



RAPID DIAGNOSTICS: STOPPING UNNECESSARY USE OF ANTIBIOTICS

**THE REVIEW ON
ANTIMICROBIAL RESISTANCE**

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EXECUTIVE SUMMARY

At the heart of the global rise of drug-resistant infections, or 'antimicrobial resistance' (AMR), there is a fundamental supply and demand problem that needs to be fixed.

The supply of new medicines is insufficient to keep up with the increase in drug resistance as older medicines are used more widely and microbes evolve to resist them. In May 2015, we outlined specific proposals to address this supply problem, which have been echoed most recently by the governments of the G7 group of countries in October 2015.

At the same time, the demand for these medicines is very badly managed: huge quantities of antimicrobials, in particular antibiotics, are wasted globally on patients who do not need them, while others who need them do not have access. Fundamental change is required in the way that antibiotics are consumed and prescribed, to preserve the usefulness of existing products for longer and to reduce the urgency of discovering new ones.

Rapid point-of-care diagnostic tests are a central part of the solution to this demand problem, which results currently in enormous unnecessary antibiotic use.

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

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

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

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

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

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

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

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

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

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

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

In this paper we have set out three policy interventions to support the development of game-changing new rapid diagnostics and their widespread adoption over the next five years. These three interventions do not just consider the needs of the richest health systems, but instead seek to be useful to the largest number of patients, in the widest possible range of settings globally.

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

“ Even if it were possible, it would not be good enough to make the standard of antibiotic prescription in the BRICs reach a similar level to that of the United States. For material progress to happen over the next five years healthcare systems need to leapfrog to using rapid diagnostics wherever possible, before using an antibiotic. ”

1.

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

The use of diagnostics represents a classic example of a ‘public good’: the benefits are better antibiotic conservation and slower development of resistance and accrue to society at large over time, while the near-term costs are incurred by individual doctors or patients. It is simply more expensive and more time-consuming for a doctor or a patient to use a diagnostic than simply to use a drug ‘just in case’ it is needed, even if a test could help save costs and reduce waste at a health system-wide level, and help preserve the usefulness of antibiotics for all, over the longer term.

Many drug companies, meanwhile, including those producing affordable generic antibiotics, have no commercial interest in the advent of rapid diagnostics, which would act to limit the number of antibiotics prescribed. So it is not hard to see why diagnostic innovation has been so slow, with limited financial incentives to sell or buy these innovative products. Prize initiatives in the UK, the US and the EU have been important catalysts in raising attention for the need for rapid point-of-care diagnostics. But to sustain innovation in the medium and long term, and to encourage uptake of the resultant technology, further and more sustained intervention is needed.

To overcome this mismatch between the costs and benefits of diagnostics, we propose a bold, globally-coordinated Diagnostic Market Stimulus pots (DMS), which would ensure a market-based revenue stream for developers of products that match a recognised area of need. DMS would not pre-judge which diagnostics are best, rather they would follow the success of actual products bought by healthcare providers, by topping up the payments to developers to make sure the commercial benefits and the needs of society are better aligned.

We envisage this support would come from the same global payer we proposed in our last paper on incentivising new antibiotics, but that the funding needed would be on a scale far less than what is necessary to stimulate the antibiotic market. As such, it could be incorporated within the same 16 – 37 billion USD market intervention that we recommended in May. We envisage that as well as incentivising future innovation, this would also encourage the uptake of relevant products that are already being developed or that are available today. Based on these initial proposals, we will continue to work on how to structure an effective DMS.

2.

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

There needs to be greater funding available to product developers to support early-stage R&D activities. Many developers are small or medium-sized companies, which may face difficulties in securing private investment given an uncertain market backdrop. We believe the Global Innovation Fund for AMR, of 2 billion USD over 5 years – described in our February 2015 paper – has a key role to play in supporting the early-stage development of rapid diagnostics. This support should not be limited, though, to developers of what we classically think of as a diagnostic test to improve antibiotic use. Rather, it should also seek to support other complementary innovative technologies that may guide prescription or improve use – such as advanced computer learning or artificial intelligence-based systems for use by clinicians during diagnosis, guiding them towards optimal treatments.

3.

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

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

If the world is serious about tackling the threat of drug-resistant infections, we need to fully embrace the step-change in technology that rapid point-of-care diagnostics represent. Only by doing this can we fundamentally and sustainably reduce our misuse and overuse of antibiotics. Incremental behaviour change alone will not have a big enough impact, and regulation can only go so far. Through targeted, measured interventions, on a global scale, we can ensure the use of rapid diagnostic tests that allow for a true “right patient, right antibiotic, right time” approach.

INTRODUCTION

In this fourth paper published by the independent Review on Antimicrobial Resistance, we consider the role that rapid diagnostics can play in improving how we can: i) use antimicrobials to better treat infections; ii) slow the rise of drug-resistance by reducing the unnecessary use of antimicrobials, in particular antibiotics; and iii) ultimately change our approach to treating bacterial infections through targeted and precise therapies.

This paper follows a four-part outline. First, it shows how our global unnecessary use of antibiotics is wasteful and builds up massive cost and health risks for the near future. Second, it describes how new rapid diagnostic tests could transform the fight against superbugs by changing the way we use antibiotics and other precious drugs. Third, it analyses why innovation and take up of new diagnostic tests has been so slow, despite

great advances in other areas of medical technology. Fourth, it proposes three specific policy interventions with the aim to accelerate practical innovation in the area of rapid diagnostics for bacterial infections over the next two to five years.

This paper considers the human use of antibiotics and the role that diagnostics can play in improving this. We will publish another paper on antibiotics in agriculture and the environment, which will consider, among many issues, the role of diagnostics for animal use, so the focus of this discussion is human health. The Review plans to publish papers on the following, before its final report to the British Prime Minister in mid-2016: agriculture and the environment, preventing and limiting the spread of infections and alternatives to antibiotics.

The work of the Review

Our Review was commissioned by the British Prime Minister to recommend by the summer of 2016, a comprehensive package of actions to tackle AMR globally. In the meantime, we are publishing a series of papers looking at individual aspects of the wider AMR problem, of which this is the fourth.

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 2 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 16billion and 37billion USD over ten years.

After publishing this fourth paper on the role of rapid diagnostics, we will publish a further paper looking at the use of antibiotics in agriculture and the environment (including the use of diagnostics in animal settings). Further reports will come out between now and the spring of 2016 exploring alternatives to conventional antibiotics, and the role of sanitation and infection prevention and control measures in reducing the global burden of drug resistance.

1. OUR GLOBAL UNNECESSARY USE OF ANTIBIOTICS IS WASTEFUL AND BUILDS UP MASSIVE COSTS AND HEALTH RISKS FOR THE NEAR FUTURE

For individual patients with an infection, and to limit the spread of that infection, access to the right antibiotic is crucial. However, any use of antibiotics encourages resistance, so it is vital that we limit the unnecessary use of antibiotics to keep our drugs useful for as long as possible, as well as making sure the right patients get the right drugs.

This is not just a problem for those who regularly take antibiotics because it is the bacteria that become resistant, and they can be transferred from person to person. Therefore, someone living in an area where resistance levels are high might need to use powerful antibiotics with bad side effects, even if they personally have never taken antibiotics in their life before.

Antimicrobial resistance is a global problem that needs a global solution, because drug-resistant infections travel and will not stop at the border of even the best managed healthcare systems. Solving it in one country alone is not an option.

1a.

For lack of rapid diagnostics, the world vastly overuses antibiotics, in rich and poorer countries alike.

There are no data to show our unnecessary use of antibiotics globally but the scale of the problem is no doubt enormous. The example of respiratory conditions in the United States is telling; these account for 40 percent of antibiotic prescriptions.

An academic study of prescriptions in US primary and outpatient care considered adult patients visiting their doctor with a respiratory problem¹. It found the following pattern of antibiotic use. For a total of 106 million visits in one year, 86 million patients were thought to have a respiratory issue that antibiotics could not help treat, for example bronchitis or asthma. Of this 86 million group however, 27 million patients still received an antibiotic.

This suggests it is possible that 27 million courses of antibiotics were wasted on patients who did not need them in one year in the United States alone, for respiratory symptoms only.

If the problem is this bad in an advanced healthcare system like the United States, it is hard to imagine that emerging economies with much larger populations and often less tightly regulated systems will manage to control their consumption of antibiotics as they improve access to private and public healthcare for their citizens, without a shift in technology.

Stewardship programmes to change the prescribing habits of doctors and the expectations of patients can go some way towards addressing the issues of overuse. Countries like Sweden and The Netherlands have shown how it is possible to keep antibiotic use low with current technology. More recently other countries like India, China and Brazil have introduced a formal ban on over-the-counter sale of antibiotics and have made progress in enforcing these bans in some large urban centres. Much more must be done however, to implement these regulations and change behaviours. For instance doctors must not have financial incentives to prescribe antibiotics when they are not necessary (in some countries doctors' incomes are a function of the volume of drugs they prescribe).

“ This suggests it is possible that 27 million courses of antibiotics were wasted on patients who didn't need them in one year in the United States alone, for respiratory symptoms only. ”

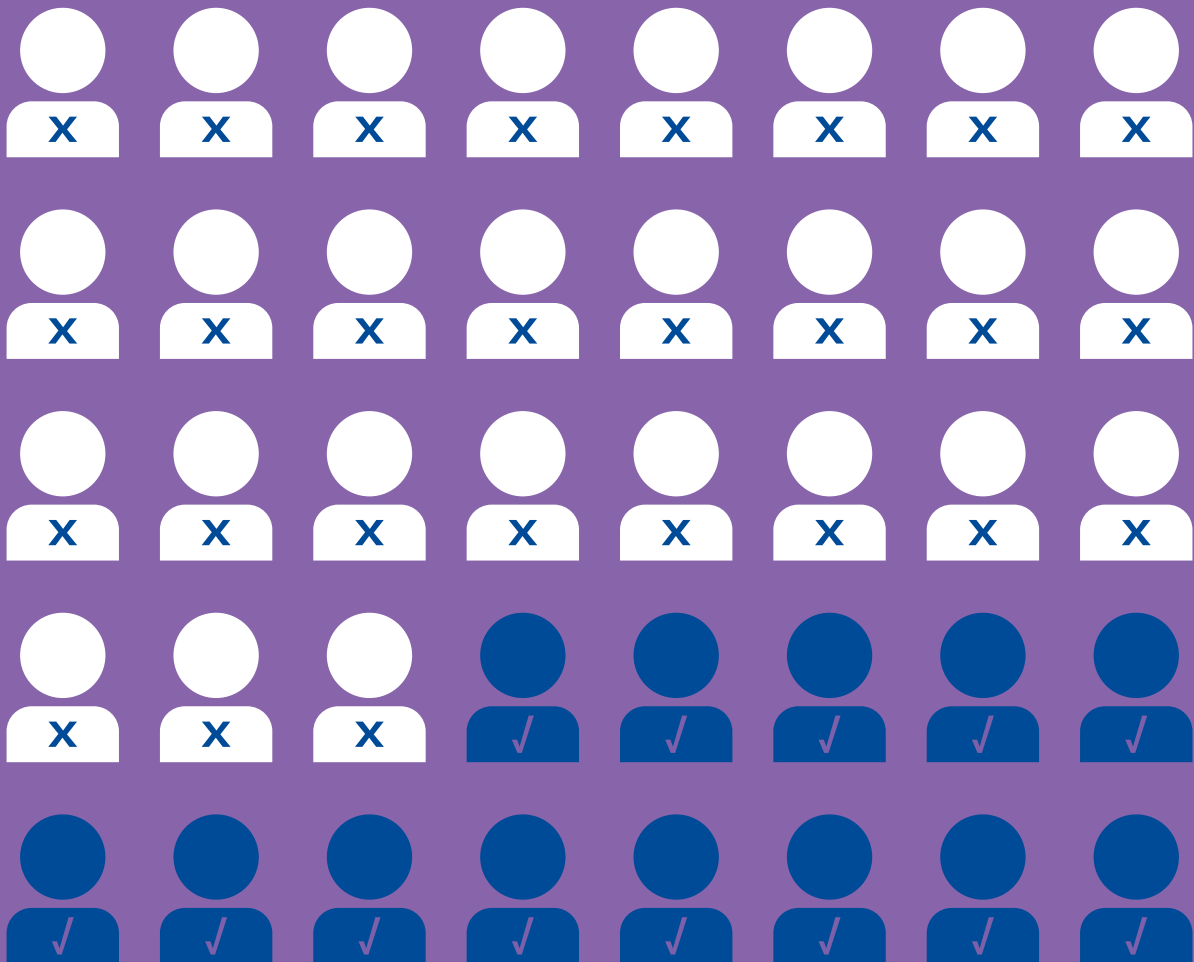
¹ The figures used are from the following article: Shapiro DJ, Hicks L.A., Pavia AT, Hersh AL, 'Antibiotic prescribing for adults in ambulatory care in the USA, 2007-2009', Journal of Antimicrobial Chemotherapy, 2014, doi: 10.1093/jac/dkt301.

