

“*The availability of antimicrobials has shifted the focus from prevention towards treatment*”

INTRODUCTION

"The only sustainable, long-term solution to the global problems of AMR lies in action to address the 'demand side'"

In our work so far to address the global problem of rising drug-resistant infections, we have made a set of recommendations that can address the supply side of the problem: interventions to support the development of new antimicrobial medicines and improved use of diagnostics technology to better manage global antibiotics use. If successful, these interventions can address the problem of antimicrobial resistance (AMR) for a period of time, by making treatment available.

But the only sustainable, long-term solution to the global problems of AMR lies in action to address the demand side – the factors that drive our often excessive and wasteful consumption of antimicrobials, in animals as well as in humans. We have already addressed such issues in our previous reports, proposing action to reduce the volume of antibiotics in use globally, through reductions in the amounts consumed in animals and agriculture, and released into the environment; as well as through the use of vaccines, alternative therapies and rapid diagnostics.

In this paper, though, we turn to simpler but equally crucial interventions to reduce demand for antibiotics by preventing infections occurring, stopping them spreading where they do, and improving our understanding of both.

First, we look at the role of clean water and effective sanitation to prevent the spread of infections in the community and ultimately reduce antimicrobial resistance.

Second, we look at ways to prevent and control infections in health and care settings.

Last, we address the need to continue improving our information and understanding of the infectious disease burden globally, and to improve how the surveillance of drug-resistant infections is included within these systems.

The work of the Review

Our Review was commissioned by the UK Prime Minister, and is hosted by the Wellcome Trust, tasked with recommending by the summer of 2016 a comprehensive package of actions to tackle AMR globally. In the meantime, we have published a series of papers looking at individual aspects of the wider AMR problem, of which this is the final one. All of these publications and accompanying infographics can be found on our website at www.amr-review.org.

Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations was published in December 2014, and set out the findings of rapid economic modelling work to quantify the global human and economic burden of an unchecked rise in drug resistance between now and 2050. We estimated that unless effective action is taken, drug-resistant strains of tuberculosis (TB), malaria, HIV and certain bacterial infections could by 2050 be claiming 10 million lives each year. This would come at an economic cost of 100 trillion USD wiped off global GDP over the next 35 years.

Our second paper, **Tackling a Global Health Crisis: Initial Steps** was published in February 2015, showing the extent to which research on tackling AMR has been neglected over several decades and setting out five areas for immediate action to slow the rise of drug resistance. This included the establishment of a two billion USD Global Innovation Fund for AMR; steps to reverse the 'brain drain' that is undermining research efforts in microbiology and other relevant fields of research; and a greater focus on research into combination therapies, and other means of making existing antibiotics last longer.

In May 2015, **Securing New Drugs for Future Generations** examined the problems of antibiotic development and outlined our initial proposals for bold action by governments around the world to stimulate and incentivise the development of much-needed new antibiotics. This identified key gaps in the antibiotics pipeline, and called for a global system of antibiotic market entry rewards, offering lump-sum payments to successful developers of antibiotics that meet a defined clinical need. This package of action – designed to support a pipeline of 15 new antibiotics over a decade – was costed at between 16 billion and 37 billion USD over ten years.

Published in October 2015, **Rapid Diagnostics: Stopping the Unnecessary Use of Antibiotics** examined the extent of unnecessary use of antibiotics and how the world can combat this with rapid diagnostics. We proposed three interventions to encourage innovation and uptake of diagnostics for bacterial infections: firstly, Diagnostic Market Stimulus pots to provide payments for successful products that are purchased. Secondly access for diagnostic developers to bid for funds from a Global Innovation Fund, and thirdly, support to build the economic evidence for rapid diagnostics.

Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste, released in December 2015, analysed the widespread use of antibiotics in food production as well as how antibiotics reach the wider environment. We proposed solutions to tackle these issues, including: 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, as well as the rapid development of minimum standards to reduce antimicrobial manufacturing waste into the environment, and improved surveillance to advance the monitoring of these problems.

Most recently, in February 2016, **Vaccines and Alternative Approaches: Reducing our Dependence on Antimicrobials**, provided an overview of the pipeline and markets for vaccines and other alternative approaches to tackling drug-resistant infections. This report made three recommendations; first, available vaccines should be more widely used in humans and animals which may require financial support. Second, there needs to be a renewed push for research into new vaccines and alternatives, through different funding mechanisms such as the Review recommended Global Innovation Fund and other long-term funding from philanthropic, public and private sources. Finally, it recommends strengthening the market for new vaccines and alternatives through interventions such as market entry rewards and advance market commitments (AMCs).

This paper is our final thematic report that explores the role of sanitation, infection prevention and control measures and surveillance in reducing the global burden of drug resistance. We plan to present our final report to the UK Prime Minister and the wider global community in May 2016.

1.

ACCESS TO WATER AND SANITATION HELPS TO PREVENT THE SPREAD OF INFECTIONS IN THE COMMUNITY, AND TO CONTAIN THE RISE OF DRUG-RESISTANT DISEASES

There is still a great burden of infectious disease, especially in low and middle-income countries

In high-income countries the burden of infectious disease has progressively declined for more than a century as infections have been better prevented and controlled, even if the HIV/AIDS epidemic and the more recent emergence of infections like the Zika virus show that there is no room for complacency, anywhere in the world.

In many low and middle-income countries however, infectious diseases still account for more than half of the burden of disease, and a large proportion of the population face significant, pervasive threats to their health on a daily basis.

The reasons for this are multi-faceted but there is no doubt that they owe a great deal to the environments in which people live and whether they have access to clean water and effective sanitation. While providing populations with access to health services is of course important, it should build on having basic sanitation infrastructure first.

> *“In many low and middle-income countries however, infectious diseases still account for more than half of the burden of disease”*

Historically, infectious diseases were tackled by focussing on prevention rather than relying on a cure

In many countries, the so-called ‘epidemiological transition’ that saw the burden of infectious diseases brought under control was well underway long before health services were established as we would recognise them today, and many decades before the discovery of effective antimicrobial drugs. Although comparisons should be drawn with caution, it is telling that the ‘first wave’ of public health interventions by governments in Western Europe during the 19th century focussed on prevention, tackling the root causes of communicable diseases[1]. The understanding of the spread of disease was still limited, but there were nonetheless concerted efforts to tackle the squalid urban environment of the day, through structural interventions to improve living conditions and access to clean water and sanitation.

These investments in sanitation infrastructure, and other early public health interventions such as the development of the first vaccines, were based on a simple premise. Industrialisation and urbanisation had brought with them growing wealth, but also a growing infectious disease burden that represented a clear threat to national health and prosperity. With inadequate healthcare infrastructure, and no means to effectively treat many infectious diseases in the pre-antimicrobials era, there was a critical need to address the disease burden through public investment and interventions to *prevent* illnesses and the spread of infections in the first place.

The development of this infrastructure, along with wider improvements in the quality of urban living conditions, yielded huge dividends in terms of population health. For instance, whilst cholera was once commonplace in the major cities of the west, and remains endemic in Southern Asia and many other low and middle-income countries today[2], progressive improvements in water quality and sanitation meant that there were no urban outbreaks in Western Europe after 1892. This infrastructure provided the foundation on which all subsequent improvements in how we manage and treat infectious diseases have been overlaid.

The lesson from history is clear: investment in improved water and sanitation infrastructure, particularly in urban areas, is an important part of industrialisation and economic development, and plays a crucial role in protecting populations from the burden of infectious diseases.

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1 Davies SC, Winpenny E, Ball S, et al., For debate: a new wave in public health improvement, *The Lancet*, 2014, 384, 9957, 1889-1895.

2 Nygren B L, Blackstock A J, Mintz E D. Cholera at the crossroads: the association between endemic cholera and national access to improved water sources and sanitation, *American Journal of Tropical Medicine and Hygiene*, 2014, 91(5), 1023-8.

LIFE EXPECTANCY IS LONGER WHERE THERE IS BETTER SANITATION

Controlling for income, increasing access to sanitation in a country by 50% is correlated with more than nine years of additional life expectancy.

Graph includes all countries with a GDP per capita of less than $25000 for which data was available, high-income countries were excluded as almost all have close to 100% sanitation rates. Sanitation and life expectancy data are from the World Health Organization, income data is from the World Bank and the calculations are the Review's own. Results are statistically significant at 1%, T-value-5.33, p-value- 0.000.

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Research we undertook based on publicly available data underlines the importance of access to water and sanitation for economic prosperity and health outcomes (see Appendix) Looking across nearly 170 countries, and controlling for national income and for expenditure on health services, an improvement in national access to sanitation by 50 percent is associated with a nearly nine and a half year increase in population life expectancy. When ranking countries according to their 'expected' levels of sanitation and life expectancy given their level of income, a stark trend becomes apparent: that those countries with much better sanitation infrastructure have better-than-expected life expectancy, and those with the worst access to sanitation compared to their income peers have the poorest life expectancy. More detail on this analysis can be found in the Appendix.

