VACCINES AND ALTERNATIVE APPROACHES:
REDUCING OUR DEPENDENCE ON ANTIMICROBIALS

**THE REVIEW ON
ANTIMICROBIAL RESISTANCE**

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CONTENTS

EXECUTIVE SUMMARY

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

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

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

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

There are also many vaccines that we know would play a crucial role in tackling drug resistance but that are not on the market or even in early stages of development. The three "urgent" resistance threats highlighted by the US Centers for Disease Control and Prevention (CDC) are carbapenemase-producing bacteria (including *Klebsiella*, *E. coli*), gonorrhoea and *C. difficile*. There are no vaccines currently in use for any of them and too few candidates in clinical trials. Vaccine development is a high risk endeavour, with high chances of failure, and often takes

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

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

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

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

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

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

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

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

INTRODUCTION

In this latest paper published by the independent Review on Antimicrobial Resistance, we consider the impact and the potential of vaccines and other alternative approaches to tackling infection and drug resistance. In previous papers we have assessed the market for antibiotics and diagnostics, and analysed what could be done to kick-start early-stage research to develop products that can treat the biggest threats we face from drug-resistant bacterial infections. Antibiotics have dramatically improved life expectancies across much of the world over the last 70 years, and will continue to do so. However, because of the inevitability of drug resistance, and the significant scientific challenges of discovering new antibiotics, it is right to also consider the potential of alternative medical interventions to slow the spread of resistance to antibiotics[1]. On the current trajectory we are not moving fast enough – we are losing antibiotics and not finding enough replacements or alternatives to keep up with the spread of resistance. The medical advances we have seen over the last 70 years are in danger of being seriously eroded unless action is taken now to renew development pipelines.

Some of these alternatives will be therapeutic, treating an existing infection. Others, including vaccines, are more likely to be preventative – given to healthy people (or animals), or groups at high risk, to protect them against infection. While we will continue to need a robust and sustainable pipeline of therapeutics, we also need to consider the value of preventing infections in the first place: to the individual patient in question, to wider society and to healthcare systems. In this paper we will discuss the potential that we see in such products and the barriers to their development and uptake.

There has been international recognition of the importance of vaccines and other interventions as part of the package of measures to combat antimicrobial resistance (AMR), including by the World Health Organization (WHO) in the Global Action Plan, adopted at the 2015 World Health Assembly. This agreement stated that this area should be encouraged and needed more investment. This investment should include basic research, since there are many fundamental scientific problems to be overcome in addition to problems with the markets for these products.

In this paper we assess the problems faced in developing vaccines and alternative approaches to tackle drug resistance, and set out how the world could take action to encourage further innovation and improve the uptake of products. It follows a five-part outline: First it examines the current pipeline for vaccines, how they could be used, and which vaccines we need most to tackle AMR now and in the future. Second it examines the market for these vaccines and the difficulties faced to develop successful products. Third it discusses other alternative approaches that have the potential to fight infection and tackle resistance. Fourth it looks at the particular problems faced in the market for alternatives. Finally, it proposes policy interventions to tackle the problems identified for vaccines and alternatives.

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[1] In this paper, 'antibiotics' refers to antibacterials, although similar considerations would also apply to antifungals.

The work of the Review

Our Review was commissioned by the UK Prime Minister, and is hosted by the Wellcome Trust, tasked with recommending by the summer of 2016 a comprehensive package of actions to tackle AMR globally. In the meantime, we are publishing a series of papers looking at individual aspects of the wider AMR problem[2], of which this is the latest.

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

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

In May 2015, *Securing New Drugs for Future Generations* examined the problems of antibiotic development and outlined our initial proposals for bold action by governments around the world to stimulate and incentivise the development of much-needed new antibiotics. This identified key gaps in the antibiotics pipeline, and called for a global system of antibiotic market entry rewards, offering lump-sum payments to successful developers of antibiotics that meet a defined clinical need. This package of action — designed to support a pipeline of 15 new antibiotics over a decade — was costed at between 16 billion and 37 billion USD over ten years.
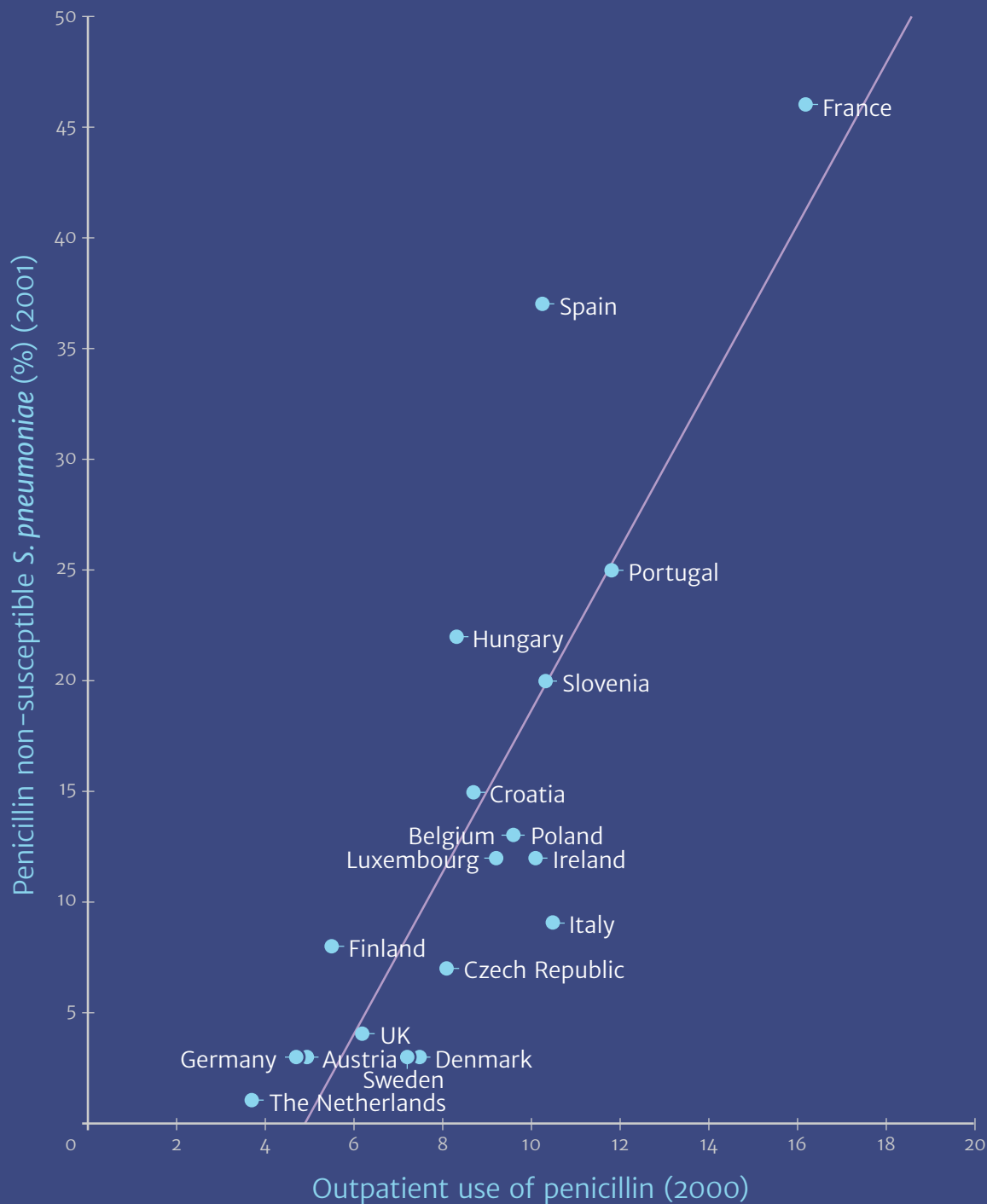
In October 2015, *Rapid Diagnostics: Stopping the Unnecessary Use of Antibiotics* examined the extent of unnecessary use of antibiotics and how the world can combat this with rapid diagnostics. We proposed three interventions to encourage innovation and uptake of diagnostics for bacterial infections: firstly, Diagnostic Market Stimulus pots to provide payments for successful products that are purchased. Secondly access for diagnostic developers to bid for funds from a Global Innovation Fund, and thirdly, support to build the economic evidence for rapid diagnostics.