RAPID DIAGNOSTICS WOULD REDUCE UNNECESSARY PRESCRIPTION

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

27m
get antibiotics unnecessarily

13m
who need antibiotics get them



1b.

For lack of rapid diagnostics, we do not always use the right drug at the right time.

Without rapid diagnostics, it is harder for clinicians to give the right drugs to the right patient. This is a well-known and well managed problem for long term infections like tuberculosis or HIV/AIDS where, at least in richer health systems, patients are tested for drug resistance before starting on a specifically tailored drug regimen.

It is surprising, however, how untailed treatments are for bacterial infections, for lack of rapid diagnostics at the point-of-care. Take the example of one of the most common sexually-transmitted diseases: gonorrhoea. Most patients with gonorrhoea are over-treated to prevent under-treating the few.

“ *Most patients with gonorrhoea are over-treated to prevent under-treating the few.* ”

We have taken gonorrhoea treatment for granted since penicillin became the first antibiotic to cure it in 1943. As of 2013 in England, more than 80 percent of gonorrhoea cases were still susceptible to one of our oldest antibiotics, penicillin, and more than 70 percent of cases were still susceptible to ciprofloxacin, both easy to take drugs with few side effects. Yet neither drug is now used to treat this infection. Instead, doctors prescribe the last line of defence available against gonorrhoea, which is a combination of two different drugs from different antibiotic classes, a cephalosporin and a macrolide. This is because doctors cannot take the chance that up to 30 percent of their patients may not be cured if they prescribe anything else. In turn, these antibiotics are put under selective pressure and, as expected, resistance to cephalosporins and macrolides has started to emerge, with the real threat that untreatable gonorrhoea infections will become a reality. Indeed, there has already been an outbreak of highly drug-resistant gonorrhoea in the North of England.

There are currently rapid tests to diagnose gonorrhoea but no rapid tests for drug susceptibility, which would enable doctors to know which drugs will be effective. Without knowing whether the infection is susceptible to specific drugs, the doctor has no choice but to initially use the antibiotic to which the fewest strains are resistant, which is a waste of a precious resource in more than 70 percent of cases. New diagnostic tests could help here and their development should be supported.

2.

RAPID DIAGNOSTICS CAN TRANSFORM THE FIGHT AGAINST SUPERBUGS BY CHANGING THE WAY WE USE ANTIBIOTICS

2a.

How new tools would transform the way we treat infections:

Picture the future; you go into your local doctor's surgery and sit down to be assessed. However, instead of simply looking down your throat, or in your ear, for clinical signs or symptoms of an infection, she has a rapid diagnostic tool. This can tell you both within five minutes whether you have an infection, a purely viral infection (which, of course, means no antibiotics are needed) or, if you have a bacterial infection, which antibiotics will be able to treat it. At the same time a computer programme is able in minutes to look through your electronic medical records, the symptoms that you are experiencing, the relevant medical literature and the latest surveillance information about local bacterial resistance, to support the doctor as she recommends the best line of treatment. On a personal level you are already on your way to the most appropriate treatment available. On a societal level the threat of more bacteria developing resistance through unnecessary antibiotic use has been reduced.

The data captured by these processes could feed into a real-time digital surveillance map of the world for infectious disease and resistance. In this future, countries and companies have agreed to share these data to improve patients' health and global health security, and we can spot where resistant infections are emerging in real-time and take swift action to combat them. We no longer have to rely solely on sporadic historical data released by a relatively small number of laboratories and hospitals to track the spread of resistance.

This may sound like distant science-fiction, but it could well be closer than you think. At least some of these technologies are already there and, with the right focus, funders, companies, universities and governments can accelerate their development and adoption.

Improving prescription with artificial intelligence

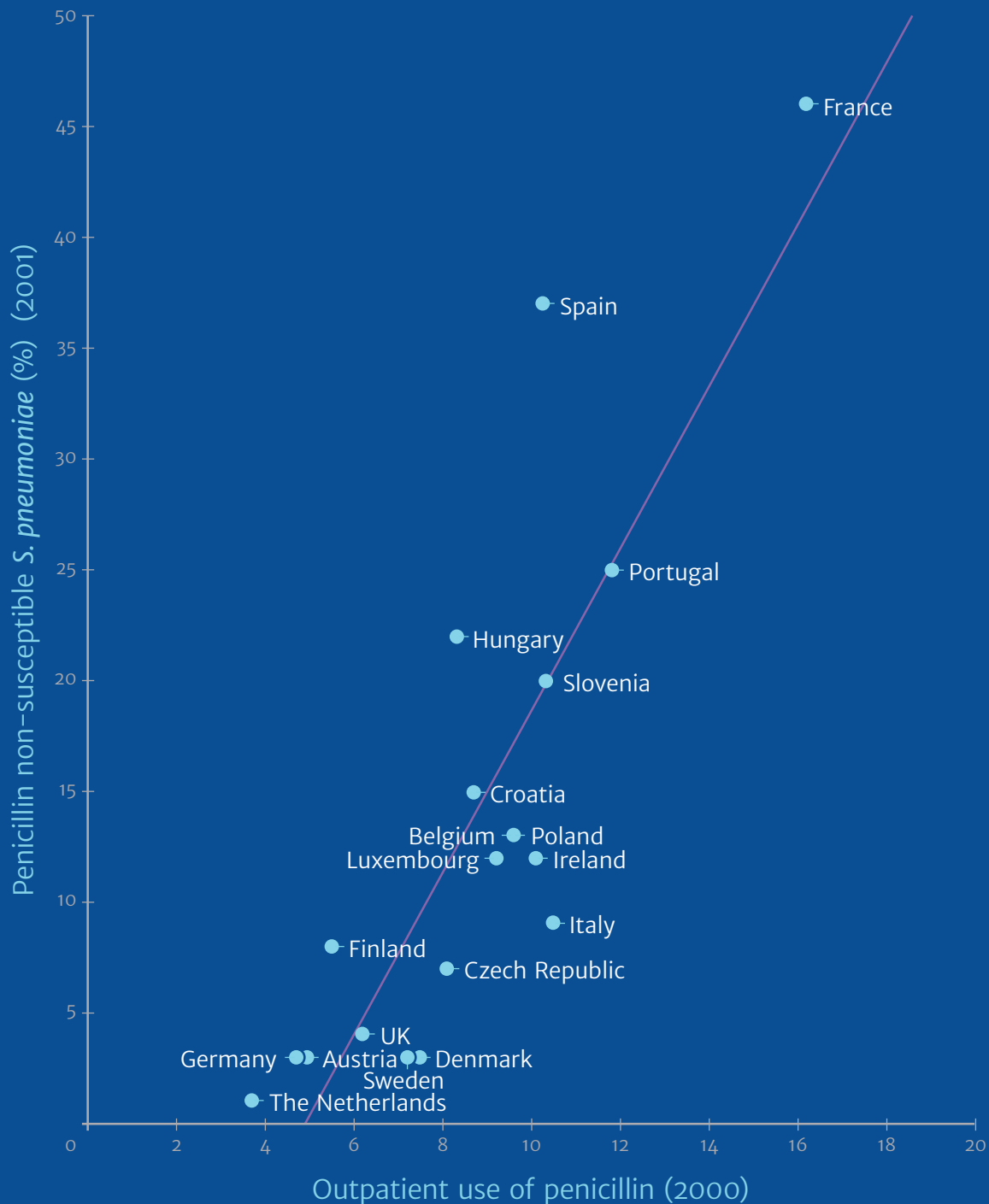
As well as the opportunities for using new technology with diagnostics that take samples from patients, advanced computers could also aid diagnosis.

Developments in artificial intelligence in recent years have brought many exciting opportunities, including a rapidly expanding interest within the health sector. The concept of "deep learning", whereby computers are taught to become experts in specific areas by analysing, comparing and interpreting vast amounts of information is already being developed for application in oncology². Advanced computer systems are effectively being taught to be cancer specialists, assessing a patient's electronic medical record alongside huge amounts of other, clinical trial data and published evidence, to provide a diagnosis to the doctor.

The process by which most doctors currently prescribe antibiotics, especially in primary care, is referred to as empirical prescription. Based on the patient's symptoms and the doctor's experience they will provide a diagnosis, and potentially an antibiotic if they believe an infection is bacterial. While there are clear differences between diagnosis of cancer and that of infectious disease, developments in artificial intelligence have the potential to provide an "empirical +" form of diagnosis, scanning huge amounts of data and an encyclopaedia of medical knowledge in minutes, and making it available to the doctor and patient.

² Fakoor R, Ladhak F, Nazi A, Huber M, Using deep learning to enhance cancer diagnosis and classification, Proceedings of the 30th International Conference on Machine Learning, Atlanta, Georgia, USA, 2013,

THERE IS A HIGH CORRELATION BETWEEN ANTIBIOTIC USE AND RESISTANCE



Source: Goossens H, Ferech M, Vander Stichele R, et al. *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study*. Lancet 2005; 365(9459): 579-87.



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2b.

The perfect new rapid diagnostic test would answer four questions.

The perfect new diagnostic would answer four broad questions rapidly and conclusively enough that it could inform diagnosis and treatment with the correct antibiotic, before any antibiotics are given to the patient. Current diagnostic tests can answer all four questions conclusively, but not quickly: lab tests take at least 36 hours, by which time empirical treatment has started, possibly with the wrong drugs, or with drugs that offer an unnecessarily broad-spectrum, thereby increasing the potential for ecological damage and promoting resistance. Most of our current testing methods are based on the methods developed by Louis Pasteur and Robert Koch in the nineteenth century. The ambition – as set out by great initiatives such as the Longitude Prize³, for example – must be to develop tests that do all of the below within minutes. But on the journey to this perfect rapid diagnostic, tests that give partial answers are useful too and should be supported and used.