Although difficult to disentangle the complex factors that affect life expectancy, it is clear that for developing countries, the relationship between the quality of their water and sanitation infrastructure, and the overall health and wealth of their population, is a strong one.

> *"The lesson from history is clear: investment in improved water and sanitation infrastructure, particularly in urban areas, is an important part of industrialisation and economic development"*

Preventing the spread of TB, malaria, and HIV infections

TB, malaria and HIV are among the so-called 'diseases of the poor', those that disproportionately affect poor populations, and together accounted for nearly 18 percent of the disease burden in the poorest countries in 2002[3]. Poor hygiene standards and consequent malnutrition and poor health leave populations more vulnerable to these devastating diseases and effective infection prevention and control practices play an important role in reducing their spread.

In TB, inadequate living conditions (particularly overcrowding) play an important role in driving the continued airborne spread of the infection and increasing the probability of developing clinical disease. Other factors include poor ventilation, lack of access to clean water and adequate sanitation, all of which increase susceptibility to TB, especially among the poorest communities who also tend to lack access to basic healthcare. TB rates have been shown to be higher in urban than in rural areas, and this is attributed to higher populations and poor living conditions, which is common in urban settings[4]. Improvements in housing, sanitation and nutrition have been shown to play a role in reducing TB incidence, especially in England and Wales before the 1940s, when antibiotics and vaccines against TB were made available for the first time[5].

In 2015, there were 214 million cases of malaria in the world and 438,000 deaths. Around half the world's population remains at risk from the disease. Malaria has one of the clearest relationships with the environment in general, as the disease is spread through mosquitoes that breed in standing or uncovered water (in common with other mosquito-borne illnesses like dengue fever or Zika virus – diseases that themselves are also associated with stored domestic water supplies in settings where access to running water is inadequate.) Vector control strategies play a central role in reducing disease incidence, such as pesticide spraying and use of insecticidal bed-nets. There are, however, reports of emerging resistance to pesticide-based vector control measures; and at a community level, interventions such as the distribution of bed nets remain a cornerstone of the infection prevention strategy for malaria[6].

Finally, for HIV, infection control plays an important role in reducing opportunistic infections that are characteristic of the disease. People with HIV are more likely to contract water-related diseases such as diarrhoea, typhoid and skin diseases than healthy people, and these infections tend to take a greater toll on them[7]. For HIV treatment to be effective, access to clean and adequate amounts of water is crucial and women are particularly affected by inadequate access to safe water, sanitation and hygiene[8].

Preventing the spread of each of these diseases comes with its own challenges, but success in prevention advances the battle with the disease and drug resistance. It is clear that preventing the root cause of infections needs to form a central part of any holistic strategy to tackle them.

3 Stevens P., Diseases of poverty and the 10/90 gap, 2004, International Policy Network.

4 Lönnroth K, Jaramillo E, Williams BG, et al. Drivers of tuberculosis epidemics: The role of risk factors and social determinants, *Social Science and Medicine*, 2008, 68(12), 2240-6.

5 Schmidt CW, Linking TB and the Environment: An overlooked mitigation strategy, *Environmental Health Perspectives*, 2008, 116(11), A478–A485.

6 WHO, World Malaria Report 2015, World Health Organization, 2015, ISBN 978 92 4 156515 8.

7 StopAIDS, Factsheet: WASH and HIV, 2013, available at: http://stopaids.org.uk/wp-content/uploads/2013/08/STOPAIDS-WASH-and-HIV-factsheet-final.pdf.

8 USAID/Hygiene Improvement Project and WB/Water and Sanitation Programme, 2007, *Research and resources linking water, sanitation and hygiene with HIV/AIDS home-based care*.

Preventing infections by improving access to safe water and sanitation is key to beating rising drug resistance

The lack of investment in sanitation infrastructure in many countries is, of course, linked to very difficult economic and practical constraints. But attitudes towards large, government-led sanitation investment programmes have also been influenced by the widespread availability of effective antimicrobials as treatments: the emphasis has drifted away from disease prevention and control, towards treatment and cure.

This reliance on cures instead of prevention means there is over-use of medicines such as antibiotics, which in turn contributes to the development of antimicrobial resistance. Ultimately this will critically undermine these drugs' effectiveness everywhere as people and microbes travel – the impact will not be confined to those places with bad infrastructure.

This issue extends beyond the over-consumption of antibiotics, though. In areas where poor sanitation means that humans are more regularly exposed to faecal waste and bacterial infections, there is likely to be a continual and rapid 'recycling' of bacterial strains between humans and the surrounding environment, catalysing the development and transfer of drug resistance genes[9,10]. Improved infrastructure can easily break these cycles of transmission – by improving the quality of drinking water, reducing exposure to excreta, and providing better opportunities for handwashing.

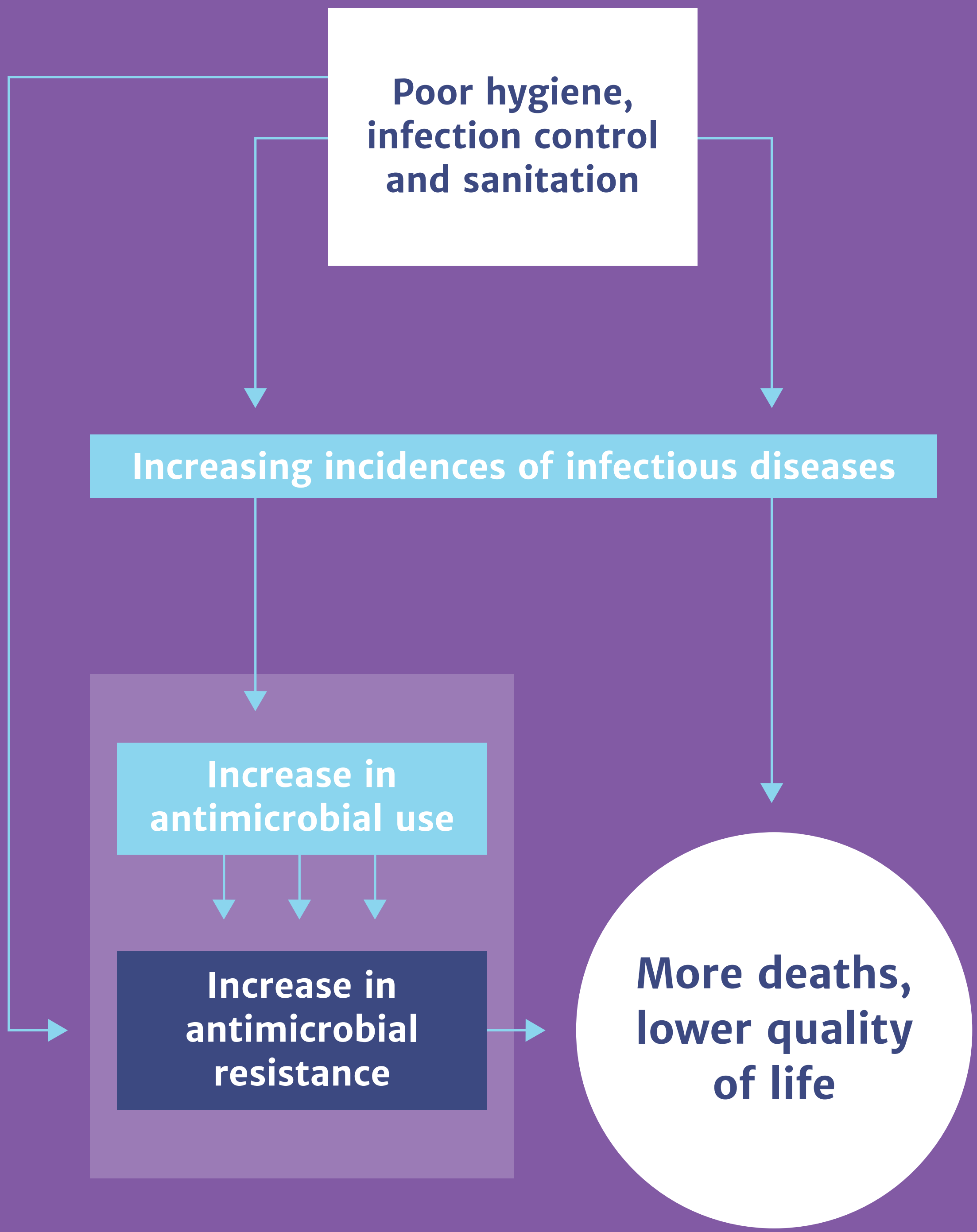
Investment in water and sanitation infrastructure needs to be a central component of a comprehensive global response to the problems of drug resistance.

“This reliance on cures instead of prevention means there is over-use of medicines such as antibiotics, which in turn contributes to the development of antimicrobial resistance”

9 Curtis, VA, Cairncross, S, Yonli, R, Domestic hygiene and diarrhoea, pinpointing the problem. *Tropical Medicine and International Health, 5*(1), 22-32.

10 Adremont A, Walsh TR, The Role of Sanitation in the development and spread of antimicrobial resistance, AMR and the Environment, *AMR Control*, 2015.