In December 2015, *Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste* analysed the widespread use of antibiotics in food production as well as how antibiotics reach the wider environment. We proposed solutions to tackle these issues, including: a global target to reduce antibiotic use in food production to an agreed level per kilogram of livestock and fish, along with restrictions on the use of antibiotics important for humans, as well as the rapid development of minimum standards to reduce antimicrobial manufacturing waste into the environment, and improved surveillance to advance the monitoring of these problems.

After publishing this paper on vaccines and alternatives to antibiotics, we will publish one more themed paper in the spring of 2016, exploring the role of sanitation and infection prevention and control measures in reducing the global burden of drug resistance. Thereafter we plan to publish our final report to the UK Prime Minister in May 2016.

[2] All the publications of the Review on AMR are available on the website:
http://amr-review.org/

THERE IS A HIGH CORRELATION BETWEEN ANTIBIOTIC USE AND RESISTANCE

Scatter plot. Y-axis: Penicillin non-susceptible *S. pneumoniae* (%) (2001), ranging 0 to 50. X-axis: Outpatient use of penicillin (2000), ranging 0 to 20.

Data points:
- France
- Spain
- Portugal
- Hungary
- Slovenia
- Croatia
- Belgium
- Poland
- Luxembourg
- Ireland
- Italy
- Finland
- Czech Republic
- UK
- Germany
- Austria
- Denmark
- Sweden
- The Netherlands

Review on Antimicrobial Resistance

1.

DO WE HAVE THE VACCINES WE NEED TO PREVENT INFECTIONS? A PICTURE OF THE CURRENT PIPELINE

Vaccines are considered among the most cost-effective ways to prevent morbidity and mortality from infectious diseases[3]. Indeed, vaccines against infectious diseases have had a huge impact on human health in the last 50 years by controlling, and in some cases eradicating, many diseases, both viral (for example, smallpox, measles and polio) and bacterial (for example, diphtheria and tetanus) that were the cause of much death and disability in the 20th century. Many studies have shown the gains for human health, as well as costs avoided, by using vaccines. Globally, vaccination against smallpox is estimated to have prevented five million deaths, and vaccinations against measles and tetanus are estimated to save 29 million and 12 million Disability-Adjusted Life Years (DALYs) respectively[4]. Vaccines do not suffer from resistance in the same way that antibiotics often do, though the disease burden of vaccine-preventable diseases can shift to non-vaccine strains (see Appendix B).

There are four broad categories of vaccines useful to contain the rise of drug-resistant infections

In order to assess the landscape of relevant vaccines, we looked at those currently being used and the pipeline of new products. We then divided the pipeline into four broad categories of vaccine that are useful for AMR:

1. The first category is vaccines that prevent bacterial infections commonly acquired by the general population, often called 'community-acquired infections'. These vaccines prevent bacterial infections, thereby protecting individuals, while also negating the need for antibiotics, reducing the opportunity for bacteria to develop resistance. They might typically be considered for use on a universal basis or across large sections of a population, for instance as part of national vaccination and immunisation programmes. Examples include diphtheria, tetanus and infections caused by the pneumococcus or *Haemophilus influenzae* type B. We have vaccines in this category, including market 'blockbusters'. There are also some new candidates in development for this category, in part because there is evidence that the commercial returns can be good[5].

2. The second category is vaccines that would prevent bacterial infections commonly acquired in hospital, often called 'hospital-acquired infections'. Hospitals are where many fatal resistant infections often develop. Rather than being used across large sections of the population, such vaccines might typically be used on a more targeted basis amongst particularly high-risk populations. These infections are often caused by bacteria such as *C. difficile*, or those termed the 'ESKAPEE' group: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species* and *E. coli*. We lack licensed vaccines in this category, and the pipeline for these products is far from comprehensive, which is in part due to expected weaker commercial returns, despite the acute need. Furthermore, the poor immune status of many hospital patients will pose a scientific challenge to the success of any vaccines in this category.

3. The third category is vaccines that prevent viral infections. From the perspective of bacteria becoming resistant to antibiotics, these vaccines are important because a large proportion of unnecessary prescribing of antibiotics occurs for patients who have viral infections, even though the drugs will not help in these cases. Improvements in rapid diagnostics may reduce this inappropriate use, but more effective and widespread viral vaccines could reduce the incidence of infection itself, which would be good for patients and for prescribing trends. Examples of such vaccines would include those targeting flu and other respiratory viruses. These have the added advantage of preventing bacterial superinfections (an infection following a previous viral infection), further reducing antibiotic prescription. For instance, it is common for bacterial infections, which would need antibiotics, to follow viral infections such as the flu, which do not.