“Most of our current testing methods are based on the methods developed by Louis Pasteur and Robert Koch in the nineteenth century”

- 1. Is the infection causing the illness bacterial or viral?** A diagnostic test that could indicate clearly whether a patient has a bacterial infection could dramatically reduce unnecessary antibiotic prescription for viral infections, particularly in the primary care setting. In most countries around 80 percent of antibiotics are used in the community, rather than the hospital, and around half of this use is thought to be inappropriate⁴.
- 2. If bacterial, what type of bacteria is causing the infection?** A diagnostic that could not only detect a bacterial infection, but also quickly confirm the type of bacteria causing it, would enable doctors to tailor treatment, and potentially decrease reliance on broad-spectrum drugs.

3. Are the bacteria that are causing the infection resistant to available antibiotics? Diagnostic tests that detect resistance (or lack thereof) can steer doctors away from potentially inappropriate antibiotics and towards those more likely to be effective. In acute settings, ruling out even one or two therapies – absent a full susceptibility test as described in 4 below – can save a patient’s life. Examples of these tests exist now and can be considered as partial surrogates for the tests that confirm susceptibility.

4. Are the bacteria that are causing the infection susceptible to existing drugs? A diagnostic test that could rapidly measure the susceptibility of the infecting bacteria to existing antibiotics would be even better than one that detects resistance, as it gives the doctor greater confidence that the drug they choose should be effective. Rather than ruling out, for example, penicillin, which would empirically push a doctor towards cephalosporins, it would actively rule cephalosporins in on day one. In acute settings this could again save a patient’s life. In all settings, it would minimise inappropriate use of antibiotics.

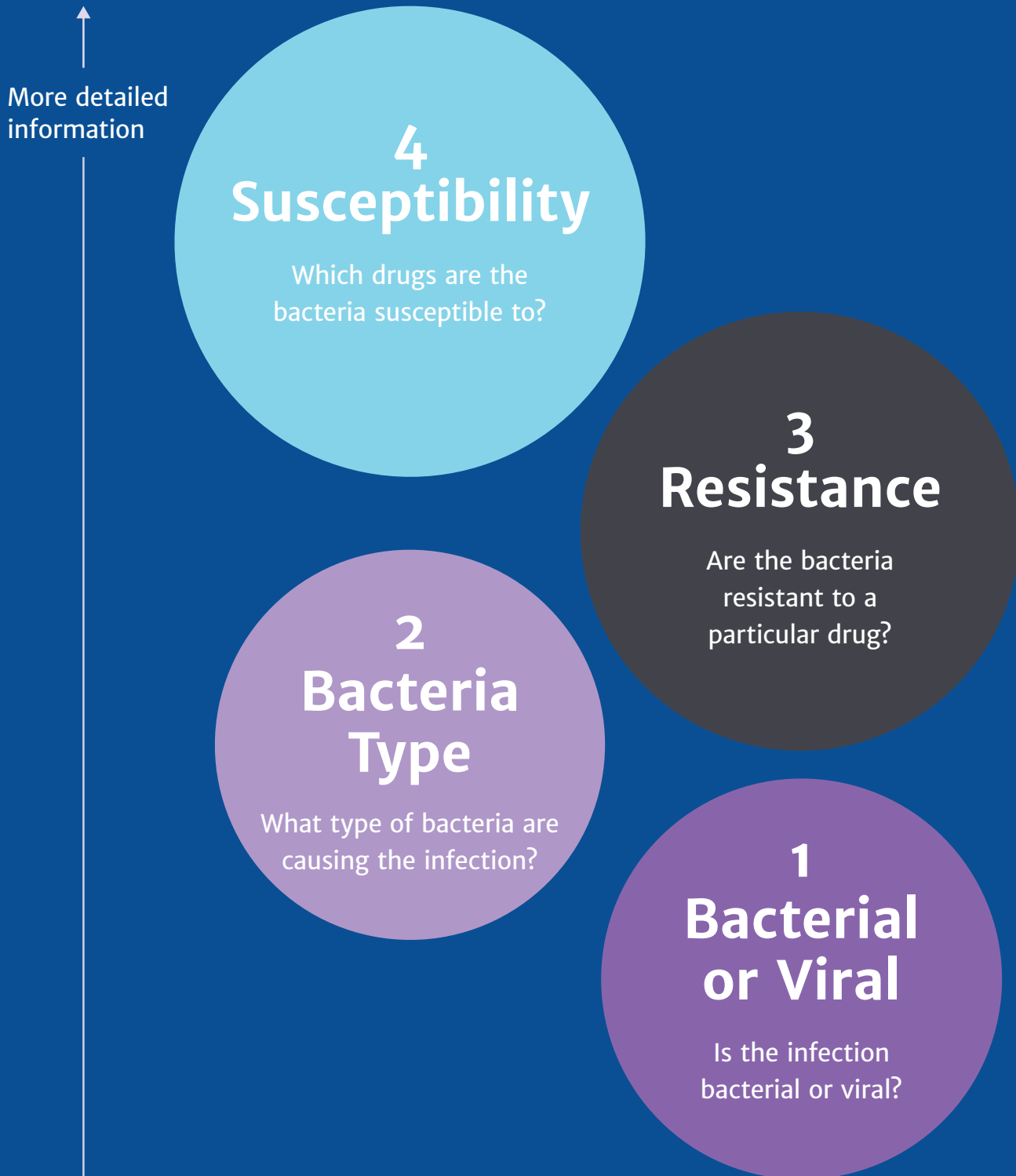
We need diagnostics that can be deployed widely throughout the developed and developing world. These might be used at home, or in pharmacies, primary care clinics, or hospitals. These new generations of diagnostics will do at least three crucial things. First, they will improve patient treatment by getting the right drug to the right patient quickly. Second, they will make our arsenal of existing drugs go further and last longer. Third, they may reduce our need to develop new ‘broad-spectrum’ drugs, which are often the hardest drugs to find. In order to achieve this, we not only need to have diagnostics available in the right settings, which may differ by country, we also need to ensure that financial rewards, culture and systems support their use.

Ultimately what we want are high quality, affordable rapid diagnostics that can be rolled out as widely as possible.

³ Longitude Prize, Available from: www.longitudeprize.org, [Accessed: 12th October 2015]

⁴ Center for Disease Dynamics, Economics & Policy, ‘State of the World’s Antibiotics, 2015’, CDDEP: Washington, D.C., 2015.

WHAT RAPID DIAGNOSTICS COULD TEST



2c.

Diagnostics can reduce costs for hospitals, patients and healthcare systems

Cost is often thought of as a barrier for rapid diagnostics. With most antibiotics being so cheap, it is often said that for a doctor, pharmacist or patient to use a diagnostic test before prescribing or using an antibiotic is an added cost, falling on hard pressed patients and healthcare systems. Yet this is a very narrow way of looking at the costs of diagnostics, and makes clear the ‘public good’ issue, in which individuals bear additional upfront costs but patients in aggregate reap benefits and healthcare systems save money.

Drug-resistant infections are a large drain on hospital resources, with a study by Tufts University estimating that in a US hospital a resistant infection costs between 18,588 USD and 29,069 USD per patient⁵. A rapid diagnostic that allows doctors to target the right drug to the right patient immediately could save money by reducing the length of stay in hospital for these patients. Identifying patients with a drug-resistant infection quickly also prevents their infection being passed on to patients around them because they can be rapidly isolated and infection control measures put in place. Conversely, patients who might otherwise be identified empirically as being at high risk of carrying drug-resistant infections like Methicillin-resistant *Staphylococcus aureus* – and thus subjected to precautionary isolation pending confirmatory diagnosis – could be quickly screened using a rapid diagnostic and unnecessary (and costly) isolation and expensive infection control measures more promptly stepped down. One Netherlands-based study of such an approach found that rapid diagnostics could reduce the demand for scarce hospital intensive care unit isolation rooms by more than 40 percent⁶.

Even when an infection is not drug-resistant, it is common that without a rapid and reliable test a doctor can ‘miss out’ on giving an antibiotic to someone who actually needed it. That patient may deteriorate and end up in a hospital, out of hours: in this case, from a financial point of view, the doctor’s surgery has shifted much higher costs to the hospital system that dwarf any ‘saving’ derived from not using a test to guide the prescription.

Another important aspect in the cost-benefit debate about diagnostics is their potential for saving precious doctor’s surgery time by allowing a first ‘screening’ for bacterial infections to be done in pharmacies, or even at home like self-tests that are now available in other areas. In some countries diagnostic tests, for

example for strep throat, are already used in certain pharmacies, enabling the pharmacist to prescribe an antibiotic if the test indicates that the infection is highly likely to be bacterial. This has the potential to alleviate some of the pressure on primary care facilities, enabling someone who has a sore throat, for instance, to walk into a local pharmacy and take a quick test, rather than wait to see a doctor.

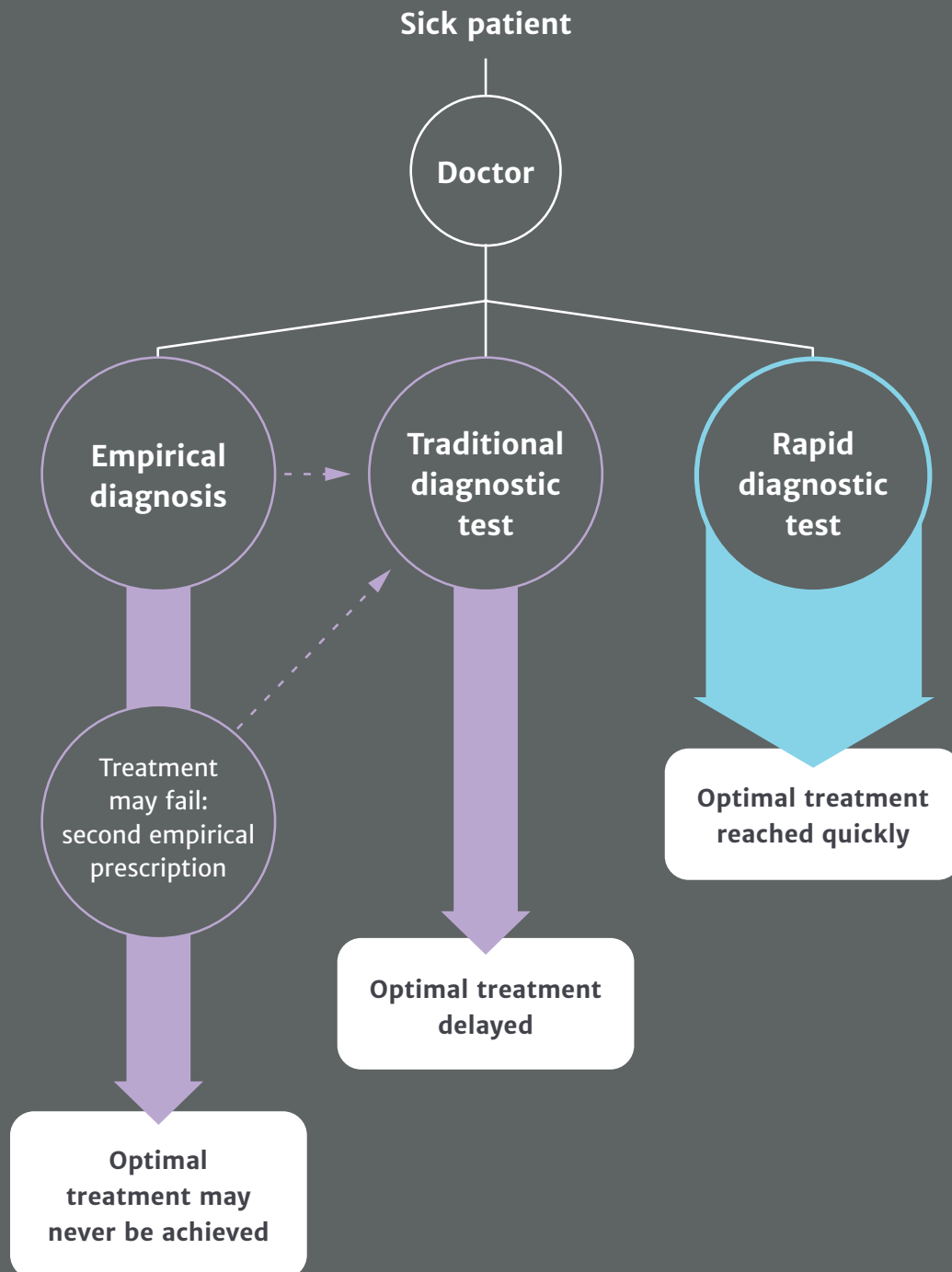
And, of course, diagnostics that reduce overall antibiotic use should also slow the rise of resistant bacteria, meaning fewer patients with resistant infections end up presenting to doctors across primary care and hospital settings.