POOR INFECTION CONTROL CONTRIBUTES TO INCREASED RESISTANCE AND LOSS OF LIFE



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The example of diarrhoeal disease shows how better sanitation could substantially reduce global consumption of antibiotics

Diarrhoeal conditions claim 1.1 million lives in low and middle-income countries each year, and are the second most common cause of death amongst children under the age of five – as well as accounting for one death in nine in all children[11,12]. These conditions are the most common illnesses associated with water and sanitation infrastructure: nearly 60 percent of episodes of diarrhoeal illness can be attributed to poor sanitation and unsafe water[13], representing a sizeable proportion of the overall global burden of communicable disease.

The significant majority – 70 percent by some estimates[14] – of episodes of diarrhoeal illness are caused not by bacterial infections but by viruses, against which antibiotics are not active. Furthermore, in most adults the illness is self-limiting, and can be treated symptomatically (using oral rehydration therapy, for instance.) Despite this, we know that antibiotics are frequently used to treat the condition, either as an act of self-medication or with prescription from a clinical professional.

Having reviewed the literature available, we found that the relationship between water and sanitation infrastructure and the consumption of antibiotics has not been well quantified. We therefore commissioned analysis from a team of postgraduate research students at the London School of Economics (LSE) to look at the broad connections between i) access to improved water and sanitation infrastructure[15], ii) burden of diarrhoeal disease, and iii) consumption of antibiotics in four major emerging economies (India, Indonesia, Nigeria, and Brazil). These four countries were chosen to provide a simplified snapshot of the interrelation between sanitation, diarrhoeal disease and use of antibiotics across middle-income countries where industrialisation and population growth has often outstripped the pace of development of water and sanitation infrastructure.

Their analysis highlights the significant variations that exist in access to improved water and sanitation both across and within these countries, with rural areas, for instance, facing very different provision (and levels of access) compared to urban ones. In turn, these differing challenges and levels of existing infrastructure mean that the costs of achieving significantly improved – or near universal access – in these countries vary significantly.

The team began by finding existing data on the burden of diarrhoeal disease, and the extent to which this is currently attributable to inadequate water and sanitation infrastructure. They were then able to model the potential reduction in the disease burden that might be associated with widespread improvements in access to water and sanitation, and the consequent reduction in unnecessary antibiotic prescribing.

Their findings estimate that across these four countries, at least 494 million cases of diarrhoea are treated each year with antibiotics. With no improvement in sanitation infrastructure between now and 2030, this number can be expected to increase by more than a quarter to 622 million cases. In turn, their model suggested that the volume of antibiotics prescribed to treat diarrhoea caused by inadequate water supplies and sanitation could be reduced by as much as 60 percent if there were universal access to improved water and sanitation for these countries' populations.

Of course, the rationale for investing in water and sanitation need not be predicated on tackling the development of drug-resistant diseases: the societal benefits that these interventions bring are far wider in their scope. But this example of how sanitation exacerbates the use of antibiotics and the problems of AMR significantly bolsters the case for governments to invest in protecting the welfare of their populations in this way.

> *"Across these four countries, at least 494 million cases of diarrhoea are treated each year with antibiotics."*

11 Moran M, Guzman J, Chapman N, et al., *Neglected Disease Research and Development: The Public Divide*, G-Finder, 2013, Policy Cures.

12 Liu L, Johnson HL, Cousens S, et al., Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000, *Lancet*, 2012; 379(9832), 2151-61.

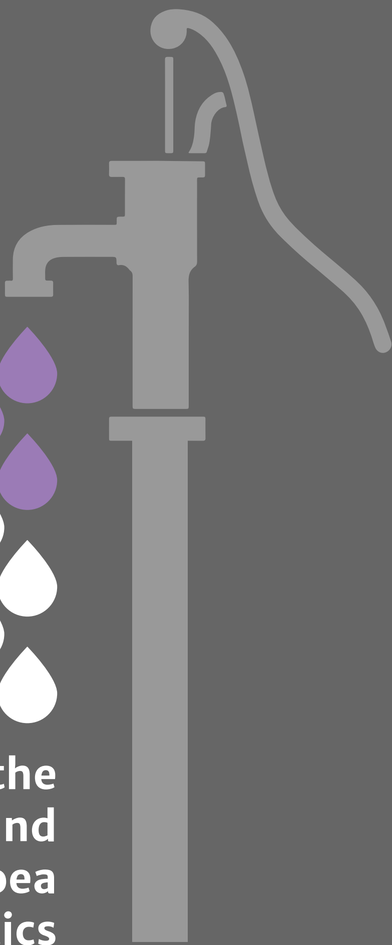
13 Tate JE, Burton AH, Boschi-Pinto C, et. al. Estimate of worldwide rotavirus-associated mortality in children younger than five years before the introduction of universal rotavirus vaccination programmes: A systematic review and meta-analysis, *The Lancet Infectious Diseases*, 2012; 12(2), 136–141.

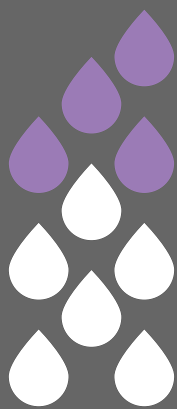
14 Cheng AC, McDonald JR, Thielman NM, Infectious Diarrhea in Developed and Developing Countries, *Journal of Clinical Gastroenterology*, 2005, 39 (9), 757-773.

15 For the purposes of this analysis, an 'improved' drinking-water source is defined as one that is adequately protected from outside contamination, particularly faecal matter. An 'improved' sanitation facility is one that hygienically separates excreta from human contact. These are based on WHO / UNICEF definitions.

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.





60%

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

Analysis commissioned by the Review.

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2.

GREATER FOCUS IS NEEDED ON INFECTION PREVENTION AND CONTROL IN HEALTH AND CARE SETTINGS

Failing to tackle infections in care settings comes at a high cost

In all parts of the world hospitals and other care settings (such as residential care homes for the elderly) represent high-risk territory for the development and spread of bacterial infections, including drug-resistant strains. Interventions that reduce the opportunities for infections to spread within health and care facilities therefore have significant potential not just to lower the burden of mortality and morbidity associated with such infections, but also to limit opportunities for drug-resistant strains to emerge.

The numbers of patients affected by healthcare-associated infections (HAIs – that is, infections that are contracted or manifest themselves whilst admitted to or resident in a care facility, sometimes also referred to as nosocomial infections) are surprisingly large. There are no perfect estimates but the World Health Organization (WHO) estimates that at least seven percent of all patients admitted to hospital in high-income countries will experience a nosocomial infection. This increases to one in three patients in intensive care units (ICUs), because of the high risks of infection associated with invasive ventilation[16].

In low and middle-income countries, the situation is far worse: according to the WHO at least 10 percent of all admitted patients in these settings will develop an HAI infection. Other studies have suggested much higher rates still, with the incidence of nosocomial infections in resource-constrained settings found to be three times higher than that in the US, for example[17].

The human cost of these infections is obvious: a patient who gets any type of HAI will face greater suffering and a higher mortality risk, and this is even worse where the infection is a drug-resistant strain. The mortality rate associated with methicillin-resistant *Staphylococcus aureus* (MRSA – an antibiotic-resistant 'superbug'), for instance, has been estimated to be about 50% higher than that for patients contracting methicillin-susceptible *Staphylococcus aureus* (MSSA – an infection that responds far more readily to antibiotic treatment)[18].

The financial costs are also great. Costs vary by health system, but in the US it is estimated that a case of ventilator-associated pneumonia will cost an additional 25,000 USD to treat; while a healthcare-associated bloodstream infection will cost an extra 23,000 USD. Outbreaks of drug-resistant infections within a hospital can be even costlier to manage: one hospital in the Netherlands that experienced an outbreak of vancomycin-resistant *Enterococcus* (VRE) in 2012 estimated that it cost more than 2.3 million USD to bring under control[19].

Given these figures, the financial case for organisations to invest in infection prevention and control (IPC) seems self-evident, especially since healthcare payers (such as governments or insurers) will not reimburse the vast majority of the excess costs. Furthermore, avoidable HAIs may expose healthcare providers to legal action by affected patients, and inflict significant reputational damage. From the perspective of the healthcare system as a whole, HAIs result in wasted resources and inefficient utilisation of scarce capacity in hospitals and other care facilities.

Yet this investment case is often not so clear cut, as cost savings may be difficult to calculate at an operational level – particularly where they do not manifest themselves in a tangible way, or are subject to 'siloed' budgets within and across organisations. Therefore, even though good IPC practice has the potential to avert significant extra expenditure, it will always be liable to be seen as a cost-increasing activity, rather than something that directly raises (or protects) revenue for an organisation.

> *"At least seven percent of all patients admitted to hospital in high-income countries will experience a nosocomial infection"*

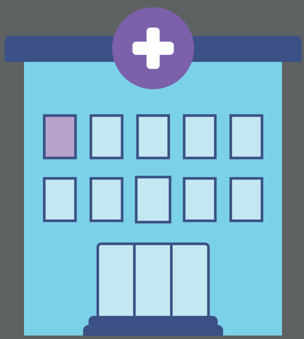
16 WHO, Report on the Burden of Endemic Health care-Associated Infection worldwide, 2011, ISBN 978 92 4 150150 7.