4. The fourth category is vaccines to prevent infections in animals, particularly farm animals, where a large volume of antibiotics are used. These can protect livestock and fish from infection, reducing the need for prophylactic and therapeutic antibiotic use. There are already vaccines on the market and in the pipeline. However, we note the importance of all-in costs (including of administration, e.g. through feed) when considering whether these are commercially attractive to farmers.

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[3] WHO, UNICEF, World Bank, State of the world's vaccines and immunization, 3rd ed. Geneva, 2009, World Health Organization.

[4] Ehreth J, The global value of vaccination, *Vaccine*, 2003, 21, 596–600.

[5] Tufts Centre for the Study of Drug Development, Impact Report: Analysis and insight into critical drug development issues, Vaccine products in the R&D pipeline have more than tripled since 2005,. 2015; 17: issue 4 (Jul/Aug)

We need to use existing vaccines more widely and effectively

Development of new vaccines is important, but even more important in the short term is ensuring that the vaccines that have been developed are accessible and being used for the people that need them most. Data from the WHO on global immunisation coverage in 2014, show that coverage by pneumococcal and rotavirus vaccines is only 31 percent and 18 percent, respectively[6].

In high-income countries, access to vaccines is often very good and is facilitated via robust and longstanding national vaccination programmes, which are run by governments through their public health authorities. In the UK, for instance, systematic vaccination of infants against smallpox was provided as early as the 1850s, and the national routine vaccination programme now provides more than 20 vaccines to infants, children, the elderly, and vulnerable groups. National systems in high-income countries of this type – offering universal or near-universal coverage across a population – represent significant purchasers of vaccines, effectively guaranteeing markets for vaccines that can be shown to be work, whilst also being cost-effective. They are supported in this work by expert advisory groups such as the National Vaccine Advisory Committee (NVAC) in the US and the Joint Committee on Vaccination and Immunisation (JCVI) in the UK.

In low and middle-income countries, however, improving access to vaccines has been a major issue over many decades. Multiple factors can result in uptake being low, and uptake can differ by income level. The prohibitive prices of new vaccines for low and middle-income countries mean that vaccine coverage is often the lowest in places where the disease burden is highest. A report by Médecins Sans Frontières (MSF) showed that the cost of immunisation of children in 2014 was around 68-times higher than in 2001, mainly due to the addition of expensive vaccines such as the rotavirus, pneumococcal conjugate and Human Papilloma Virus (HPV) vaccine[7]. Other factors that make access to vaccines more difficult include poor health infrastructure and systems that make it difficult to deliver them to the places where they are needed. In 2009 UNICEF estimated that almost 20 percent of the children born each year in low and middle-income countries did not have access to vaccines[8].

Low vaccine coverage can also be seen in high-income countries, where the issue is often uptake rather than access. This can be due to several factors, including anti-vaccination scares[9] and vaccines targeting the wrong strain of virus.

Support for vaccines in low and middle-income countries

Vaccine access initiatives for low and middle-income countries have contributed to the increase in vaccine coverage in many countries over the last few years, though there is still much more to be done. There are several public-private initiatives such as Gavi, the Vaccine Alliance, PATH, the Gates Foundation, and Clinton Health Access Initiative, among others, that use different funding strategies to bolster development and access to vaccines.

One of these strategies is the use of Advance Market Commitments (AMCs), which have come to play an important role in improving access in low and middle-income countries. They work by creating a market for products that were not deemed economically viable by promising a pre-agreed, legally binding price and volume guarantee for the vaccine when it comes to the market. AMCs have been used by the Gavi with great success over the last decade or so. Gavi pools the vaccine demand of low-income countries and tops up the price that the developer receives for producing vaccines for these countries. This has two advantages, firstly by pooling demand Gavi ensures that the prices for vaccines drop and the top-up on the price of the vaccine that comes from Gavi ensures that

producers get sufficient reward. The producer, in turn, commits to a long-term supply of the vaccine at the pre-agreed price to ensure that the Gavi-eligible countries are assured a supply of these vaccines. Gavi initiated a pilot project for an AMC for pneumococcal vaccines that has achieved much in the last few years. It is estimated that more than 25 million children were vaccinated with AMC-supported pneumococcal vaccines in 2014[10].

Though there has been an increase in vaccine coverage in low and middle-income countries, there is still a very long way to go, before we can ensure that the benefits of vaccination are felt equally across the world. In particular, there remain significant challenges associated with ensuring the sustainability and affordability of vaccines for the growing number of emerging economies which are 'graduating' from eligibility for development aid and Gavi support – key mechanisms for supporting access to vaccines in the developing world. Access to and uptake of vaccinations, such as those against rotaviruses and pneumococcal disease, by low and middle-income countries should be a priority for the international community.

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7 Médecins sans Frontières, The Right Shot: Bringing down barriers to affordable and adapted vaccines, 2015, 2nd Ed.

8 WHO, UNICEF, World Bank. State of the world's vaccines and immunization, 3rd ed. 2009, Geneva, World Health Organization.

9 Parry J, No vaccine for the scaremongers, 2008, Bulletin of the World Health Organization, Volume 86, Number 6, June 2008, 417-496

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VACCINES CAN REDUCE ANTIBIOTIC USE IN HUMANS

Reduce the number of bacterial infections that need antibiotics

Reduce the number of drug-resistant infections

Reduce the number a of viral infections for which antibiotics are unnecessarily given

Proportion of reduction shown is only for illustrative purposes

We also need a much more robust pipeline of new vaccines to help contain rising drug resistance

Vaccines to prevent bacterial infections would protect against both antibiotic-resistant and antibiotic-susceptible strains. Indeed, they would have two high-level positive effects from the perspective of resistance: 1) preventing infection by drug-resistant bacteria, which may be hard or impossible to treat with current therapeutics; and 2) reducing the overall number of bacterial infections and so the need to use antibiotics, which is itself a driver of drug resistance.

Community and hospital-acquired infections

A recent study in the Lancet journal estimated that global coverage with a universal pneumococcal conjugate vaccine could potentially prevent 11.4 million days of antibiotic use per year in children younger than five. These children would otherwise have been treated for pneumonia (from *Streptococcus pneumoniae*)[11].