We need a better understanding of the benefits to healthcare systems of using diagnostics but it seems reasonable that increased use of diagnostics to better inform treatment decisions is not only in patients’ interests, but also in the financial interest of healthcare systems. We return to this question below, with a recommendation for the payer organisations in health systems to support cost-effectiveness studies.

⁵ Roberts RR, Hota B, Ahmad I, et al Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship, *Clinical Infectious Diseases* 2009; 49:1175–84

⁶ Wassenberg M, Kluytmans J, Erdkamp S, et al. Costs and benefits of rapid screening of Methicillin-Resistant *Staphylococcus Aureus* carriage in intensive care units.

NEW RAPID DIAGNOSTICS WOULD OPTIMISE TREATMENT



2d.

Rapid diagnostics are essential for the transition from broad to targeted antibiotics

By indicating to doctors what bacteria are harming their patient diagnostics will make it easier for them to prescribe narrow-spectrum antibiotics (Appendix B sets out more details).

The terms ‘broad-spectrum’ and ‘narrow-spectrum’ are regularly used to describe antibiotics and indicate whether antibiotics are active against a wide variety of bacteria or a more limited range of species.

Bacteria may be divided into two major groups, called Gram-positive and Gram-negative. Antibiotics that can be used to treat infections caused by (at least some) bacteria in both of these groups are defined as broad-spectrum. Broad-spectrum antibiotics are needed when a doctor suspects that a patient has a bacterial infection, but does not have any information about what bacteria are causing it; if they consider antibiotics necessary they must prescribe one (or more) that ‘covers’ a wide range of possible causes and so must reach for broad-spectrum agents. Other antibiotics, however, are active only against Gram-positive or Gram-negative bacteria and are described as narrow-spectrum. Doctors use these when they are more confident about the type of bacteria causing an infection, for example after diagnostic test results have become available.

When someone takes antibiotics, even if used appropriately, many bacterial species in or on their bodies (their ‘good bacteria’) are exposed to some extent, not just those that

are causing the infection. Narrow-spectrum antibiotics do not cause as much ‘collateral damage’ to these ‘good bacteria’ as broad-spectrum agents; they cause less disruption to someone’s normal bacteria, and do not exert as much selective pressure for the emergence and spread of resistance as broad-spectrum agents.

In addition to enabling better targeting of therapies to patients, rapid diagnostics can reduce the cost of clinical trials for narrow-spectrum drugs by making it easier to find patients who have a potentially susceptible infection of interest and therefore reducing the number of patients that need to be screened to join a trial. Ideally clinical trial patients need to be found and enrolled before they start treatment with a different drug in order to best capture the effect of the drug of interest. Because culturing bacteria to see what is wrong with a patient takes too long, clinical researchers must enrol people in a trial through empirical diagnosis. For example when trying to test a drug against *Pseudomonas* (a bacterium that causes a wide range of infections), because patients are enrolled before their bacteria can be cultured, only one in four people on the trial may actually have this infection. This means that in order to run a trial with 200 truly eligible patients, researchers have to screen, register and treat at least 800 people, which drives up the costs of trials ⁷. Appendix B sets out more details about the use of diagnostics in clinical trials.

Diagnostics for fungal infections

Improvements in the quality and uptake of diagnostics for fungal infections will play an important role in reducing antifungal and antibiotic resistance as well as improving human health as a whole. *Candida* spp. bloodstream infections and invasive candidiasis are more common than often appreciated. In many institutions, *Candida* spp. is the most common fungal healthcare associated bloodstream infection ⁸. They are often misdiagnosed as bacterial infections, which leads to patients being prescribed unnecessary antibiotics, putting selection pressure on bacteria in their gut and increasing resistance. Early treatment for *Candida* can greatly

improve outcomes, and with up to 75% of patients with blood stream infections dying in some parts of the world, diagnostics could save many people’s lives ^{9 10}.

Similarly, fungal lung infections are often misdiagnosed as TB, in part because the high number of false negative TB tests lead doctors not to trust the results. This leads to patients being treated with a series of ineffective and often toxic drugs, sometimes for as long as two years, when a simple anti-fungal might have worked.

⁷ Rex, JH, Coordinated Diagnostics & Therapeutics: A Clinician Developer’s Overview, [Presentation], AstraZeneca Pharmaceuticals, FDA-NIH Overview of diagnostics & development, 2014-09-23

⁸ Magill SS, Edwards JR, Bamberg W, et.al., ‘Multistate point-prevalence survey of Healthcare-Associated Infections’, *The New England Journal of Medicine*, 2014, ;370:1198-208. DOI: 10.1056/NEJMoa1306801.

⁹ Garey KW, Rege M, Pai MP et.al., ‘Time to initiation of Fluconazole Therapy Impacts Mortality in Patients with Candidemia: A multi-institutional study’, *Clinical Infectious Diseases*, 2006 43 (1): 25-31. doi: 10.1086/504810

¹⁰ Chakrabarti A, Sood P, Rudramurthy SM, et.al. ‘Incidence, characteristics and outcome of ICU-acquired candidemia in India’, *Intensive Care Medicine*, February 2015, Volume 41, Issue 2, pp 285-295

A PLAN TO OVERHAUL DIAGNOSTIC DEVELOPMENT

Barriers

Difficult to show
cost and clinical
effectiveness



**Fund and
facilitate
research**

Difficulty
raising capital



**Global
innovation
fund**



Diagnostics are more
expensive than empirical
prescribing



**Diagnostic
Market
Stimulus**

Solutions

3.

WHY HAS INNOVATION AND TAKE UP OF NEW DIAGNOSTICS BEEN SO SLOW?

3a.

What diagnostics for bacterial infections do we have at the moment?

While we clearly need to encourage more innovation, there are products available on the market now that could reduce levels of unnecessary antibiotic prescribing, particularly in the primary care setting and notably for areas in which there is high inappropriate use of antibiotics, for example respiratory complaints. As mentioned previously, respiratory complaints account for 40 percent of antibiotic prescriptions to US adults in primary care and outpatient care¹¹. Therefore tests that can have a significant impact in this area have the potential to drastically reduce unnecessary prescriptions.

There is a strong case for making step-by-step progress, rather than waiting for the perfectly accurate diagnostic to come to market, as providing the clinician with more information and a strong indication as to the problem, could be very helpful in improving treatment.

Some of the current tests on the market in primary care are laid out below. They may not be perfect and uptake is low in most countries, but there is evidence that they can reduce unnecessary use, such as:

- Rapid tests for strep throat, with some evidence of success, but with a high number of false negatives. These tests are already used in many pharmacies in the US and there is evidence that they can reduce the amount of antibiotics prescribed. However there are criticisms over the accuracy of the tests which have been shown to have high specificity¹² rates of 100 percent, but lower sensitivity rates of between 62–95 percent¹³;
- Quick tests for gonorrhoea, syphilis and chlamydia, but all three suffer from lower than ideal levels of accuracy; and
- C-reactive protein (CRP) tests, some of which also assess pro-calcitonin and white blood cell counts to give a probability of

the patient having a bacterial respiratory infection. CRP tests are increasingly being used in the primary care setting to give an indication of whether an infection is likely to be bacterial or viral, and therefore whether an antibiotic is needed. They have also been used for years in The Netherlands and Scandinavia, who have some of the lowest rates of prescribing antibiotics for human medicine in Europe. Systematic reviews have shown that CRP tests reduce antibiotic prescribing for certain suspected respiratory infections, though not necessarily for other complaints such as pharyngitis¹⁴.

There are also already rapid diagnostic tests for use in hospitals and more in development. However, the majority of tests lack clinical trial data, validation and cost-effectiveness assessments. More needs to be done to improve the evidence base for the diagnostics that exist, and make them cheaper, quicker, more accurate and easy to use.

While diagnostic technology can and will improve, there needs to be greater uptake of the devices that are already available, many of which have the potential to reduce unnecessary prescription. The biggest indictment of current uptake is the huge variation between different countries and regions. Many systems are too slow rolling out new technology and innovation and going forward this should change.

“*There is a strong case for making step-by-step progress, rather than waiting for the perfectly accurate diagnostic to come to market, as providing the clinician with more information and a strong indication as to the problem, could be very helpful in improving treatment today.*”

¹¹ Shapiro DJ, Hicks L.A., Pavia AT, Hersh AL, ‘Antibiotic prescribing for adults in ambulatory care in the USA, 2007–2009’, *Journal of Antimicrobial Chemotherapy*, 2014, doi: 10.1093/jac/dkt301.

¹² Sensitivity can be described as if a person has the disease, how often will the test be positive, whereas specificity is if a person does not have the disease, how often will the test be negative.

¹³ Plüddemann A, Onakpoya I, Harrison S, Shinkins B, Tompson A, Davis R, Price CP, Heneghan C, Position Paper on Anti-Microbial Resistance Diagnostics, 2014, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford.

¹⁴ Ibid

The state of current diagnostics pipelines for HIV, Tuberculosis and Malaria

HIV, Tuberculosis and Malaria, together known as the Big Three, pose a major challenge to global human health, with approximately 5 million people dying each year from them¹⁵. In 2013, diagnostics R&D for these three stood at 49 million USD, 22 million USD and 11 million USD respectively, compared with diarrhoeal diseases (0.7 million USD) and bacterial pneumonia and meningitis (2.5 million USD)¹⁶.

The diagnostic technology landscape for these three diseases is relatively advanced compared with diagnostics for many bacterial infections. Many diagnostics, including rapid point-of-care tests, are already available in the market, and more innovative products are in the pipeline. In contrast, diagnostics for bacterial infections have lower levels of public funding, as well as some additional scientific difficulties associated with development. Many bacterial pathogens can also exist without causing infection and it can be very difficult for diagnostics to distinguish the majority that are harmless from those that are making patients unwell. For example, a third of people carry harmless *Staphylococcus aureus* bacteria in their noses without having an infection, and very few will even harmlessly carry the hospital superbug variety, MRSA. In contrast, if someone has the HIV virus in their body, it is evident that the patient needs treatment. This is one of the reasons why rapid and conclusive diagnostic tests are particularly difficult to develop for bacterial infections.