17 Allegranzi B, Bagheri Nejad S, Combescure C, et al., Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis, *Lancet*, 2011, 377(9761):228-41.

18 Hanberger H, Walther S, Leone M, Barie PS, Rello J, Lipman J, et al. Increased mortality associated with methicillin-resistant Staphylococcus aureus (MRSA) infection in the intensive care unit: results from the EPIC II study. *International Journal of Antimicrobial Agents*, 2011, 38(4), 331-5.

19 AMR Next – One Health Ministerial Conference in the Netherlands, 2016. Outbreak control vs Outbreak Prevention. Available at http://english.eu2016.nl/documents/publications/2016/02/10/amr-next, accessed March 2016.

HEALTHCARE-ASSOCIATED INFECTIONS ARE A CONCERN IN ALL COUNTRIES

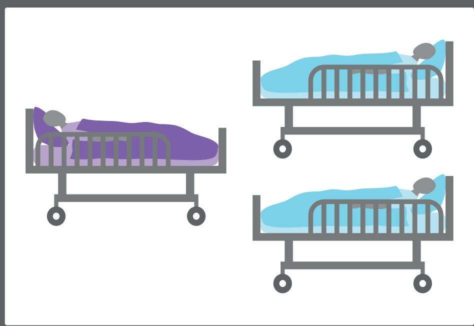


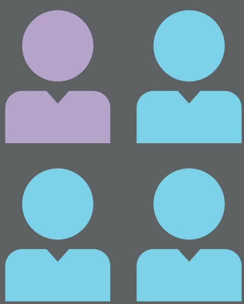
7 to 10%

Of every 100 hospitalised patients, 7 in high-income and 10 in low and middle-income countries, will acquire at least one healthcare-associated infection.

1 in 3

A third of patients in intensive care units (ICUs) in high-income countries are affected by at least 1 healthcare-associated infection.





1 in 4

A quarter of healthcare-associated infections in long-term acute care settings are caused by antibiotic-resistant bacteria.

Sources: WHO Healthcare-Associated Infections, Fact Sheet, 2014, WHO, The Burden of Health Care-Associated Infection Worldwide: A Summary, 2010, and CDC, Vital Signs Report, March 2016.

Investment in infection prevention and control as a public good

In common with so many other areas of AMR that we have looked at, there are issues of so-called 'externalities' at play in how individual healthcare providers approach IPC. The risk that an individual provider faces from drug-resistant HAIs will be influenced by the standards in other providers with whom they share a patient population; and in turn, the effects of their own good or bad practice will be felt by other organisations locally.

For instance, some of the burden of poor IPC practice in a given hospital will be felt in the nursing homes or rehabilitation facilities to which it discharges its patients; and conversely, a hospital will face the challenge of dealing with patients admitted carrying drug-resistant bacteria like MRSA as a result of poor practice in surrounding care homes.

Seen through the eyes of an economist, this represents a classic 'free-rider' problem: since no single provider enjoys the full benefits of its own investment in IPC, and yet can reap the benefit of others', individual hospitals will be liable to act 'selfishly' and invest less than would be socially optimal in their own IPC programmes[20].

If this free-rider problem is overcome, though, and greater cooperation and coordination between different providers in an area is achieved, there can be significant benefits in terms of patient outcomes[21]. For example, the US Centers for Disease Control and Prevention (CDC) undertook modelling in 2015 of a nosocomial outbreak of one particularly hard-to-treat type of superbug, Carbapenem-resistant Enterobacteriaceae (CRE), within a network of 10 hospitals. They found that this would affect 80 percent fewer patients if all organisations in the network implemented IPC best practice, cooperated, and shared information, compared to the more common approach of working within organisational siloes[22].

Healthcare-associated infections foster drug resistance

It is difficult to predict the emergence of individual drug-resistant pathogens but the overall trajectory of rising drug resistance is clear. New strains of resistant pathogens present new and unforeseen threats as HAIs, that may be harder to treat than those infections that currently represent the greatest concern in care settings.

Not all HAIs are drug-resistant strains of infection; and not all drug-resistant infections of the greatest concern represent a particular control challenge in care settings. But nonetheless, the issues of preventing and controlling infections are intrinsically linked with wider issues associated with the use of antibiotics and the development and spread of drug resistance. Moreover, the relationship is a symbiotic one, since poor IPC practices will speed the pace at which new drug-resistant infections of concern emerge. A failure to control infections in care settings provides greater opportunities for resistance to emerge, while high incidence of infection results in increased demand for antibiotics – again, a catalyst to rising drug resistance.

“Issues of preventing and controlling infections are intrinsically linked with wider issues associated with the use of antibiotics and the development and spread of drug resistance”

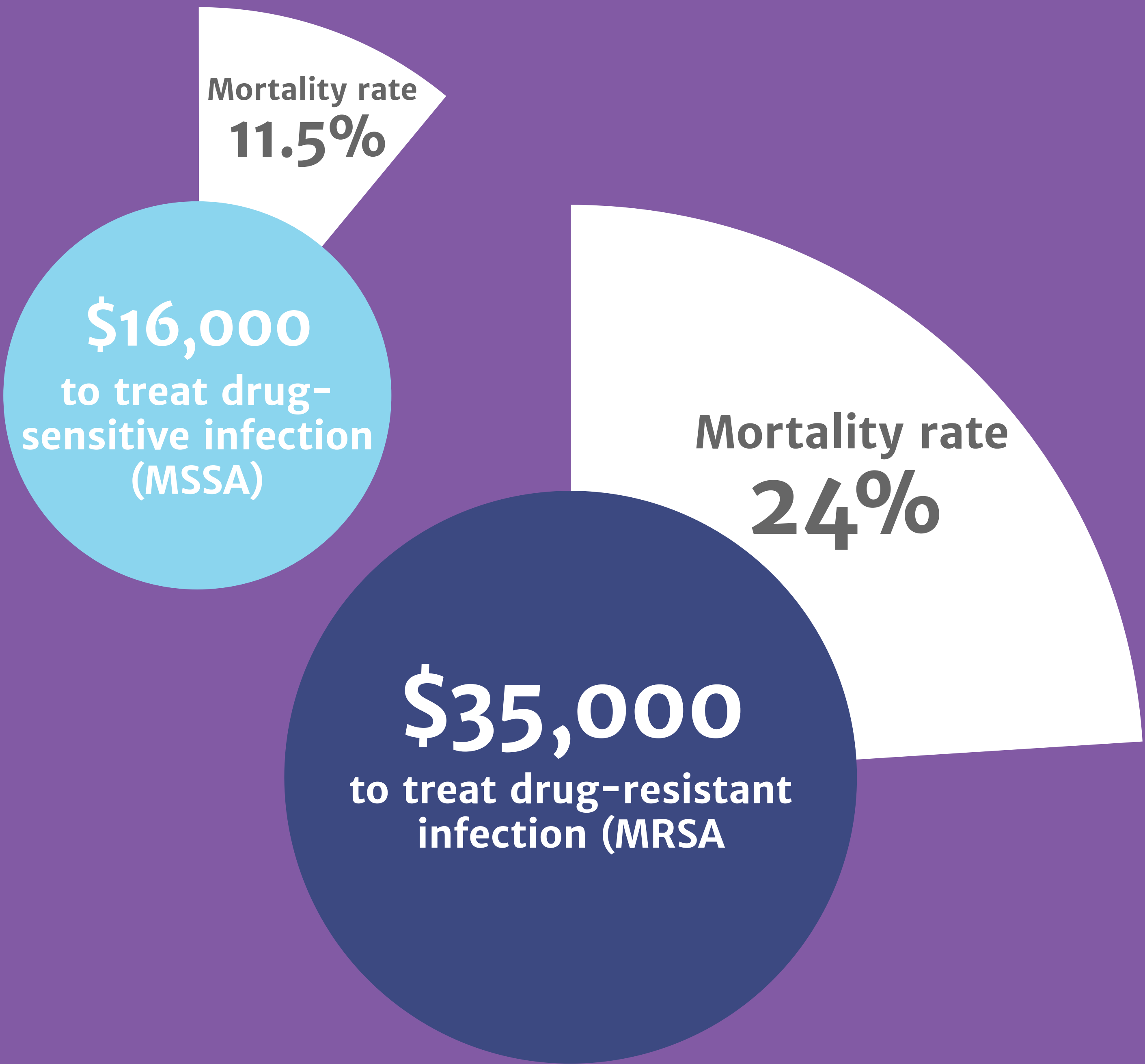
20 Smith DL, Levin SA, Laxminarayan R, Strategic interactions in multi-institutional epidemics of antibiotic resistance. *Proceedings of the National Academy of Science* 2005, 102(8),3153-8.

21 Kaye KS, Engemann JJ, Fulmer EM, Clark CC, Noga EM, Sexton DJ, Favourable impact of an infection control network on nosocomial infection rates in community hospitals. *Infection Control and Hospital Epidemiology* 2006, 27(3), 228-232.