Another example of a vaccine that would be of enormous global benefit would be one against certain *E. coli* strains, notably those that cause diarrhoea, urinary tract infections (UTIs) and bloodstream infections, in both community and hospital settings. We do not currently have a vaccine against *E. coli*. Though there are several development programmes underway, only two candidates are in the early stages of clinical development. These are focused on *E. coli* UTIs[12] and have the potential to also reduce incidences of both UTIs and bloodstream infections (because many *E. coli* bloodstream infections have a urinary origin).

We have no licensed vaccines for any of the bacteria that are considered by the US Centers for Disease Control and Prevention (CDC) to represent our most urgent AMR threats[13]- carbapenemase-producing bacteria (including *Klebsiella, E. coli*), drug-resistant gonorrhoea, and *C. difficile*. There are vaccines in clinical development to prevent *C. difficile* infections, but there are only two candidate vaccines in Phase I trials for *E. coli*, and none in any stages of clinical development for *Klebsiella* or gonorrhoea (more information is available in Appendix D). As with all clinical development, there are no guarantees that any of these pipeline products will prove efficacious and safe, and so progress to licensing and use. More generally, we also have no licensed vaccines for those bacteria that together are responsible for the majority of hospital-acquired infections.

Viral infections

Vaccines against viral infections also offer the potential to reduce antibiotic resistance. In 2013 there were over 70 vaccines in development for viral infections other than HIV, with many targeting flu and other respiratory viruses[14]. If vaccines against viral infections successfully reduce the number of people visiting the doctor, either because of symptoms of a viral infection, or superinfections by bacteria, there would be less demand for, and prescribing of, antibiotics, reducing the potential for bacteria to be exposed to antibiotics unnecessarily[15]. A study highlighted in our paper, *Rapid Diagnostics: Stopping the Unnecessary Use of Antibiotics*, suggested that, in the US in one year, out of 40 million adults given antibiotics for respiratory symptoms, 27 million of these courses (67 percent) were unnecessary. This gives an indication of the scale of unnecessary prescription for one set of symptoms in one country. Taken more broadly, therefore, vaccines to combat viral infections could have a large impact on unnecessary use of antibiotics globally.

> *We have no licensed vaccines for any of the bacteria that are considered by the US CDC to represent our most urgent AMR threats*

11 Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J, Klugman K, Davies S, Access to effective antimicrobials: A worldwide challenge, Antimicrobials: access and sustainable effectiveness, *Lancet*, 2016, 387: 168–75

12 PR Newswire, GlycoVaxyn announces the initiation of a Phase I clinical trial collaboration with Janssen for a vaccine against Extra-intestinal pathogenic Escherichia coli causing urinary tract infection, July 1, 2014.

13 Centres for Disease Control, Antibiotic resistance threats in the United States, 2013, U.S Department of Health and Human Services.

14 PhRMA, Vaccines: A Report on the Prevention and Treatment of Disease Through Vaccines, 2013

15 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.

VACCINES FOR BACTERIAL INFECTIONS IN THE PIPELINE

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

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

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

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

Review on Antimicrobial Resistance

Vaccines for TB, Malaria and HIV

The immense burden that TB, malaria and HIV have on the world, collectively causing more than five million deaths a year[16], means the need for effective preventative vaccines is urgent. Efforts have been underway for more than a decade, but with limited success so far. These efforts must be continued and it is worrying that funding appears to be beginning to fall in some of these areas. On current trends, the United Nations' Sustainable Development Goals for TB, for example, are unlikely to be met unless a vaccine can be found[17]. A multitude of groups are involved in this area, including governments, multilateral organisations and several large product development partnerships (PDPs), but this momentum must be maintained. There are currently quite a few vaccines in the pipeline but many are early-stage, meaning – statistically – a low chance of bringing to market a successful vaccine in the near future. Even if some are successful we may well be waiting many years, if not decades, for them to come to market. It is therefore crucial that efforts in this area are increased to reduce the burden that these diseases place on several million people.

Tuberculosis (TB)

The WHO has highlighted that vaccines may be the single biggest contributor to overcoming the huge global problem of TB. There is in particular an urgent need for more effective and long-lasting childhood vaccines and an adolescent/adult booster vaccine[18]. There is only one vaccine against TB today, the Bacille-Calmette-Guérin (BCG). It was developed in the 1920s and is given to children to prevent more severe forms of TB, though it does not offer complete protection from the disease. Currently, there are 16 candidates in clinical development[19] and 25 early-stage discovery leads and preclinical candidates[20]. As a result of the dire need, there has been significant investment in the area, with around 600 million USD invested in vaccines for TB over the past decade or so, though there has been a worrying decline in investment in recent years[21].

HIV

There are currently no HIV vaccines. R&D has moved back into early-stage, preclinical and phase I trials[22], and there have been some recent vaccine candidate failures[23]. This means that we are still quite far from a usable vaccine, though there are some encouraging signs. Global investment into a preventative AIDS vaccine was 841 million USD in 2014[24], up 23 million USD versus 2013, though before this there had been a decreasing level of investment. The HIV preventative vaccines pipeline in 2013 included 31 candidates at various stages of clinical trials.

Malaria

In a major advancement, the vaccine candidate known as Mosquirox, was approved last year by the European Medicines Agency[25], and is the first vaccine ever licenced for use against a parasite. The vaccine was developed through a partnership between industry, academia and non-profit organisations. Though the efficacy of the vaccine is relatively low, it still represents a milestone achievement in the fight against malaria. 28 percent of total funding for malaria goes into preventative vaccines research, around 170 million USD in 2014[26], and the vaccine pipeline has approximately 33 candidates that are in clinical trials in 2015[27].

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17 Stop TB Partnership, UNOPS, The Paradigm Shift 2016-2020, Global Plan to end TB.

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2.

IS THERE A PROBLEM WITH THE MARKET FOR VACCINES – SHOULD IT BE CORRECTED?

An overview of the vaccine market

The world vaccine market is worth about 30 billion USD[28], within a total market for medicines of more than one trillion USD, although is characterised by several market failures. In some respects the failures in this market are similar to those in the antibiotics market, which were discussed in our third paper[29].