HIV

HIV diagnostics can detect rapidly the presence of the virus and whether it is resistant to specific antiretroviral drugs. These tests are part of the standard of care in Europe and the US and for patients across the world with good healthcare provision^{17 18}. The pipeline for further improvements in HIV diagnostics remains promising with several technologies for different types of testing under development¹⁹.

Tuberculosis

There have been major advancements in tuberculosis diagnostics in recent years, including the roll-out of the GeneXpert MTB/RIF diagnostic tool. This is an automated test that detects tuberculosis and can test resistance to rifampicin in less than 2 hours. The tuberculosis diagnostics landscape appeared promising in 2014, with many product developers and technologies in the pipeline, with focus on developing technologies that can be used outside the lab setting²⁰. More innovation is needed however to bring costs even further down and make it possible to test for resistance to drugs other than rifampicin.

Malaria

While there are gaps in research and development, the malaria diagnostics pipeline is also promising. For diagnosing the disease itself there are currently over 200 commercially-available products²¹.

However, there are still gaps in relation to rapid diagnosis of artemisinin drug resistance as well as reliable detection of *Plasmodium vivax* malaria. This is important with respect to AMR to prevent inappropriate prescription of frontline antimalarials.

Going forward

Although there is still more to be achieved in these areas, the need to stimulate the pipeline for bacterial and fungal diagnostics is a particular priority at the moment, in part because of the great work from NGOs and health system funders already working in HIV, Tuberculosis and Malaria.

¹⁵ Vitoria, M., Granich, R., Gilks, C.F., Gunnenberg, C., Hosseini, M., Were, W., Raviglione, M., De Cock, K.M., 2009, "The Global Fight against HIV/AIDS, Tuberculosis and Malaria: Current Status and Future Perspectives", *Am J Clin Pathol*, 131: 844-848.

¹⁶ Moran et al. GFINDER Report, 2014, Neglected Disease Research and Development: Emerging Trends, Policy Cures

¹⁷ WHO, 2015, List of diagnostics eligible to tender for procurement by WHO in 2015 (including WHO prequalifies diagnostics)

¹⁸ The Global Fund to fight AIDS, Tuberculosis and Malaria, 'List of diagnostic test kits for HIV classified according to the GF QA Policy Version-8, June 2015'

¹⁹ UNITAID, 2014, HIV/AIDS Diagnostics Technology Landscape, 4th Edition, WHO

3b.

Why innovation and the use of new diagnostics has been slow

There are problems with the market for diagnostics

The market for diagnostics is characterised by the following problems: (i) a lack of investment in innovation, and (ii) a lack of uptake. The first problem can be explained by weak commercial returns for the developer as current pricing does not reflect the social value of using diagnostics. The second seems to relate to a combination of real and perceived product quality and clinical value, cost-effectiveness, and a perceived mismatch between what is needed and what is on offer. There also appears to be a challenge from inertia – i.e. it is hard to overcome deeply engrained practices of empirical prescribing.

We explore the issues below:

- A. Mismatch between individual, commercial, and social value of using diagnostics:** The value of rapid diagnostics that could reduce unnecessary use of antibiotics is not fully reflected in pricing and adoption. This is because doctors focus on the best diagnosis and treatment they can provide to an individual patient at a certain cost and at a particular point in time. Wider and longer-term health and economic benefits that might accrue to society as a whole, or even to the hospital as a whole, are rarely taken into account either by the doctor or by those paying for diagnostic tests.

Because antibiotics are generally cheap, whereas rapid diagnostic tools add an expense, few doctors are incentivised to use them. This means that although there are diagnostic developers with products ready to come to market in certain areas, they are not being bought and used.

This issue is exacerbated by the fact that the costs of point-of-care diagnostics are often accrued in a different area to the gains, for example a primary care facility may pay for a diagnostic device that reduces the probability of a patient being admitted to an intensive care unit.

Not only are these financial gains very hard to quantify, but even if they are calculated, the primary care facility might not receive the benefit of saving money for the system as a whole, even though it pays for the test.

- B. Creating the right product:** Coordination between diagnostic developers and doctors/ purchasers / policy makers could be much improved, in order to avoid products coming to market that do not address vital needs or are impractical for those using them. The situation is also complicated by the lack of a single diagnostic platform, with common standards, an area on which the World Health Organisation (WHO) is consulting at the moment. Clinics are not able to maintain, supply and repair multiple platforms, and the platforms that they have are likely to drive the diagnostic tests that they buy. In addition, collaboration with drug developers could facilitate the development of diagnostics, which would aid more efficient enrolment into clinical trials and could guide appropriate use of new antibiotics.
- C. Evidence – cost, speed and degree of accuracy:** As well as the financial hurdles, doctors need to be convinced that a diagnostic is accurate and reliable (sensitive and specific) enough to make a diagnosis. We recognise that doctors are bound by a duty of care to each individual patient and may therefore prescribe a course of treatment that is unlikely but may in a few cases help, in the absence of clearer diagnostic evidence.

In acute hospital settings the hurdles that payers and doctors expect devices to reach are even higher. The doctor needs to know incredibly quickly and accurately if the patient is infected and, if so, by what. Unless they have a test to target therapy which is very accurate, reliable and quick, they will give broad-spectrum antibiotics, at least as a first dose, to minimise the chance of harm or, indeed, death. For example, giving an ineffective drug in sepsis has been shown to double mortality rates.

20 UNITAID, 2014, Tuberculosis: Diagnostics Technology and Market Landscape, 3rd Edition, WHO

21 Jacobs J, Barbé B, Gillet P, Aidoo M, Serra-Casas E, Van Erps J, Daviaud J, Incardona S, Cunningham J, Visser T, 2014, Harmonisation of malaria rapid diagnostic tests: best practices in labelling including instructions for use, Malar.J. 13: 505. 1–10

22 Morel C, McClure L, Edwards S, Goodfellow V, Sandberg D, Mossialos E, Ensuring Innovation in Diagnostics for Bacterial Infection : Implications for Policy, World Health Organization European Observatory on Health Systems and Policies, 2015, chapter 12)

4.

THREE POLICY INTERVENTIONS TO ENCOURAGE INNOVATION AND IMPROVE ADOPTION OF RAPID DIAGNOSTICS OVER THE NEXT TWO TO FIVE YEARS

We propose three policy interventions to encourage game-changing new rapid diagnostics and their widespread adoption over the next two to five years. These three interventions aim to be useful to the largest number of patients globally. We do not underestimate the behaviour change needed to alter long-established ways of using antibiotics, which will need to occur alongside interventions to encourage this technology, but we believe regulation and behaviour change alone cannot solve this problem.

4a.

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

Diagnostic use for bacterial infections represents a classic example of a ‘public good’. The benefits are better antibiotic conservation and slower development of resistance and these accrue to society at large. The costs are incurred at the doctor or patient level and add expense and time.

How it would work

Diagnostic Market Stimulus pots (DMS), would be pots of money, which would be allocated by a global payer and paid out to incentivise the development and purchase of diagnostics technology to help tackle the problem of drug resistance. Companies would sign up to a DMS and sell their products under certain conditions, such as at affordable prices. Every time a product was sold, a payment would be made from the pot, until it ran out.

This approach is informed by the work undertaken by Gavi (the Vaccine Alliance), to purchase pneumococcal vaccines. However our proposed solution has several key differences, in particular it tops up a payment per product sold, without guaranteeing or pre-agreeing a minimum volume of sales or overall payment. This would mean that firms would still need their products to be adopted and face competition with other products, as in a

‘normal’ market. The DMS would incentivise future innovation by increasing the overall potential value of the market, thereby increasing firms’ incentives to devote resources to innovation.

From the global payer’s perspective, DMS are attractive because they would only pay out when a product reaches the market and is bought. Under the DMS the global payer would only pay for success. This also means that companies would have an added incentive to be efficient and only pursue research that is promising and relevant to users.

The greatest advantage of this system is that it allows multiple companies to come up with useful products, and lets health professionals decide which is the most useful. Companies then get rewarded based on the number of products they sell. This means that if there are two diagnostic devices and one is quicker or easier to use, whilst the other is more accurate, doctors can decide which one makes more sense for their specific circumstances and the needs of their patients, and the companies will be rewarded as they normally would in a market except they gain an additional subsidy²². A ten year notional projection of how this could work for three different diagnostic devices is outlined in ‘How a \$1BN Diagnostic Market Stimulus could work’ (Page 23), with company one receiving 15 percent of payments from the DMS, company two receiving 25 percent, and company three receiving 60 percent.

“ *The costs of point-of-care diagnostics are often accrued in a different area to the gains, e.g. a primary care facility may pay for a diagnostic device that reduces the probability of a patient being admitted to an intensive care unit.* ”

The Challenges

The difficulty in implementing this system would be deciding which parts of the diagnostic market need to be stimulated, and how big the stimulation should be. If the pot was too small then innovation might not be encouraged, too big and it might

waste precious resources. Further to this, the global payer's commitment to provide funds also needs to be credible, as companies need to know the money would be paid for success before they invest in innovation. The experience and track record of Gavi (the Vaccine Alliance) provides assurance that such a system can be put in place, with credible guarantees to convince companies to put up investment upfront.

The main drawback of this approach is that the financial reward goes to the investor late in the development cycle for making the product²³. This exposes the developer to considerable risk at early stages, and small firms may particularly struggle to fund early research. However this could be mitigated with a combined element of push funding – something we have recommended the global innovation fund could provide²⁴. We also believe that it is better to have the payments being made later and companies taking on more of the risk, than to have health system funders and governments pick winners long before they know what type of innovation might prove most useful to doctors and patients.

How it could help AMR now

We are also keen that DMS pots help increase the uptake of existing diagnostic technology and technology which is soon to come to market, by making successful products more affordable to purchasers.

In order to test how a DMS would work in practice, and to support some of the technology which is already available, we recommend that urgent work should be done to set up a pilot.

This pilot would be backed by health system funders who have an interest in reducing the impact and cost of AMR. It would support payers in buying devices and tests and undertaking training on how to use them. Removing the upfront cost of equipment and training would alleviate the immediate financial impact of adopting the new technology for healthcare providers. Training would be essential to ensure appropriate use.

“*In order to test how a DMS would work in practice, and to support some of the technology which is already available, we recommend that urgent work should be done to set up a pilot.*”

Taking this proposal forward

The way we envisage this working, is that a global payer – the same body that we recommend should be created to incentivise drug innovation to combat AMR²⁵ – will create DMS pots for different specifications or bacterial infections. Great consideration will need to be given to issues such as how many different DMS are needed, how the specification criteria are set, and what level the reimbursement prices should be set at. We look forward to discussing the practical details of implementation with interested stakeholders, and we will attempt to do further analysis on the size of the intervention that would be needed to stimulate the diagnostics market. From our work so far, however, we expect this cost to be significantly less than the cost of new drugs. We also think it could be funded as part of the 16 billion USD to 37 billion USD a decade that we estimated would be needed to solve the antibiotic supply problem.

²³ Ibid

²⁵ Ibid

²⁴ Review on Antimicrobial Resistance, Securing New Drugs for Future Generations: The Pipeline of Antibiotics, 2015.