22 CDC Vital Signs, August 2015. Available at http://www.cdc.gov/vitalsigns/stop-spread/infographic.html#infographic2, accessed March 2016.

RESISTANT INFECTIONS LEAD TO HIGHER DEATH RATES AND ARE MORE EXPENSIVE TO TREAT

A study in the US in 2010 found that infections caused by the superbug methicillin-resistant *Staphylococcus aureus* (MRSA) were more than twice as expensive to treat as infection caused by the easier-to-treat methicillin-sensitive *Staphylococcus aureus* (MSSA)



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

Review on Antimicrobial Resistance

Three steps to strengthen infection prevention and control

Many of the issues associated with IPC are more technically and scientifically complex than we could substantively address in this paper. However, we see three broad areas where action is needed to strengthen the way in which IPC is approached by governments and policymakers around the world.

1.

Healthcare system leaders must prioritise infection prevention and control: doing so has delivered results in the past

Where governments, regulators, insurers, or other health system leaders have focussed on reducing healthcare-associated infections, the results have often been stark. In the UK, for instance, growing concern about high and rising rates of MRSA and *Clostridium difficile* during the 2000s led to ministers establishing ambitious reduction targets amongst NHS providers, for which hospital chief executives would be held personally accountable. This approach was underpinned by wider efforts to implement mandatory surveillance and public reporting of key HAIs[23]. Around the same time, similar high profile top-down initiatives were launched in countries such as the Netherlands, and by the Centers for Medicare and Medicaid Services in the US.

In the cases of MRSA and *C. difficile*, the effects of their prioritisation were pronounced. In the NHS in England, the introduction of national MRSA reduction targets was associated with a 56% decline in cases over a four-year period between 2004-8, with continued significant reductions in the following years[24] (although there has been an increase in reported cases in the past 12 months). In the US, since 2008 the CDC has recorded a 50% reduction in bloodstream infections, and a 17% reduction in surgical site infections associated with 10 common procedures[25].

These initiatives and others like them have been analysed at length. Improvement targets are sometimes criticised as being arbitrary, and the sanctions applied to them as punitive or heavy-handed. Another criticism is that the highest profile initiatives are often narrowly focussed on certain issues (such as MRSA and *C. difficile*) to the exclusion of other types of infection which may be as concerning but are less widely recognised as such. Similarly, performance targets (and the surveillance networks that underpin them) have most commonly focussed upon bloodstream infections generally, sometimes at the expense of robust surveillance of infections caused by specific procedures[26].

Despite these shortcomings, the overall lesson is clear: significant change can be achieved where there is a stated political, regulatory or financial imperative applied to reducing HAIs. Governments, regulators and other health system 'stewards' should therefore continue to take leadership on this important topic, as part of an approach that establishes IPC as a priority as part of wider patient safety and AMR strategies. Such national programmes need to be broader in their scope, encompassing a wider range of types and sources of infection. The embedding of collaboration across all parts of a local health economy is also crucial, recognising the critical interdependencies between hospitals and other parts of health and community care.

> *"The overall lesson is clear: significant change can be achieved where there is a stated political, regulatory or financial imperative applied to reducing HAIs"*

2.

Modest funding for targeted studies could demonstrate the efficacy and cost-effectiveness of interventions to improve infection prevention and control

Enough is already known from experiences of successful national HAI-reduction programmes to give policymakers a clear picture of how to guide and promote a system-wide prioritisation of better IPC. Lessons can be learned from the successes and shortcomings of past initiatives.

However, evidence gaps remain, the result of either the way in which national IPC initiatives have been administered in the past, or of inherent difficulties with doing trials in this field. This means that we often lack a granular picture of what works at an operational level.

Major IPC programmes have usually been multi-pronged, incorporating multiple measures such as improved cleaning,

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23 Johnson AP, Davies J, Guy R, et al. A. Mandatory surveillance of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia in England: the first 10 years, *Journal of Antimicrobial Chemotherapy*, 2012, 67, 802-809.

24 Pearson A, Chronias A, Murray M, Voluntary and mandatory surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteraemia in England, *Journal of Antimicrobial Chemotherapy* 2009;64.

25 Centres for Disease Control, *Healthcare Associated Infections* (HAIs) Progress Report, US CDC, Atlanta, 2016.

26 Millar M, Coast J, Achcroft R, Are meticillin-resistant *Staphylococcus aureus* bloodstream infection targets fair to those with other types of healthcare-associated infections? *Journal of Hospital Infection*, 2008, 69, 1-5.

27 Pittet D, Allegranzi B, Sax H, Dharan S, Pessoa-Silva C L, Donaldson L, et al. Evidence-based model for hand transmission during patient care and the role of

patient screening, more rigorous antibiotic stewardship, and better hand hygiene. This approach is desirable, but has meant that it is hard to evaluate the effectiveness of individual interventions because the effect of one cannot be isolated from the others.

There are further problems with the assessment of novel technologies and approaches that may yield improvements in IPC in care settings – for example, new technology to allow for the automated cleaning and decontamination of healthcare facilities. It is challenging to assess these new technologies in busy working hospital environments, and there are fundamental gaps in how operational trials would be financed. Access to public research funding for such technology is often limited, whilst trials of new products funded by their own manufacturers may be perceived to lack credibility.

These issues mean that we do not understand well enough the efficacy of individual interventions. The same applies to demonstrating whether an intervention reduces costs and whether it is more or less cost-effective than another approach.

To support improvements in IPC practice, modest funding for objective studies would go a long way to establish which approaches work best, and what the true potential of new technologies might be.

> *"Modest funding for objective studies would go a long way to establish which approaches work best"*

3.

Even simple, proven steps like hand washing or following checklists do not always happen in practice – we should understand why and change behaviours

Hand hygiene by clinicians, for instance, is often regarded as the single most important IPC intervention in a hospital setting: by washing hands before and after patient contact, doctors, nurses and other carers can break a common chain of transmission from patient to patient, and prevent exposure to pathogens brought in from outside[27].

Yet when faced with the day-to-day reality and pressures of providing patient care – something that could require doctors, nurses and other carers to clean their hands dozens of times a-day – a gap emerges between intended and true behaviour.

In places where hand hygiene compliance by clinicians is established as a target or performance indicator, very high rates of adherence (sometimes 90 percent or more) will frequently be reported. However, figures of this type could be obtained through open observation (and therefore liable to be skewed as a result), or influenced by the very existence of a performance target. More reliable and systematic observations place actual typical rates of hand hygiene compliance by hospital clinicians as low as 30-40 percent, and consistently lower amongst doctors than nursing staff[28].

With actual adherence to something as straightforward and as powerful as hand hygiene so imperfect, we need to consider how our growing understanding of human behaviour can improve how things are done. There is significant potential for the ideas of behavioural economics to be applied to this – that is, developing an in-depth understanding of how and why our innate behaviour traits so often subconsciously encourage us to take shortcuts that bypass hand hygiene best practice, and in turn considering how the physical environment and training can be adjusted to correct such tendencies.

Although these principles of designing 'nudges' towards better behaviour is increasingly of interest to academics and policymakers, it is a science that has so far been applied to IPC and hand hygiene only on a very limited basis[29] – despite these things having human behaviour at their heart[30]. Research in this area has the potential to deliver simple, low-cost, but highly effective ways of improving adherence to what is already accepted good practice in hospital settings in countries at all income levels.

In just one example, the use of basic visual or even smell-based prompts, designed to subconsciously 'prime' individuals to wash their hands or use alcohol hand gels, could be a simple but important way to promote better hand hygiene. Demonstrating this potential, one study found that placing a picture of male eyes above a hand gel dispenser, or piping a 'clean' smell into the entrance to a hospital ward, improved adherence to good hand hygiene practice amongst staff and visitors by factors of two and three, respectively[31].

improved practices. *Lancet Infectious Diseases* 2006, 6(10), 641-652.