Some vaccines have, however, still proven to be commercially attractive for developers. In 2014, for example, five vaccines were highly successful and could be termed 'blockbuster products', with annual sales of one billion USD or more. The 'top seller' was Pfizer's Prevnar vaccine(s), with sales worth over four billion USD in 2014[30]. These vaccines reduce community-acquired infections caused by *Streptococcus pneumoniae* bacteria, such as pneumonia and meningitis. Other successful vaccines include ones to prevent bacterial infections such as whooping cough, diphtheria, and tetanus.

A key driver for the economic success of these and other 'blockbusters' lies in their focus on protecting against infections that are acquired in the community, and represent a threat in developed countries as well as lower-income ones. Not only are the vaccines effective, but the population that needs to be vaccinated is often large and well defined and there are usually well-established national immunisation programmes in place, giving greater certainty to developers of the demand for their product.

However, as we have highlighted in previous papers, many drug-resistant infections, particularly those with the potential to be fatal, are acquired in hospitals and are caused by bacteria that are less common in community settings (although *E. coli* and *Staphylococcus aureus* are clear exceptions to this). Among the many scientific challenges in developing these products, the target population is likely to be far smaller and many vulnerable patients in this setting will be elderly, reducing the likelihood that the vaccine will be fully effective, due to a higher chance that the patient would have a weaker immune system.

The economics of the vaccine market

1.

The supply side of the vaccines market is concentrated, with only five companies collectively having 80 percent of market share[31]. This is a result of many factors, such as high market entry costs, high costs of production and low revenues when compared with drugs[32,33]. Estimates suggest that the cost of bringing a vaccine to market can range between 500 million USD and two billion USD[34]. The latest vaccine to be approved for use is against dengue and the company developing it reported a cost of over 1.5 billion euros[35]. Though the development costs for vaccines – over their entire lifecycle – may not be that different from those for an antibiotic, the products are generally narrower in their spectrum of application, being specific to a particular bacteria or virus or even to a particular strain of that pathogen. This can reduce the number of settings in which they are useful, and so reduce commercial returns.

The large cost of developing vaccines has also led to the stagnation of many vaccine candidates in late stages of the pipeline. These often do not advance further due to the lack of funding for large trials. This was seen most recently during the Ebola crisis, where extensive basic research before 2007 had resulted in at least seven candidates for Ebola vaccines that had been tested in animals with promising results. However, due to lack of investment and the lack of a market during non-epidemic periods, most of these vaccines were languishing in the pipeline when the crisis hit[36].

2.

The demand side for vaccines depends on their nature (how broad they are in what they target) and where they are being used (in the community or in hospital).

Over time, there have been a number of game-changing public vaccination programmes to protect against what were potentially life-threatening and/or highly contagious diseases, both viral

Ebola Effect, 2015, Policy Cures

27 WHO. January 2016, Malaria Vaccine Rainbow Tables. http://www.who.int/vaccine_research/links/Rainbow/en/index.html

28 Tufts Centre for the Study of Drug Development, Impact Report: Analysis and insight into critical drug development issues,Vaccine products in the R&D pipeline have more than tripled since 2005,. 2015; 17: issue 4 (Jul/Aug)

29 Review on AMR, Securing New Drugs for Future Generations – the pipeline of antibiotics. 2015.

30 Tufts Centre for the Study of Drug Development, Impact Report: Analysis and insight into critical drug development issues,Vaccine products in the R&D pipeline have more than tripled since 2005, 2015; 17: Issue 4 (Jul/Aug)

31 Ibid

32 Lagerwij A, Suman S, Hintlian J, Chen K, Robust Supply Chains Could Help Pave the Way, in Special Report: *The Path to Vaccine Profitability*, 2015.

33 Pronker ES, Weenen TC, Commandeur H, et al. Risk in Vaccine Research and Development Quantified, *PLoSONE*, 2013, 8(3).

34 Sanofi Pasteur, Vaccine Development Cycle, Available online: http://www.sanofipasteur.com/Documents/PDF/Vaccine_development_cycle.pdf, Accessed on 1st February 2016

35 Sanofi Pasteur website, Available at: http://en.sanofi.com/our_company/news/2014-09-03_dengue.aspx, Accessed 29th January 2016.

36 Plotkin S, Mahmoud AAF, Farrar J, Establishing a Global vaccine - development fund, 2015, *The New England Journal of Medicine*, 373;4

and bacterial, for example smallpox and tetanus. Generally, these community-wide programmes are coordinated by and paid for by governments or multilateral organisations such as UNICEF or Gavi. National governments, in fact, form a large portion of the market. The buyer base is concentrated, but the addressable market is large. Using the scale of demand, these buyers tend to be able to negotiate lower prices for vaccines: this is something of benefit to public health in all settings (and of particular importance in low and middle-income countries), but can dampen the commercial case for some vaccines.

In the context of these broad vaccination programmes, public perception can be crucial to uptake. The classic example of how public perceptions can make or break vaccine uptake is the MMR vaccine in the UK. The MMR vaccine is a combined vaccine that acts against measles, mumps and rubella (or German measles) and is recommended as part of childhood immunisation schedules, as a combination vaccine – although single vaccines can be used. In 1998, a paper suggested a link between the vaccine and increased cases of childhood autism, a story reinforced by the media. Though this study was later widely discredited, the damage had been done and vaccine uptake fell. In the UK MMR vaccine uptake among two year olds declined to around 80 percent in 2003 and 2004 compared to around 92 percent in 1995 before the paper[37]. In England, measles and mumps rates subsequently increased to endemic levels, with measles being classified as endemic in the UK in 2008[38].

In the case of LYMERix, a vaccine against Lyme disease, the product was withdrawn after being on the market for four years in 2002[39]. As with MMR, this was, again, partly due to the fear of adverse reactions which stemmed from unfavourable media coverage and led to a lack of trust among the public.

The demand side picture for any future vaccines against hospital-acquired infections would look rather different, and we have noted above that there are too few of these in development and none licensed. These would likely be used to protect specific high-risk populations. There is lower buyer concentration, but a smaller addressable market.

3.

Regulatory requirements in the vaccine market contribute significantly to the cost of developing new vaccines. Clinical trials required for vaccines generally have higher safety requirements than those for drugs as they are used on healthy subjects rather than people who are already ill. It may also be challenging to recruit into trials due to the challenges of identifying 'at risk' patients. There are also large upfront capital costs for building and certifying production facilities, which often needs to take place before the results of clinical trials are available. Should a vaccine candidate not be successful during phase III trials, then the company could stand to lose their research and development costs, and the cost of their manufacturing facilities which were constructed in parallel with the phase III trials.