An illustrative example of how this system could work

The global payer in charge of the scheme would need to decide how big a DMS to create, and what products would qualify, based on criteria of critical need. In addition to assessment of clinical need, the size of each DMS should take into account how much companies would have to spend in research and development costs to create the diagnostic and how long it would take to develop (the longer it takes, the larger the DMS could be). It would be important to give developers enough money to encourage innovation, but not so much that it is wasteful. If 'infection x' was thought to need a 1 billion USD market commitment to encourage innovation, the best way to spend this could then be to give the first 100 million tests sold a subsidy of 10 USD each.

Any firm that comes up with a product that meets the requirements set by the global payer would receive a 10 USD subsidy every time their test was bought, until the 1 billion USD pot runs out (the subsidy can either be given directly to them or to the purchaser – both should have a similar impact upon

the market). The diagnostics that benefit from the DMS would not need to be specifically designed for 'infection x' – broad platforms that test for different types of infection, including 'infection x', would also be eligible, and indeed should be encouraged. If these tests also meet the criteria for another clinical area they would be able to benefit from multiple DMS.

Whether it will take six months or 20 years to come up with such products would not matter, the payer would commit to maintaining the market until the diagnostics are available, provided the pot does not run dry in the meantime due to subsidies paid to competing products that are earlier to the market. Firms would be incentivised to surpass the minimum requirements because this would make doctors more likely to use their product, thus increasing the amount of the pot they get. More ambitious requirements could act as a guide to developers of what clinicians would want in order to use their products.

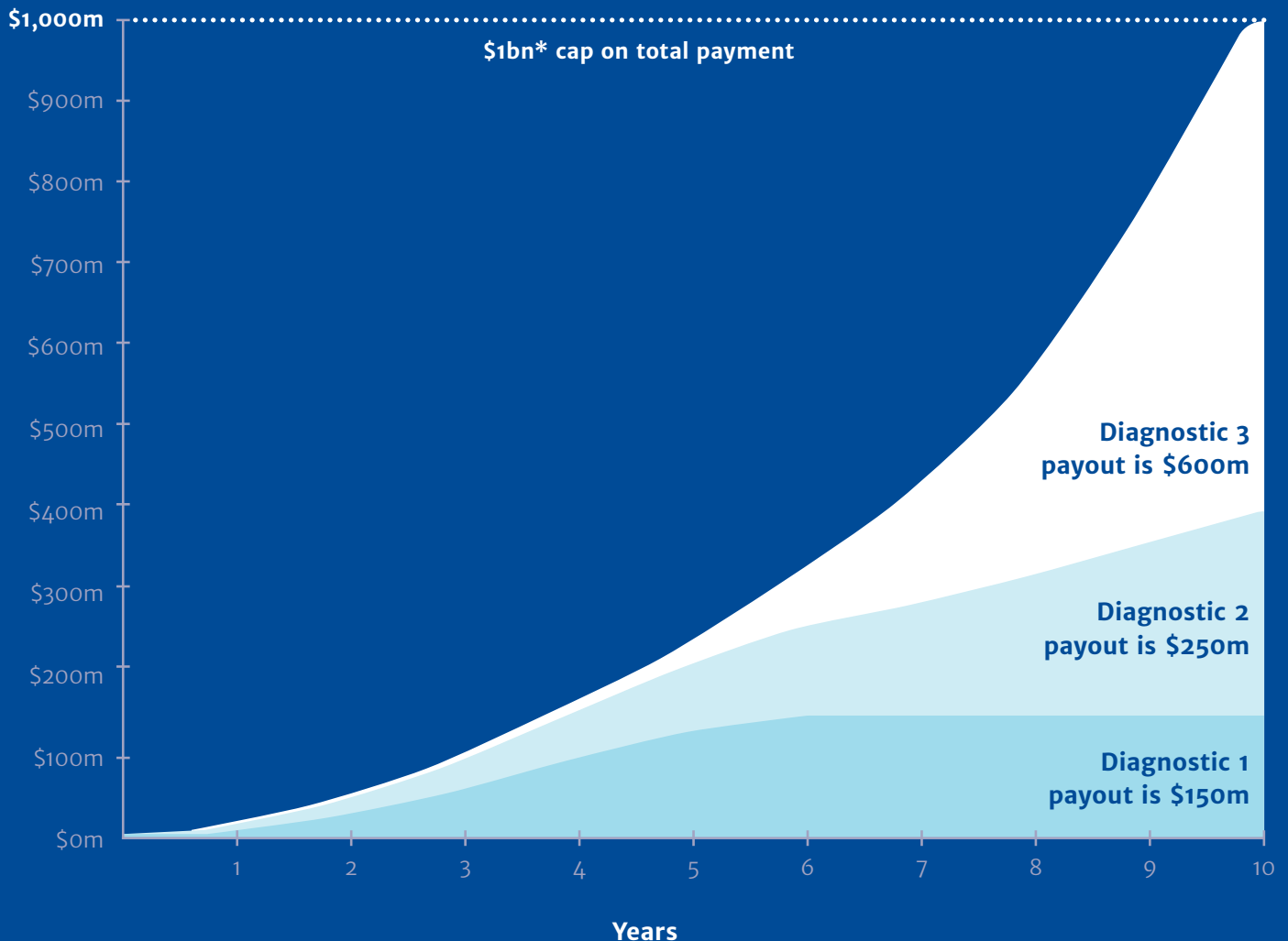
Why infectious disease diagnostics differ from those in other areas of medicine

What particularly justifies subsidising infectious disease diagnostics, in contrast to innovations relating to non-communicable diseases, is that other people in society face negative consequences when infections are not dealt with properly. As we have already discussed, one of the problems with diagnostics for antibiotics is that often the test costs more than the medication. For the patients it thus often makes

sense to take the drug and not use the test. In some other areas of medicine this might be fine. But taking antibiotics unnecessarily can lead to drug resistance that impacts others. So it makes sense for everyone in society to help pay for the diagnostic, in order to protect society from the spread of infections, in particular drug-resistant infections.

HOW A \$1BN* DIAGNOSTIC MARKET STIMULUS COULD WORK

An illustrative example: Cumulative payout from a Diagnostic Market Stimulus



- Diagnostic 1 is good and the first one on the market so receives first mover advantage
- Diagnostic 2 is the cheapest and is used in some low resource settings
- Diagnostic 3 enters the market four years after the other two, but is far better than the first diagnostic so replaces it on the market

* The "\$1BN" figure has been used for simplicity and does not refer to the actual amount that may be needed. More research is needed to estimate the cost of each Diagnostic Market Stimulus.

N.B. This is a cumulative graph, so the figures listed in each year represent the total pay-out that each company has received up until year 10.

4b.

Funding from a Global Innovation Fund to jump-start innovation of rapid diagnostics

In addition to DMS pots, there is a strong case for push funding for rapid diagnostics. In the Review's **February and May 2015 papers**, we recommended a global innovation fund of 2 billion USD over five years to jump-start early stage research. This Fund should be made available to those looking to create new rapid diagnostics and those in other technology sectors or even the social sciences that may influence prescription or improve use. One example would be advanced computer systems that can guide clinicians effectively to appropriate treatment.

'Push' funding is generally best used when there is a high risk of failure that the private sector is unwilling to take on. With early stage medical research the risks can be so high that people will not invest, regardless of potential future rewards.

There is also a case for funding innovations through early clinical development stage, the so-called 'valley of death', when many small and medium-sized developers struggle to raise enough capital to progress.

There may be areas of diagnostics where it makes sense to support (particularly early stage) research being made publically available through common platforms or a standard code of practice. In these areas we believe it might make sense for the innovation fund to help navigate blockages in the system.

4c.

Health systems should help build the economic case for rapid diagnostics and also support developers to build the clinical case

For health systems to adopt new technology, clinical value and cost benefit must be demonstrated. The best way to do this is through large controlled trials to demonstrate clinical effectiveness, and cost benefit studies to demonstrate economic value to regulators and healthcare providers. The cost of clinical trials is usually born by the company developing the technology and can be in the region of tens of millions of USD for new diagnostic technology. There is a strong case for health system funders, or non-profit funders, to support interventions to accelerate the pace of innovation.

Firstly, we think healthcare systems can make clinical trials cheaper in this area by encouraging shared clinical trial platforms – this is true for both diagnostics and new therapeutic products. While developing our proposals on diagnostics, we have also been struck by the scope for publicly-supported clinical trial platforms. They could reduce the cost and accelerate the process of achieving clinical effectiveness. Appendix D sets out some of these ideas in more detail.

Secondly, payers should fund cost-effectiveness studies that consider how diagnostic tests may decrease overall costs for a hospital or a healthcare system, despite increasing spending in parts of that hospital or healthcare system budget.

Prizes

We welcome the UK Longitude prize, as well as the US and European Commission prizes in this area. They have reinvigorated this space by giving far more attention to AMR and the important role that diagnostics can play in tackling it, which has been incredibly valuable. In our last paper we recommended lump sum payments in order to incentivize the development of new antibiotics (a prize based system) and we think that in this field they can also play an important role.

But to go further the sums involved would need to be larger to truly change the landscape, and for such an intervention lump sum prizes are not our preferred choice. The diagnostic market is more diverse than the drug development market, making it harder to definitively pick winners. Diagnostics, unlike drugs, do not have negative externalities, and their value can be judged based on the amount that they are used. Because of this we feel that a payment based on the amount the product is used is the best way forward.

5. WE CAN IMPROVE OUR USE OF ANTIBIOTICS TODAY BASED ON EXISTING DIAGNOSTICS, COUPLED WITH PUBLIC EDUCATION

5a.

Clearer guidelines for doctors and awareness of cultural attitudes to prescribing, could help reduce unnecessary use of antibiotics, alongside diagnostics

It is clear that behaviour change, for doctors and patients, will be needed in order to encourage the appropriate use of diagnostics. However, even when a diagnostic is not needed to guide prescription, we waste antibiotics, allowing an opportunity for drug resistance to increase.

The problem of unnecessary use of antibiotics is widespread even where there is clear medical evidence, for example with respect to 'prophylactic use' (where antibiotics are used preventatively to ward off potential infections in vulnerable people).

For example, it is established in medical literature²⁶ that a very short course (one or possibly two doses over less than 24 hours) of pre-operative antibiotics is the correct duration for most clean surgical procedures such as a hip replacement. But, a study by Michael Borg²⁷ of European hospitals found that there is enormous regional variation in practice, ranging from less than a day to multiple days. Indeed, a recent survey published by the European Centre for Disease Prevention and Control (ECDC) indicated that in 70 percent of the participating countries more than half of surgical procedures were preceded by prophylactic antibiotic courses lasting more than 24 hours²⁸.

Why is there such variation when the evidence is clear that dosing for longer than 24 hours is not necessary? Borg found that at least part of the difference was attributable to cultural biases, in particular the extent to which the particular society tolerates uncertainty. The doctor in this circumstance may think they are 'going the extra mile for their patient'. However this did not seem to be purely attributable to the doctor's behaviour, but also reflected the expectations of the patient

and the patient's family. Strategies for improving stewardship, including assimilating new diagnostic tests into patient care need to consider these cultural factors. This also highlights the importance of raising public awareness of AMR and to improve the use of antibiotics.