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

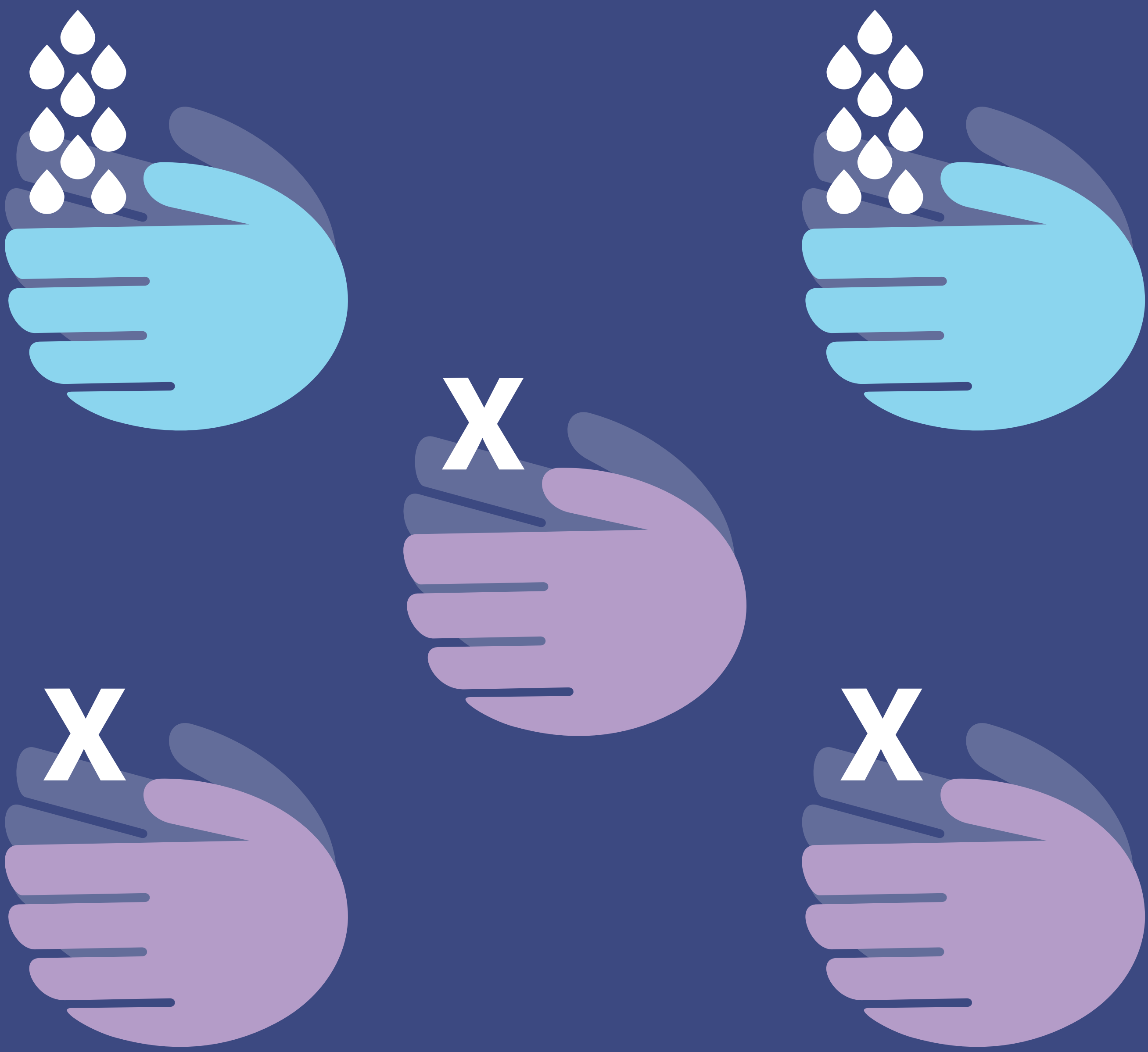
29 Vlaev I, King D, Dolan P, Darzi A, Theory and practice of 'nudging': changing health behaviors. *Public Administration Review*, 2016 (forthcoming)

30 Dyson J, Lawton R, Jackson C, Cheater F, Development of a theory-based instrument to identify barriers and levers to best hand hygiene practice among health care practitioners. *Implementation Science* 2013, 8, 111.

31 King D, Vlaev I, Everett-Thomas R, Fitzpatrick M, Darzi A, Birnbach D J, "Priming" hand hygiene in clinical environments. *Health Psychology*, 2016, 35(1), 96-101.

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%.



Source: Eramus V, Daha TJ, Brug H, et al., Systematic review of studies on compliance with hand hygiene guidelines in hospital care, *Infection Control and Hospital Epidemiology*, 2010, 31(3), 283-294.

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> *Top-down target setting can be no substitute for strong, empowered leadership at the front line*

Similarly, when undertaking surgical procedures, 'aseptic procedure' (i.e. the steps that must be taken by the surgeon and their team to reduce the risks of infection) is generally well-established, and yet surgical site infections remain a considerable concern. The use of checklists, though, has the potential to significantly reduce the chances that any of these important steps will be missed out.

Ultimately, to embed better practices within any organisation requires effective internal leadership and professional ownership. We have highlighted previously[32] the extent to which infectious diseases is an under-valued specialty amongst doctors, giving as an example the fact that it is the lowest paid medical specialty in US hospitals. IPC issues (like microbiology and aspects of AMR more broadly) are afforded only limited coverage in general training curriculums for doctors and nurses.

Similar trends, regrettably, apply to specialists working in IPC. It is often the case that the person responsible for IPC in an organisation such as a hospital is a relatively junior member of staff; and there are limited formal standards for training and accreditation.

It is thus easy to see that individuals responsible for overseeing and improving IPC may lack the influence necessary to guide budget and procurement decisions, or to change engrained practices and shift priorities across multiple clinical disciplines. Top-down target setting can be no substitute for strong, empowered leadership at the front line.

32 Review on AMR, Tackling a global health crisis: Initial Steps, 2015.

3.

IT IS VITAL THAT WE IMPROVE THE GLOBAL SURVEILLANCE OF DRUG-RESISTANT INFECTIONS

If we cannot measure the development and spread of drug resistance, we cannot manage it

Much like the importance of good infection control, the notion that it is vital to track and analyse the spread of a disease is nothing new, having first been demonstrated by the work of pioneers like John Snow and Florence Nightingale in the 19th century. More recently, the Ebola crisis in West Africa showed us how critical surveillance is for managing the spread of an epidemic. However, it also revealed the alarming gaps in global and regional surveillance capabilities and their coordination, even where such things are in theory mandated by international regulations.

In the case of AMR, too, there are startling gaps in how we identify and then track the emergence and spread of drug-resistant strains – and if this cannot be adequately measured, it cannot be adequately managed. Even in some of the world's most developed health systems, AMR surveillance data is often patchy and retrospective – virtually none is 'real time'. Without effective monitoring, we will lack early warning of emerging patterns of drug resistance, and lack the insights needed to guide and evaluate our response.

In the specific context of monitoring drug-resistant infections, there are two key strands of data needed, both of which should be gathered in parallel. One is monitoring the number or percentage of infections (or 'isolates' – i.e. analysed specimens from patients with a known infection) in a region that are resistant to given drugs. The other is monitoring antimicrobial consumption, so that we understand the link between antimicrobial use and the development of resistance, and so that we can measure performance against antimicrobial stewardship objectives.

Surveillance of drug resistance is far from straightforward, though. The unpredictable nature of resistance, along with the wide variety of 'drug and bug' combinations and their many manifestations, mean that it requires the tracking of multiple moving targets. The most successful global disease surveillance programmes established thus far have been focussed upon so-called 'vertical' disease control programmes, such as gonorrhoea infections, HIV, TB and malaria, monitoring one particular disease. Such programmes are still inherently challenging (particularly where the patient population is large and resources constrained), but are made comparatively simpler by the singular nature of the surveillance target.

> *There are startling gaps in how we identify and then track the emergence and spread of drug-resistant strains*

Better surveillance delivers benefits at all levels – but these are often under-valued

The surveillance of drug-resistant pathogens is useful at three levels, described below. These benefits would be felt globally, but the most important aspect of surveillance is that the data can inform local policy and clinical practice, to the direct benefit of patient outcomes.

- **Improved patient health**
  Data from surveillance of drug resistance would be used to inform treatment decisions in a way that will directly benefit patient health. For instance, if data were to reveal abnormally high rates of infections caused by bacteria resistant to a particular antibiotic in an area, then clinicians there could change their prescribing behaviour accordingly – benefitting the patient directly and improving antibiotic stewardship.

- **Inform public health policies and standards**
  At a national level, richer AMR surveillance data would inform policymakers in designing policies for responding to the challenges of drug resistance.

- **Enhance our understanding of resistance**
  Systematically collecting better data on AMR, over long periods and across human and animal health, will enable us to deepen our understanding of the epidemiology and transmission of resistance. As well as supporting the efforts of public health authorities, this will inform the work of researchers and innovators involved in the development of new drugs and other products to counter the AMR threat.

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

Yet despite these benefits, the level of investment and funding for surveillance falls far short of what is needed. For public funders, the difficulty of quantifying these benefits (particularly over the short-term), and the large costs associated with both the set-up and maintenance of networks, mean that it is often hard to make the economic case for investment.

The benefits delivered by surveillance systems are widely dispersed and the global, societal benefits of surveillance are far larger than the benefits to any individual or single country – another instance of 'positive externalities'. As with any such 'public good', in the absence of government intervention or support, there is likely to be under-provision, as most beneficiaries are unwilling to pay for, or do not perceive, the wider benefits to others.

> *"The level of investment and funding for surveillance falls far short of what is needed"*

Global surveillance of AMR has begun to improve – but there is a great deal more to do

At present, there is no integrated global system for the surveillance of resistance and antibiotic consumption in humans. However, there are a number of initiatives coming to the fore that will deliver significant incremental improvements and will help to demonstrate what can be achieved.