37 Public Health England, Guidance: Measles, mumps and rubella (MMR): use of combined vaccine instead of single vaccine instead of single vaccines, 014, Available at: https://www.gov.uk/government/publications/mmr-vaccine-dispelling-myths/measles-mumps-rubella-mmr-maintaining-uptake-of-vaccine, [Accessed on: 22nd January 2016].

38 Editorial team, Measles once again endemic in the United Kingdom, *Euro Surveillance*, 2008;13 (27): pii=18919. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18919.

39 Nigrovic LE, Thompson KM, The Lyme vaccine: a cautionary tale, *Epidemiology and Infection*, 2007, 135(1): 1–8.

Vaccines for animals

So far we have discussed the market for human vaccines. However, vaccines for animals, as discussed in our paper *Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste*, are one important way that livestock and fish can be protected from infections and levels of antibiotic use can be optimised and reduced. While there are similarities between vaccines used for humans and vaccines used in animal agriculture, there are also significant differences, both scientific and economic.

There is already a range of vaccines available on the market for many of the main animal diseases. Still, there is evidence that potentially important vaccines for animals are at advanced stages of development but not yet being commercialised[40]. The all-in cost of vaccinating animals is often considered an important impediment to purchasers pursuing strategies of mass vaccination of poultry[41], fish and other animals. The importance of developing new research into alternatives to antibiotics, particularly vaccines, has also been highlighted by The World Organisation for Animal Health (OIE).

Policy interventions that might deal with these issues fall into three broad categories:

1. Those that raise the price or cap the use of antibiotics: as recommended by the Review in its previous paper, a limit on antibiotics used in farming would serve to change the financial trade-off for farmers. A tax on antibiotics for animal use could also be implemented to have this effect. This could make using existing vaccines more attractive relative to antibiotics for prophylaxis.

2. Those that lower the price of existing vaccines: subsidies to lower the effective price of vaccines could improve vaccine uptake in farming, similar to Gavi's efforts to improve access for human use in low-income countries. This might be most relevant for larger and higher value livestock where the vaccine cost may be the key driver.

3. Those that stimulate innovations that lower the all-in cost of administering vaccines: as noted by the Review in its previous paper, the development of feed, or bath, administered vaccines could dramatically change the all-in cost profile for administering vaccines, particularly to smaller and lower value livestock such as poultry and fish. Should such innovation have stalled for want of commercial reward, it could be a candidate for external stimulation.

40 Allen HK, Levine UY, Looft T, Bandrick M Casey TA, Treatment, Promotion, Commotion: Antibiotic Alternatives in Food-Producing Animals. *Trends in Microbiology*, 2013, 21(3), 114-119.

41 Cheng G, Hao H, Xie S, et al. Antibiotic Alternatives: The Substitution of Antibiotics in Animal Husbandry?, *Frontiers in Microbiology*, 2014, 5(217).

How can we make better use of existing vaccines: the example of the pneumococcal vaccine

Pneumococcal infections are caused by the bacteria *Streptococcus pneumoniae* and include pneumonia, meningitis, ear and sinus infections, and bloodstream infections. According to the WHO, an estimated 14.5 million episodes of serious pneumococcal disease (including pneumonia, meningitis, and sepsis) are estimated to occur each year in children aged less than five years, resulting in over 800,000 deaths, almost all of which occur in low and middle-income countries[42]. Antibiotics are the mainstay of treating pneumococcal infections, however since the 1990s drug-resistant strains of the pathogen have become more common.

There are currently two different types of vaccine available[43]. Though these may target only some of the 90 types of bacteria that cause the disease, they target the most dominant types[44]. Commercially, these vaccines are a huge success – two pneumococcal vaccines sold were the top selling vaccines worldwide in 2014, with sales worth 4.6 billion USD in the same year. Another pneumococcal vaccine was also among the top five best-selling vaccines[45]. According to data from the same report, pneumococcal vaccine sales from these two companies' combined, had higher revenue than the rest of the top five vaccines in 2014, over five billion USD.

One study in the US in 2011, found that the use of such vaccines led to a 64 percent reduction in antibiotic-resistant pneumococcal infections among children and a 45 percent decrease among adults over 65 years of age[46]. There is also some evidence that shows that the introduction of pneumococcal vaccines has direct effects on antibiotic purchases, as was seen from a study in Finland which showed that there was an 8 percent reduction in antibiotic purchases after their introduction[47].

Despite the advantages of the pneumococcal vaccines, access in low and middle-income countries was low, due to the higher price of the vaccines, compared with vaccines already in use, and the fact that the specific strains of infection covered by vaccines developed for European and North American markets were a poor match for those more prevalent in developing countries. To increase access, Gavi set up a pilot pneumococcal Advance Market Commitment (AMC), that would ensure a stable supply of vaccines for the Gavi eligible countries, and in doing so, would also ensure a stable demand for companies.

The experience of the pneumococcal vaccine has two important implications. First, it demonstrates the tremendous potential that vaccines against bacterial diseases have in reducing not only antibiotic use, and extending protection to non-immunised people, but resistance as a whole. Second, it shows that for the benefits of these vaccines to be realised, we need to do more to increase global access and uptake of these products, especially in places where the disease burden is highest.

42 O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates, Lancet, 2009;374:893–902.

43 World Health Organization, Weekly epidemiological record, Pneumococcal vaccines WHO position paper- 2012, 2012, 87, 129–144.

44 Callaway E, Hidden bonus from vaccination: Immunization against pneumococcus in Africa also reduces levels of antibiotic resistance, 6th August 2014, *Nature News*, 512, 14-15.

45 Tufts Centre for the Study of Drug Development, Impact Report: Analysis and insight into critical drug development issues,Vaccine products in the R&D pipeline have more than tripled since 2005. 2015; 17: issue 4 (Jul/Aug)

46 Hampton LM, Farley MM, Schaffner W, et al. Prevention of antibiotic-non susceptible *Streptococcus pneumoniae* with conjugate vaccines, *Journal of Infectious Diseases*, 2012, 205, 401–411.