Furthermore, a systematic review examining interventions to improve antibiotic prescribing practices for hospital inpatients showed that many interventions designed to stop antimicrobial resistance have a positive impact. However in most cases when prescriptions levels are measured six months later most of these benefits had gone and there were no significant differences at 12 or 24 months²⁹. This shows the need for careful and well thought out change, interventions should not simply be short term, but should try to change the way prescribers and patients act, as well as changing the culture in hospitals. One of the reasons that we strongly support diagnostics is that we believe they can make long lasting changes in the way we fight infectious disease.

5b.

Educating the public could support doctors to prescribe fewer antibiotics

In this paper we have primarily focused on the market for diagnostics as we believe that they are an essential part of the strategy to combat AMR. However, in addition, raising awareness of AMR amongst doctors and their patients, such that both parties understand the long term impact of prescribing antibiotics, is a very important goal. Such understanding could reduce pressure on doctors from patients to prescribe, a pressure that could feel particularly worrying in litigious health systems. It could also keep doctors more alert to 'decision fatigue' which has been demonstrated to lead to a higher level of antibiotic prescribing towards the end of working sessions. Antibiotic prescription levels often peak before lunch time and towards the end of afternoon clinics³⁰.

The use of delayed prescriptions has been shown to reduce antibiotic use effectively without excess morbidity³¹. This can enable doctors who are uncertain if an infection is bacterial,

²⁶ Healthcare Improvement Scotland, SIGN 104: Antibiotic prophylaxis in surgery, A National Clinical Guideline, 2008 Updated 2014, ISBN 978 1 905813 34 6, [Online] <http://www.sign.ac.uk/pdf/sign104.pdf>

²⁷ Borg, M. Prolonged perioperative surgical prophylaxis within European hospitals: an exercise in uncertainty avoidance? *Journal of Antimicrobial Chemotherapy*; 2013. doi: 10.1093/jac/dkt461

²⁸ Ibid.

²⁹ Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2013 Apr 30;4:CD003543

or who are under pressure from patients to prescribe, to send the patient away with a delayed prescription that they can only pick up a few days later. If their symptoms improve in this time, the patient is less likely to collect and use the antibiotic. This approach could potentially be enhanced by integrating existing diagnostic tests that provide conclusive results but take time.

Improving global public awareness of AMR and the negative side-effects of using antibiotics when they are not needed, would help to address some these issues and the Review recommends that a global public awareness campaign should be started that makes good use of new technology and social media, to spread important messages on AMR to audiences across the world.

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6.

NEXT STEPS

6a.

Improving the human use of antibiotics is a crucial part of the fight against AMR – but there are other issues we need to address as well

In our last paper we outlined recommendations to improve the supply of new antibiotics. We have subsequently been examining issues on the demand side, starting with this paper, which looks at the problem with unnecessary use of antibiotics in humans. This paper proposes that health system funders and international organisations make greater efforts to encourage innovation in the field of diagnostics and also make better use of the technology currently available.

Going forward we will provide analysis and recommendations in multiple areas including:

- **Agriculture and the environment.** A large proportion of the global consumption of antibiotics is in the agricultural sector. We will examine the health and economic impacts of this as well as the wider impact of antibiotics in the environment.
- **Preventing and limiting the spread of infections.** Prevention removes the need for therapeutic treatment, thereby reducing the need for antibiotics to be used. The ways we can improve this range from washing our hands better, to improving global health infrastructure and surveillance systems, to track and act on the spread of resistant infections.
- **Alternatives to antibiotics.** Although antibiotics have become the dominant treatment for bacterial infections and will continue to play a key role, there are other opportunities to tackle bacterial infections that we will explore, including the role of vaccines, phage and other alternatives therapies that could replace or accompany antibiotics.

6b.

Moving towards tangible political action

AMR is one of the biggest health threats that the world faces, but it is not beyond the world's ability to tackle, either economically or scientifically. The economic cost of inaction, with a potential hit to the world economy of 100 trillion USD by 2050, dwarves the cost of action, which will be less than 0.1 percent of global GDP. This is not to mention the many millions more lives that will be lost if rapid progress is not made.

As well as developing new drugs, we must use our existing and new drugs better. Resistance will never be eradicated but it must be managed, and by reducing unnecessary use of antibiotics we can help slow its rise, and ensure our medicines work when they are most needed. We hope that world leaders take note of this problem and use international forums including the G20 and the UN General Assembly next year, to agree specific recommendations for action.

APPENDIX A

OUR DIAGNOSTIC ‘WISH LIST’

In order to develop the Diagnostic Market Stimulus pots suggested in this paper there would need to be consultation with healthcare professionals to ensure that future products better match consensus needs and so merit wide adoption. To give some initial indication, a small group was consulted. Their suggestions for ‘game-changing’ diagnostics, by no means exhaustive, were:

1. Rapid diagnostics that could be used at home to indicate bacterial or viral infections. These would potentially reduce visits to the doctor and so reduce healthcare resource consumption.
2. Biomarker panels to distinguish whether patients admitted via A&E for pneumonia or fever have bacterial infections or not.
3. A bedside test that would reliably exclude any infection. This should reduce the empirical use of antimicrobials and could also often be used as part of the treatment protocol for sepsis. Patients with heart failure are often being misdiagnosed and treatment delayed.
4. A definitive test to confirm a viral infection. A lot of money is spent looking for the cause of viral infections, the majority of which cannot be detected by existing technology.
5. Rapid tests to rule out bacteria or fungi in blood cultures, so reducing time to conclude that a negative result is real and offering the chance to reduce the length of unnecessary antibiotic treatment by several days.
6. Rapid categorisation test for pathogens and resistance. Easier in samples from sterile sites than in samples from sites with potential pathogens and normal bacterial flora.
7. There is opportunity to develop new tests that make use of technologies and platforms that are already being adopted widely in diagnostic laboratories. It should be easier to encourage wide adoption of such tests faster than those that rely on novel technologies. Combining reliable resistance detection with ‘MALDI-ToF’³², which is increasingly used to identify bacteria would be enormously helpful and efforts to make commercial solutions available should be accelerated.
8. “Fast and frugal heuristics”³³ that can provide reliable guidance to clinicians on the need to prescribe antibiotics. These are rules of thumb that integrate a small number of immediately available data sources to support a decision that is ‘*satisficing*’ – both satisfactory and sufficient. An example of the principle is the CENTOR score³⁴ although the clinical benefits from this example are possibly not that significant.
9. Comprehensive sequence-based or rapid phenotypic resistance diagnostic able to detect ALL species and resistance working from clinical specimen (blood, urine or deep lung), or after brief (less than four hours) growth.

³² Matrix-assisted laser desorption/ionization – Time of Flight (MALDI-ToF) is a relatively new, quick and effective, lab based method for diagnosing bacterial types, that it is hoped in the future will be able to distinguish some types of resistant bacteria.

³³ <http://fastandfrugal.com>

³⁴ The CENTOR criteria is a method to predict whether patient will have culture-confirmed *Staphylococcus aureus*.
<http://www.mdcalc.com/modified-centor-score-for-strep-pharyngitis>

10.

Rapid tests to detect gonococci (which cause gonorrhoea) and confirm susceptibility at presentation to ciprofloxacin, penicillin, ceftriaxone / cefixime and azithromycin.

11.

A reliable molecular test for clinical infections with all species of *Legionella*. Most people still rely on urinary antigen testing.

12.

Tests to be used mainly in primary care that would allow the antimicrobial management of the commonest infections (chest infection, UTI, pharyngitis) to become evidence-based, with effective antimicrobial stewardship to help control resistance. These might include: (i) rapid (i.e. within one hour) detection of 'pneumococci' in sputum and measurement of their susceptibility to penicillin, erythromycin and tetracycline; (ii) rapid AMR assessment directly on urine samples for patients with suspected UTI; and (iii) rapid detection of group A streptococci plus penicillin / erythromycin susceptibility for patients presenting with a sore throat.

What this list clearly indicates is that there is no shortage of areas where diagnostics are needed, what is needed now is to have a framework to encourage innovation to tackle these problems.

APPENDIX B

HOW DIAGNOSTICS CAN CHANGE THE DRUG PARADIGM

The introduction of diagnostic tests that allow for rapid identification of bacteria at a very detailed level (for example, recognising strain types, resistance mechanisms, etc.) promises not just to bring benefits for direct patient care, but also for clinical trials that are essential to the development of new antibiotics.

At present, the efficiency of clinical trials for novel antibiotics active against bacteria resistant to existing drugs is undermined by difficulties in identifying and recruiting suitable patients; such studies take longer, cost far more and must recruit far greater numbers of patients. This is because when a patient presents with an infection – and when a hospital participating in a trial might recruit them – there is currently no way of rapidly identifying whether they are infected with bacteria of the ‘right’ species or with the ‘right’ resistance(s) to make them eligible for inclusion in the study. As a consequence, either (i) patient enrolment will be delayed until a positive laboratory diagnosis can be made, by which time another treatment will most likely have been prescribed, potentially compromising inclusion of that patient as a trial subject, or (ii) patients will be recruited to the trial but will subsequently be found not to be in the target group for the drug. These problems are particularly acute for trials of drugs that target resistant bacteria that are currently very rare, and serve to exacerbate existing problems inherent to the design of clinical trials for narrow-spectrum antibiotics.

An ability to identify the exact cause of a patient’s bacterial infection (and its susceptibilities) has the potential to overcome these issues and markedly improve the ability of drug developers to run appropriately targeted and therefore efficient clinical trials to test drug efficacy. The subset of patients suitable for recruitment to trials could be quickly and efficiently identified, allowing patients to be consented and recruited in a timely manner, before other treatments have started in earnest. Fewer patients would be recruited into trials inappropriately – something that has potential to somewhat reduce the costs and administrative overheads associated with conducting the trial.

Substantial problems will still remain in designing and conducting trials for new antibiotics, particularly in a way that demonstrates a new product’s clinical superiority to existing treatments, as opposed to simply its ‘non-inferiority’. Where the resistant strains being targeted are especially rare, it will always take considerable time to recruit an adequate number of patients to a trial, particularly when this will often need to be done at a time when a patient is acutely ill. But by reducing some important inefficiencies in the way that eligible patients are identified, a new generation of diagnostics has the potential to offer an important – if not entirely paradigm-shifting – contribution to wider efforts to facilitate successful antibiotic development.

Diagnostics will therefore allow us to use narrow agents instead of broad agents which are both easier to fund and as we discussed earlier, less likely to generate resistance.

APPENDIX C

WHY THE INVESTMENT CASE FOR FIRMS TO DEVELOP RAPID DIAGNOSTICS FOR INFECTIOUS DISEASES IS GENERALLY UNCERTAIN

Diagnostic devices do not generally have to conform to the same stringency of trials expected of drugs in order to receive approval to be sold, especially in the EU, where multiple agencies can clear, or 'CE Mark' a product. In practice, this means that diagnostic devices can reach the market with relatively little evidence of their merits in a clinical setting (both in terms of efficacy and cost-effectiveness). Purchasers may therefore feel that they do not have enough clinical evidence to buy the tests, and that there is too much risk as the testing has not been extensive enough. Different payers may also have different demands with respect to the level of evidence needed, and what test they want. These needs and preferences can be hard to navigate, especially for small companies. The speed of advances in the technology sector can also be incredibly quick. This combined with the amount of time it currently takes to get through the regulatory process, find funding and build the evidence to convince purchasers of the value of the product, means that the technology has often moved on before the product gets to market. This can be a limiting factor for change since buyers may question an investment that already appears 'out of date'.