Internationally, efforts from organisations such as the WHO developing Global Action Plans, to combat AMR, will play a very important role. The Global Antimicrobial Surveillance System (GLASS) being proposed by the WHO as part of its Global Action Plan (GAP) on AMR is an encouraging step in the direction of a global network for surveillance of drug resistance. This builds on joint commitments from the WHO and its partner bodies the Food and Agriculture Organisation (FAO) and World Organisation for Animal Health (OIE) to support integrated surveillance programmes across human and animal health[35]. The 375 million USD Fleming Fund, announced by the UK Government last year – and a response to some of our earliest recommendations on the need to improve global AMR surveillance[36] – is also a very positive step, as are the surveillance-focussed strands of

Surveillance in animals and the environment

AMR is not an issue that just affects humans. As discussed in our December 2015 paper, ***Antimicrobials in agriculture and the environment: Reducing unnecessary use and waste***, use of antimicrobials in animals has been correlated with an increase in resistance rates, and the irresponsible dumping into the environment of active pharmaceutical ingredients (APIs) during the manufacture of antimicrobials has serious implications for both human and animal health.

This was driven home with the recent discovery of transferable resistance to colistin (a last-resort antibiotic) in bacteria from animals, which was subsequently found in humans – first in China but then in many countries across the world, including Denmark and the UK[33].

Surveillance of AMR, as well as use of antimicrobials in animals and in the environment, is therefore crucial to gain a complete picture of resistance patterns. Yet there are even fewer systems for surveillance of antibiotic resistance and consumption amongst animals than amongst humans. Of the 180 member countries of the OIE, more than 110 lack either the systems or the relevant legislation to monitor and cover the use of antimicrobial products[34]. There is also no global or centralised system of surveillance to monitor resistance trends.

Systematic surveillance of issues of drug resistance in the environment – industrial pollution using antibiotic APIs, for instance – appears to be practically non-existent, with data on levels of antimicrobials coming from limited numbers of small, isolated studies rather than through routine surveillance systems.

33 Liu Y, Wang Y, Walsh TR, et al., Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases*, 2016, 16, 161–68, Published Online, doi: 10.1016/S1473-3099(15)00424-7.

34 World Organisation for Animal Health, Towards better surveillance of antibiotic use in animal health, Webpage, Online, Available at: http://www.oie.int/for-the-media/press-releases/detail/article/towards-better-surveillance-of-antibiotic-use-in-animal-health/

35 Acar JF, Moulin G, Integrating animal health surveillance and food safety: the issue of antimicrobial resistance, 2013, *Scientific and Technical Review of the Office International des Epizooties (Paris)*, 32 (2), 383-392.

36 Review on AMR, Tackling a global health crisis: initial steps, 2014.

the US-led Global Health Security Agenda (GHSA). Both have important roles to play in providing financial and technical support for building laboratory and surveillance capacity in low and middle-income countries.

Regional and national networks, especially in high-income countries (such as the National Antimicrobial Resistance Monitoring System (NARMS) in the US, and EARS-Net and ESAC-Net in Europe) currently form the backbone of what multinational surveillance there is. However, there is currently no centralised coordination of these networks, and many suffer from gaps and delays in the data that they gather.

In developing countries the needs for investment and coordination are even greater. Philanthropic organisations have only recently launched interventions that will need to be sustained and supported, such as the Institut Pasteur's BIRDY[37] project and the Bill and Melinda Gates Foundation's CHAMPS network[38]. Both rightly focus on child and maternal health surveillance, which are the necessary foundation for good health outcomes.

Conventional, largely laboratory-based infrastructure is increasingly supplemented by informal or non-traditional surveillance systems. Initiatives such as the Boston-based HealthMap (for infectious diseases generally), and the Center for Disease Dynamics, Economics & Policy (CDDEP) ResistanceMap (for antimicrobial consumption and resistance), gather information from non-clinical sources such as news and social media, or act as aggregators of data from public and private laboratory networks.

Systems using mobile phone technology and SMS messaging are also already being used in some areas – to provide real-time data on influenza-like illnesses in Madagascar[39], for instance, and during the Ebola epidemic in West Africa to report symptoms in people who had come into contact with the virus[40]. Even if such technologies are ultimately no substitute for, laboratory-based surveillance infrastructure, they can play an important role in filling gaps in data collection and analysis, and should be expanded to play a supporting role to national disease surveillance efforts.

These areas of progress are individually important and collectively encouraging. However, too many gaps still remain in our global monitoring and understanding of the current and emergent impact of drug resistance.

This needs to be fundamentally improved if the world is to respond effectively to the global challenge of AMR – but significant barriers must be overcome.

> *"The 375 million USD Fleming Fund, announced by the UK Government last year – and a response to some of our earliest recommendations on the need to improve global AMR surveillance – is a very positive step"*

We need to take action on three fronts to help the development of better global surveillance structures

There are several potential reasons for the gaps in our global surveillance of drug-resistant infections, beginning with a lack of awareness of its importance, to a lack of financial, infrastructural and personnel resources, and extending to technical, legal and ethical barriers that often stand in the way of the sharing of data.

To this end, we see three main areas where action could be taken to help improve our current surveillance systems and lay the ground for new and innovative additions.

1.

The development of globally integrated systems of surveillance needs to be better funded and better coordinated – but steps to incrementally improve our monitoring of AMR should not wait for this work to be complete

The establishment of comprehensive surveillance systems and networks will take time, especially in those resource-poor settings where infrastructure will need to be developed from scratch and personnel trained. Global leadership of this process is badly needed, whether that be from international bodies such as the WHO or from non-government organisations with a global reach like Institut Pasteur, the Wellcome Trust or the Bill and Melinda Gates Foundation. It does, of course, also need to be adequately funded – requirements that we plan to address in more detail in our final report.

37 BIRDY project website, Available at: http://www.birdyprogram.org/home.html, Accessed on: 16th March 2016.

38 Bill and Melinda Gates Foundation website, Press release, Available at: http://www.gatesfoundation.org/Media-Center/Press-Releases/2015/05/Child-Health-and-Mortality-Prevention-Surveillance-Network, Accessed on: 16th March 2016.

39 Rajatonirina S, Heraud J, Randrianasolo L et al., Short message service sentinel surveillance of influenza-like illness in Madagascar, 2008–2012, ***Bulletin of the World Health Organization*** 2012;90:385-389.

40 Tracey LE, Regan AK, Armstrong PK, et.al, Ebolatracks: an automated SMS system for monitoring persons potentially exposed to Ebola virus disease, 2015, ***Eurosurveillance***, Volume 20, Issue 1.

Transformation on the scale that is required will be a long-term process, but we need to begin collecting and analysing more and better data immediately. Analysis that can be done quickly but which is limited in scope, such as point-prevalence studies, have a role to play in enriching our often patchy understanding of drug resistance today, particularly in those places where there is presently complete absence of any sort of surveillance data.

The rapid development and movement of resistance, as evidenced recently through the discovery of colistin resistance in animals and humans, shows that there is an immediacy in the need to collect data and understand what it shows. An integrated, global surveillance network to monitor drug resistance is an important long-term goal – but there is a pressing need to plug the gaps in our knowledge that exist today.

2.

Problems with the consistency of data and how it can be shared are only going to become more complex, so they must be addressed now

Even where AMR surveillance structures are established at a national or regional level, a recurring issue is a lack of common standards for data collection and dissemination. Inevitably, data about the spread and impact of infections – whether at an aggregated or patient level – is wrapped in sensitivities about patient confidentiality and perceived negative connotations around what such data shows. As more and more countries develop their surveillance systems, and new and alternative sources of surveillance data come to prominence, the issue of sharing data will become more important yet more problematic. There is thus a need to address these issues as soon as possible, so that seamless sharing of data across countries and regions can become a reality.

For example, we have written before about the transformative potential of next-generation rapid diagnostics in changing the way that infections are diagnosed and antibiotics prescribed[41]. The use of these devices could amount to a revolution for surveillance, too. New diagnostic devices could provide valuable information on the source of the infection as well as its drug resistance pattern, from the bedside of the patient or in the clinic: properly aggregated, this data could provide rich, truly real-time data on patterns of illness and drug resistance on an unprecedented scale. With the 'internet of things', artificial intelligence and cloud computing poised to revolutionise so many other areas of medical and consumer technology, we should be thinking today about how these platforms can also transform infectious disease surveillance tomorrow[42].

Yet this information revolution is not without its challenges. Policymakers and health professionals need to consider now how the issues around data ownership, quality and security associated with this paradigm shift can be addressed in a way that allows the potential of the revolution to be realised.

In particular, there will need to be international consensus to address some key issues in the area of data sharing and privacy. There needs to be agreement on data collection protocols and also methods of data sharing to allow seamless sharing between private and public partners as well as transfer between countries, so that the benefits of surveillance systems can be felt the world over. The work already being done by the WHO[43] on these technical issues is very welcome, but deeper, long-term engagement from clinicians, industry and governments will be needed if these challenges are to be properly overcome.