47 Palmu AA, Jokinen J, Nieminen H et al., Vaccine effectiveness of the pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) against clinically suspected invasive pneumococcal disease: a cluster-randomised trial, *Lancet Infectious Diseases*, 2012 14, 205–212.

INCREASING COVERAGE OF VACCINES CAN REDUCE ANTIBIOTIC USE

Universal coverage by a pneumococcal conjugate vaccine could potentially avert 11.4 million days of antibiotic use per year in children younger than five, roughly a 47% reduction in the amount of antibiotics used for pneumonia cases caused by *S. pneumoniae.*

47%
reduction in antibiotic use
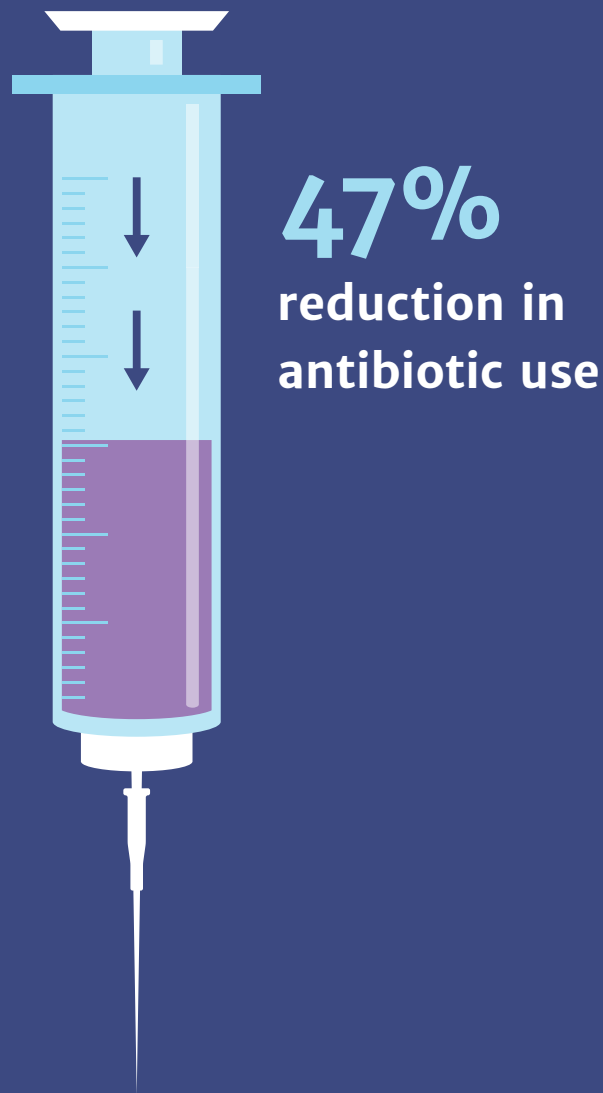
Source: Source: Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J, Klugman K, Davies S, Access to effective antimicrobials: A worldwide challenge, Antimicrobials: access and sustainable effectiveness, *Lancet*, 2016, 387: 168–75.

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3.

ALTERNATIVES TO ANTIBIOTICS – A NEW FRONTIER IN THE FIGHT AGAINST AMR?

We have discussed in detail the potential for vaccines to reduce the need for antibiotics. However, there is a wide array of other possible alternatives currently being researched and developed. Some alternatives aim to prevent infection, as vaccines do, others to replace antibiotics as treatment, and still others to make antibiotics more effective or reduce the likelihood of resistance arising by being taken alongside them.

From a public health perspective, particularly over the long-term, there is a clear benefit to having a wide array of options to prevent and treat drug-resistant infections. Following rising international concern about the AMR threat, there is an encouraging pool of new ideas emerging that could offer alternatives to using antibiotics. These ideas come mainly from academic teams and small biotechs doing high-risk work (in financial terms). However, looking more closely at that pipeline, it seems there are relatively few products coming to market to replace or compensate for weakening antibiotic effectiveness for at least another 10 to 15 years, unless there is a concerted effort to support these projects now. Here we consider what is out there and the challenges that developers face.

The pipeline

A recent pipeline review[48] drew particular attention to the following alternatives, which have the potential to come to market within the next ten years: antibodies, probiotics, lysins, wild-type and engineered bacteriophages, immune stimulation, and peptides[49]. The majority of these target local infections, typically of the gut or skin, caused by Gram-positive bacteria. Unfortunately, many of the most urgent threats are systemic in nature and caused by Gram-negative bacteria.

Nonetheless, we are encouraged by the presence of multiple therapies aimed at tackling the following three pathogens, each of which is considered a threat by the CDC:

1.

C. difficile: this Gram-positive bacterium, classified as an urgent threat by the CDC, affects the digestive system and can cause a range of unpleasant symptoms including diarrhoea and fever. It can be life-threatening, particularly in elderly patients and those who develop complications, and recurs in a proportion of

affected patients. Probiotics, amongst other alternatives, could come to market as soon as 2017. However, we note the potential for a number of competing products here, which could lead to "me-too" treatments offering limited incremental benefit and garnering weak market rewards, potentially acting as a less than optimal example to developers in other alternative fields.

2.

Pseudomonas: this Gram-negative bacterium, classified as a serious threat by the CDC, is often hospital-acquired, for instance in people being treated for leukaemia, and can be life threatening. Antibody research, amongst other areas, has yielded a number of candidates that may come to market as early as 2021.

3.

Staphylococcus aureus: this Gram-positive bacterium, classified as a concerning threat by the CDC, can cause a broad range of infections. Methicillin-resistant strains (MRSA) are a particular challenge, in hospital and community settings and developers are exploring a broad range of alternatives to tackle these, including antibodies, lysins, and peptides with potential market entries from 2021 onwards.

A broad overview of the wider pipeline is provided in Appendix A.

> *There is a clear benefit to having a wide array of options to prevent and treat drug-resistant infections*

48 Czaplewski L, Bax R, Clokie M, et al. Alternatives to antibiotics – a pipeline portfolio review, *Lancet Infectious Diseases*, 2016, Published Online January 12, 2016, http://dx.doi.org/10.1016/ S1473-3099(15)00466-1.