The fundamental problems involved in the development of diagnostic devices are somewhat different from those related to antibiotics. With antibiotics, the fact that resistance builds up with increased use makes the current model, of making profit on a per pill sold basis, problematic. In addition, given that it is difficult to predict the rise of drug resistance, a useful drug for the future may come to the market when there is not yet large demand because other cheaper drugs are still effective. If a new antibiotic is used when dictated by resistance to alternative drugs, its patent may well have expired before it is needed in large quantities, meaning that the developer cannot make the level of financial return they need to.

In contrast, diagnostics can be sold on a volume basis without fear that their use will make them ineffective. They also usually have shorter development cycles than antibiotics (which may take 10–15 years to develop). However, there are some common features, namely payers' unwillingness to pay high prices and the risk of free riders (when people try to benefit from a system without paying into it).

The cost of point-of-care diagnostics are often also accrued in a different area to the gains, e.g. a primary care facility may pay for a diagnostic device that reduces the probability of a patient being admitted to an intensive care unit.

Not only are these financial gains very hard to quantify and can accrue over a long period of time, but even if they are calculated, the primary care facility might not receive a financial gain itself, even though it is paying for the test.

As for drug development, companies investing in diagnostics must sink considerable resources into developing a number of years before they can hope to generate revenues. Once they are approved for sale, and crucially after these costs are sunk, purchasers (of which there are likely to be only a few major players, although this varies by country) will seek to obtain the lowest possible price. The device developer's bargaining power at this stage relies on their ability to demonstrate value and ideally to demonstrate that their device helps address an unmet medical need. As we have discussed previously, this can be more challenging in some infectious disease settings. This search for the lowest possible price, by necessity, may be required for rapid point-of-care diagnostics that meet the need of those on very low incomes in many parts of the world, where such diagnostics will only be available and affordable if the marginal cost of production is low along with the price.

The long-term social value of a new diagnostic, just as for a new antibiotic, is likely to far outweigh the value that accrues to any single funder. This creates the incentive for each country effectively to free-ride on medical advances achieved with the help of other funders. In other words, the incentives for any one funder to help in developing a new diagnostic test are weaker than those of all funders together. This type of under-provision of a global public good is similar to the problem that can be seen in vaccines, where concerted efforts by governments and non-profit funders have been necessary to incentivise innovation and delivery. Similarly important is the coordination problem among drug developers, sharing the need for a common companion diagnostic, which might reduce their individual costs of clinical trial recruitment.

APPENDIX D

THE CASE FOR SUPPORTING FASTER AND CHEAPER CLINICAL TRIAL NETWORKS FOR DEVELOPING RAPID DIAGNOSTICS

Standard practice for clinical trials

Clinical trials play a vital role in bringing new and particularly more complex point-of-care medical devices into the market. They are not only needed to convince regulators that the new device or system works and are safe, they also important for convincing doctors and healthcare systems of their efficacy. Regulation for point-of-care diagnostics is not as stringent as it is for drugs, meaning that developers are not forced to put their product through as many trials to get it on the market. While this is good for getting products on the market, the low levels of evidence can make doctors wary of using them.

With antibiotics and other drugs, pharmaceutical companies are often willing to invest money in trials that are not required by regulation, in order to build an evidence base to get doctors and prescribers to use their product. However in diagnostics this seems not to happen for several reasons. Clinical trials can take two to three years to run and are very expensive. This is problematic because diagnostic technology and development advances much more quickly than drugs, so by the time evidence has been built on a diagnostic it can already be out of date. Diagnostic companies at the moment are often much smaller than pharmaceutical companies who do late stage development, this means they often do not have the resources or expertise to undertake these studies.

As a solution to these problems, we propose enabling either hospitals or networks of physicians to become point-of-care diagnostic test specialists, where economies of scale can hugely reduce the cost of testing a diagnostic. Many of the delays that lead trials to take years can be avoided. Ethical approval can take 3-4 months for every new trial. While this makes sense in drugs when a patient's treatment pattern is changed, testing the accuracy of diagnostics need not change the way patients are given treatment when they are used in a clinical trial, thus a system of blanket rule giving ethical approval to these trials should be possible. If testing diagnostics is common practice, then there can be one standard process that new tests can be dropped into, rather than creating one for every test. This can include things like having a template contract and price for doing the trial, which will again reduce the trial time and cost to each trial. Finally, because it will be so much easier to set up test sites

and have the diagnostics tested, we hope that more patients can be tested more easily and this will significantly reduce the time that it takes to run a full trial. We believe that if such a system was introduced it could reduce trial times down to three to six months. These networks can be set up in such a way as to still allow companies to keep commercially sensitive information to themselves as they do at present, so long as they do not hide information that will hinder human health.

Reducing the time and cost of trials, should not only improve uptake, but it will hopefully improve the diagnostics themselves. If diagnostic companies are able to get back reliable information quickly on their products' accuracy and sensitivity, they will be able to more easily tweak their products and re-test them under the current system.

Consistent standard of evidence

As well as better procedures in place to run trials of point-of-care diagnostics, hospitals and health professionals need to standardise the evidence they use to accept such devices. A constant complaint that diagnostic companies have raised is that the evidence needed to secure adoption and uptake of a point-of-care diagnostic differs between countries, regions and even hospitals. This makes it very difficult for even the best diagnostics to be rolled out and means that a large amount of time and money sometimes has to be spent to get a diagnostic into the right settings.

There is a further role for health system funders to play in developing and disseminating a consistent evidence base about these products. Health technology assessment agencies, for instance, or major social and private insurers could play an important role in supporting the uptake of point-of-care diagnostics by developing and disseminating clear evidence reviews and best practice guidelines. These will support uptake by clinicians and overcome some of the challenges faced by product developers.

APPENDIX E

OTHER MECHANISMS TO SUPPORT INNOVATION THAT WE HAVE CONSIDERED BUT WE THINK WOULD BE LESS EFFECTIVE

Intellectual property protection

We do not think that extending the market exclusivity of a product is a sensible way to improve investment in diagnostics for two reasons. Firstly, is that extending the revenue runway by many years gives a relatively small expected return at the point of R&D spending, because developers will use relatively high discount rates for investment analysis. These discount rates will generally be higher than for government or non-profits, reflecting higher cost of funding and the individual product's risk of failure. Thus, society will have to pay developers a lot in the future to convince them to bear the development risk today. Secondly, the diagnostics market typically changes more quickly than the drugs market, meaning that something that is invented now is far less likely to be relevant in 20 years. As such an extended period of market exclusivity once on the market is less likely to be valuable for a diagnostic than for a drug or, if it is, that might reflect an inappropriate deterrent to new market entrants.

Diagnostic related groups

Many health systems use tariff-based systems of reimbursement which see hospital providers being paid a fixed sum for each patient 'episode' depending upon that individual's symptoms and the recommended treatment. All inpatient costs, including diagnostics and medication, are bundled into a single tariff for a given 'diagnosis-related group' (DRG). Such systems are a popular – and largely effective – means of promoting efficiency and cost-control within healthcare systems. However, unless they are highly responsive to the emergence of new medical innovations, that enhance overall outcomes but may increase upfront per patient costs, they can unintentionally act as a deterrent to the uptake of new technology. Policy-makers and healthcare payers therefore need to ensure that innovative diagnostic technologies are properly priced into DRGs relating to the treatment of infections. This could also go a step further, and use DRG-based systems to make the use of rapid diagnostics a condition of reimbursement against relevant conditions.

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

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Professor Mark Woolhouse OBE, Centre for Immunity, Infection and Evolution, University of Edinburgh

Dr Anna Zorzet, Coordinator for ReAct in Europe

NEW ADVISORY GROUP MEMBERS

We are delighted that three new members have joined our informal advisory group this month from India and Brazil:

Congressman Antonio Brito, Chair of the Commission on Health and Social Security of the Brazilian Parliament

Dr Yusuf K. Hamied, Chairman of Cipla

Dr Milton O. Moraes, Dean of graduate Programs, Fundação Oswaldo Cruz in Brazil

They join current members:

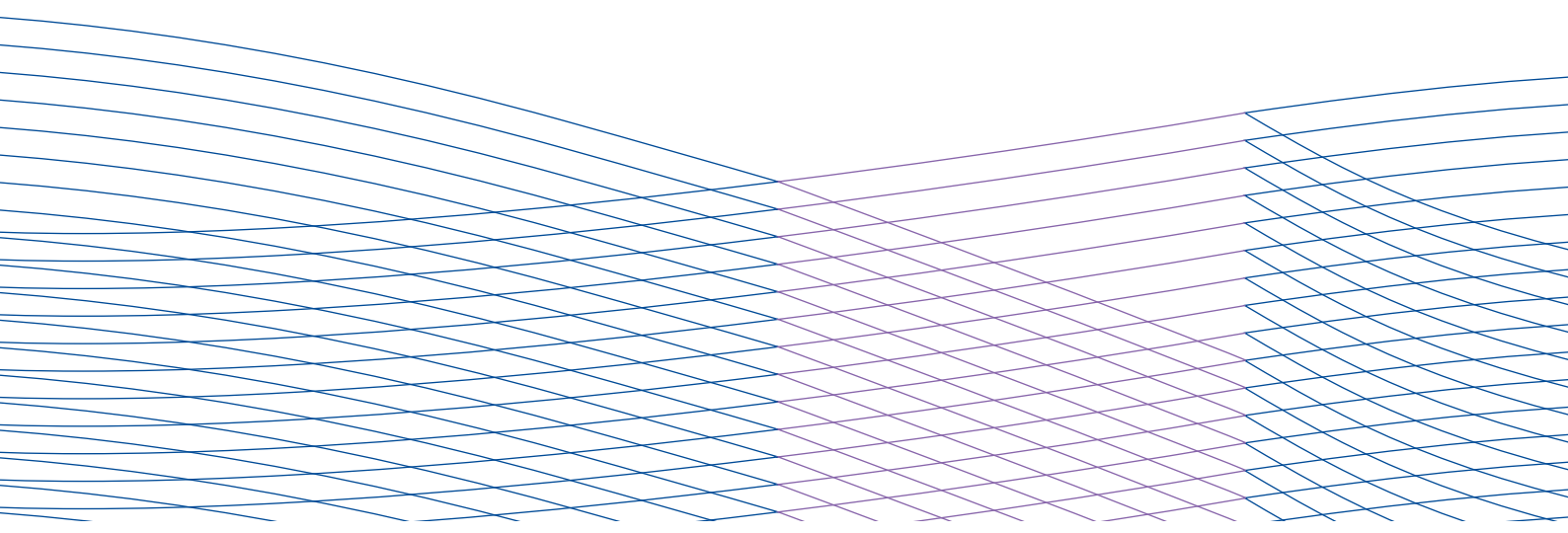
Michael W. Bonney, President and Chief Executive Officer of Cubist 2003 to 2012

Dr Sanjeev Chaudhry, Managing Director of SRL Limited, India

Nana Kuo, Senior Manager of the Every Woman Every Child Health Team in the Executive Office of the UN Secretary-General, United Nations, New York

Dr Ren Minghui, Director-General for International Cooperation, China National Health and Family Planning, Beijing

Dr Steven Solomon, infectious disease physician, formerly Director of the Office of Antimicrobial Resistance at US CDC and retired from the United States Public Health Service at the rank of Rear Admiral.



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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