> *"As more and more countries develop their surveillance systems, and new and alternative sources of surveillance data come to prominence, the issue of sharing data will become more important yet more problematic"*

41 Review on AMR, Rapid Diagnostics: Stopping unnecessary use of antimicrobials, 2015.

42 Groves P, Kayyali B, Knott D, et.al., The 'big data' revolution in healthcare, 2013, Centre for US Health System Reform, Business Technology Office, McKinsey & Company.

43 World Health Organization, Global Antimicrobial Resistance Surveillance System: Manual for early Implementation, 2015.

3.

We should examine the regulation and incentivisation of private players to ensure that where they hold valuable data, they can and do enter the field of surveillance

Data that is already being collected by private actors, such as private laboratories and hospitals in many middle-income countries, present a rich potential source of information that could also be used to fill in gaps or as a starting point for wider data collection. In some cases, typically those middle and low-income countries where private sector health facilities are better developed than government-administered ones, this data may be the best or only type that is currently available. Beyond data gathered by hospital providers, pharmaceutical companies themselves may also be a source of valuable information on drug resistance, through company representatives on the ground who can have valuable insight on emerging resistance patterns through changing demand for different antibiotics.

Such privately-held data should routinely become part of national and global AMR surveillance systems – something that is far from commonplace at present – as this will only serve to provide a larger sample and more accurate picture of the true state of affairs. However, there are often significant challenges to making use of this, and misaligned incentives that discourage companies from sharing information with public bodies nationally or internationally.

This, and the growth in the range of devices and systems generating surveillance data described above, raise challenging questions about the ownership, and value of, data that could contribute to the global surveillance picture. The questions of intellectual property alone are difficult and complex, particularly when the possibility of global sharing of this data arises. There are thus manifest risks that the opportunity to use this data for the public good could be missed as a result of commercial or technical barriers that discourage companies who hold the data from sharing it with public health authorities.

It is likely that national and international regulation will be required to overcome barriers to sharing of this data, helping to make it available to public health agencies who can act on it. Such regulation may play a role either as an enabling force, to remove practical or statutory barriers to sharing, or as an enforcement mechanism where no other option exists.

As well as exploring regulation, though, we should consider that the data generated by rapid diagnostics may itself have a value – something that could offer substantial opportunities. As we set out in our report on the market for rapid diagnostics, the development and uptake of these products is stymied by a similar set of market failures, arising from the public good nature of their use. Both this set of market failures, and those that inhibit the sharing of data for the benefit of disease surveillance, might be overcome by attaching value to the data that diagnostic products generate – creating a market pull for private companies to act more clearly in the public interest.

“*Privately-held data should routinely become part of national and global AMR surveillance systems – something that is far from commonplace at present*”

4.

NEXT STEPS

This is the seventh and last in the series of interim reports published by our Review, each of which has focussed on a particular aspect of the problem of drug resistance.

Our propositions in this report are not controversial, nor are they radically new: it has been accepted for well over a century that preventing the transmission of infectious diseases, and monitoring it where it does occur, are both cornerstones of disease management. It is clear that both of these have an important part to play in our response to the global challenges of AMR, by tackling the root causes of infections so as to significantly reduce our demand for antibiotics, and improve our capability to understand and react to the development of the drug resistance threat. Investments to improve how we prevent, control, and monitor the emergence and global spread of drug resistance are some of the most effective we can make.

However, despite the clear benefits that both a preventive focus and improved surveillance capabilities can bring, they are too frequently neglected, leaving us badly weakened.

There are, though, causes for optimism here. In India, for instance, Prime Minister Modi's *Swachh Bharat Abhiyan* ('Clean India Mission') programme is an important step in the right direction, and demonstrates the role of high-level political support for addressing the significant challenges of reducing the community spread of infections in today's rapidly-growing emerging economies. In hospitals and other care settings, our growing understanding of human behaviour offers real potential to change our approaches to ensuring adherence to simple but powerful preventive interventions like handwashing. And in addressing the chronic gaps in our global surveillance of drug resistance, individual initiatives are beginning to make headway, whilst the next phase of the information revolution presents huge promise.

Much more remains to be done across all of these fronts, though – and this requires a change in attitudes to focus on prevention as much as it requires investment in infrastructure or the development of global surveillance capabilities.

Moving towards action

Later this spring, we will deliver to the UK Prime Minister our final report and recommendations for action by the wider global community. This will set out a comprehensive set of proposals for how the world can act together to rise to the challenges of AMR. We will use it to set out a broad range of interventions, encompassing both the simple and inexpensive, and larger-scale more complex actions that will require long-term commitments and investment.

In doing so, we will make the case why a coordinated global response to drug resistance – a threat that could claim 10 million lives a year by 2050, at an accumulated cost of 100 trillion USD lost from the global economy – is essential, achievable and affordable. The issue of AMR will be discussed at the UN General Assembly later this year and continues to rise up the agenda for the G7 and G20 groups of countries. Leadership in these global forums could be transformational and is an opportunity not to be squandered.

> “*Investments to improve how we prevent, control and monitor the emergence and global spread of drug resistance are some of the most effective we can make*”

APPENDIX

ANALYSIS OF THE RELATIONSHIP BETWEEN ACCESS TO WATER AND SANITATION, AND LIFE EXPECTANCY

The populations of high-income countries enjoy significantly better life expectancy and health outcomes than their peers in low and middle-income settings. This difference is due to a complex set of interrelated factors, including access to healthcare, living conditions, and income itself. We undertook a high-level analysis of publicly available data to attempt a broad estimate of the contribution that access to water and sanitation make to these gains in life expectancy. This used data on life expectancy and access to sanitation from the World Health Organization, and data on access to clean water from the World Bank.

People in higher-income countries are much more likely to have better access to good water and sanitation and healthcare services; this means that a strict comparison between access to water and sanitation and health outcomes is not fair. Instead, looking at more than 100 low and middle-income countries, we used the natural log of countries GDP per capita to 'predict' how good life expectancy, and access to water and sanitations systems should be – i.e. to define levels of each for a 'typical' country of a given income. Countries were then ranked on how much better or worse their sanitation systems were compared to this prediction of a 'typical' standard.

This shows that countries are grouped along clear lines, with better-than-average access to water or sanitation clearly linked to better-than-average life expectancy, and vice versa. Of the countries in the top quartile for sanitation provision only 11 percent had population life expectancy lower than the prediction expected, compared to 50 percent for the group as a whole. Similarly 77 percent of countries that had a less good sanitation system than their income would suggest, also had a shorter life expectancy than their income would suggest. A similar but less pronounced pattern was found in respect of access to clean water.

This data is displayed in the infographic on page 6 of the main report.

ACCESS TO SANITATION	Life expectancy top quartile	Life expectancy second quartile (better than expected)	Life expectancy third quartile (below expectation)	Life expectancy bottom quartile
TOP QUARTILE	15	9	2	1
BETTER THAN EXPECTED	7	11	8	2
BELOW EXPECTATION	4	6	9	9
BOTTOM QUARTILE	1	2	9	16

ACCESS TO WATER	Life expectancy top quartile	Life expectancy (better than expected)	Life expectancy (below expectation)	Life expectancy bottom quartile
TOP QUARTILE	11	8	5	2
BETTER THAN EXPECTED	5	10	5	7
BELOW EXPECTATION	8	7	8	4
BOTTOM QUARTILE	3	3	9	12

We also undertook regression analysis to quantify the association between access to sanitation or clean water, and life expectancy (once GDP and health expenditure are controlled for) in 167 countries across all income levels.

The following regression table shows that improved sanitation and access to clean water has a large, statistically significant impact on life expectancy, even when GDP per capita and health expenditure are controlled for. Increasing access to improved sanitation by 1 percent is associated with an increase in population of life expectancy of 0.194 years, whilst increasing access by 50 percent nationally would be associated with an increase in life expectancy of around nine and a half years.

VARIABLES	Life Expectancy From birth	Life Expectancy From birth
ACCESS TO IMPROVED SANITATION	0.194*** (0.0234)	
ACCESS TO CLEAN WATER		0.122*** (0.0287)
HEALTH EXPENDITURE BY PPP	0.000101 (0.000585)	0.000196 (0.000669)
2ND GDP† DECILE	1.711 (1.583)	2.802 (1.787)
3RD GDP† DECILE	3.259* (1.676)	6.989*** (1.822)
4TH GDP† DECILE	2.897 (1.815)	8.570*** (1.828)
5TH GDP† DECILE	1.917 (1.975)	9.840*** (1.801)
6TH GDP† DECILE	3.746* (2.090)	12.00*** (1.954)
7TH GDP† DECILE	4.701** (2.088)	13.89*** (1.873)
8TH GDP† DECILE	5.328** (2.308)	14.84*** (2.118)
9TH GDP† DECILE	7.357*** (2.729)	18.44*** (2.627)
10TH GDP† DECILE	7.690** (3.381)	17.40*** (3.537)
CONSTANT	52.71*** (1.215)	49.49*** (2.333)
OBSERVATIONS	167	168
R-SQUARED	0.747	0.675

Standard errors in parentheses

*** p<0.01,
** p<0.05,
* p<0.1

† GDP per capita

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Tackling drug-resistant infections globally

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

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