49 Peptide types include: antimicrobial, host defence, innate defence and antibiofilm peptides.
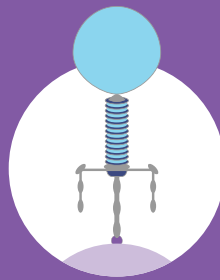
ALTERNATIVE PRODUCTS TO TACKLE INFECTIONS

A selection of alternative products that are under development, which could be used for prevention or therapy.
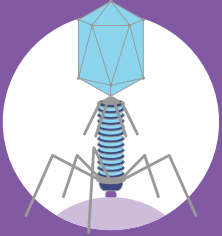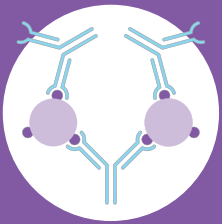
Phage therapy
Natural or engineered viruses that attack and kill bacteria

Lysins
Enzymes that directly and quickly act on bacteria

Antibodies
Bind to particular bacteria or their products, restricting their ability to cause disease
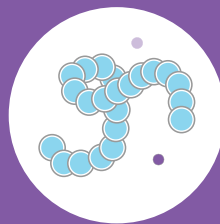
Probiotics
Prevent pathogenic bacteria colonising the gut

Immune stimulation
Boosts the patient's natural immune system

Peptides
Non-mammalian animals' natural defences against infection

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4.

WHAT ARE THE SPECIFIC CHALLENGES IN DEVELOPING THESE ALTERNATIVE PRODUCTS?

We believe there are a number of specific challenges that face subsets of alternative products, as listed below.

Narrow-spectrum agents

Most alternatives target a single bacterial species or specific strains within a species. Their application is therefore comparable to that of narrow-spectrum antibiotics (though even narrow-spectrum antibiotics are rarely active against just a single species), with similar pros and cons. On the positive side, their narrow focus may reduce collateral damage to our individual microbiomes[50] (which has been linked, by some, to chronic health concerns like asthma and obesity). However, their use is predicated on doctors being able to give an accurate and fast diagnosis of the specific pathogen causing the infection, which is challenging unless the patient has access to a rapid point-of-care diagnostic[51].

Complementary to existing antibiotics

A number of alternatives are intended to enhance the efficacy of existing antibiotics and/or reduce the resistance arising from their use. The former characteristic may be perceived as only incremental whilst the latter may not be factored into decision-making by regulators and payers at all, despite the potential benefits accruing to wider society. This latter point is also an issue for alternatives that seek to act as replacements for antibiotics for either therapeutic or prophylactic use; they may not be superior to existing traditional treatments today but, as resistance to these traditional treatments rises, they may become valuable to future generations.

New and relatively unknown mechanisms of action

Biologic alternatives experience a particular challenge because the end product is very variable – unlike an antibiotic pill for example. This means that: 1) the regulator needs to decide what level of tolerance they have with respect to manufacturing processes; and 2) doctors need to develop sufficient comfort when prescribing what are inherently varied products (to differing degrees, the most extreme of which might be phage therapy). This challenge is not unique to infectious disease and has been navigated successfully before, for example for monoclonal antibodies used in oncology and rheumatology, and against anthrax. However, developing the first few indications in a new field can be both riskier and more time-intensive than pursuing innovation in an established field, due to a lack of precedent.

We note that phage scientists have, in many cases, shifted their focus to bacteria-killing applications in food rather than humans because the path to market is perceived to be lower risk. The good news is that this work may be building an evidence base for safety in humans, though it does not provide material support on efficacy.

Limited knowledge base

While divestment has hollowed out the antibiotic industry over the years as prospective financial rewards diminished, development of alternatives has never been well-remunerated. Thus, the historical evidence base is small, the number of experts limited, and the networks for collaboration—notably between academia, small biotechs and big pharma—not well-established. These features may be self-reinforcing, with those disbursing early-stage grants less comfortable funding these sorts of innovations and developers often lacking the clinical trial, manufacturing and commercial resources, and experience of larger companies to take promising candidates through development. This has the potential to exacerbate funding and scientific risks through the innovation cycle.

Limited opportunity for collaboration

The opportunity for collaboration with big pharma and through public-private partnerships has also fallen over time. Few large pharma companies maintain a commercial interest in these fields. The exception to this is in antibody therapies, where there are candidates in phases I to III. We note that access to the evidence base associated with past, failed developments, much of which is proprietary to these companies, would be hugely valuable in helping actively rule out some of these potential treatments and would help focus funding on unexplored directions.

Taken together, these challenges mean that developers find it difficult to get a treatment to market and to know how lucrative their innovation might be.

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50 Microbiomes refer to the microorganisms that are found in a particular environment and in this case refer to those that are found in humans.

51 Review on AMR, Rapid Diagnostics: Stopping the unnecessary use of antibiotics, 2015

5.

THREE PROPOSALS TO INCENTIVISE THE INNOVATION AND UPTAKE OF VACCINES AND ALTERNATIVE THERAPIES TO COMBAT AMR

Our proposal is a three-pronged effort:

- **Use existing products more widely in humans and animals.** We need to act in the short-term to increase the use of existing vaccines and, to improve delivery of these in both the community and hospital settings, for all patients who need them regardless of income. Thinking must also start now to improve the delivery of other alternatives to antibiotics.

- **Renew impetus for early research.** We need renewed impetus in the science of vaccines and alternative approaches – ensuring researchers in a wide range of fields and countries are looking for the solutions that would reduce our dependence on antibiotics and help tackle drug resistance. To this end, our recommended two billion USD Global Innovation Fund should offer funding for the best projects researching new vaccines and alternative products, alongside other existing or new public and philanthropic research funding.

- **Sustain a viable market for needed products.** Specific measures must be considered in certain cases where vaccines and other alternatives are not at the moment an attractive commercial proposition for prospective developers. The shape of the interventions will depend on the characteristics of the different products. Our proposals focus mainly on advance market commitments and market entry rewards. Both these interventions reward developers for successful products only, rather than sharing in the risk of developing products from an earlier stage (which is the role of research funding described above). Some vaccines are very profitable and their market may not need any propping up. Others have different market failures, to different degrees, so it is important that the interventions are carefully tailored to each market and type of product, using public funding only when needed to increase public health benefits that would not otherwise be delivered.

To contain the emergence of drug resistance globally, all these interventions will need to be designed to deliver access to the patients who need them, wherever they are and regardless of levels of income. No individual country can insulate its citizens from emerging superbugs if they are left to proliferate somewhere else. There are different ways to ensure global access to medicines, including tiered pricing or patent licensing as done by groups such as the Medicines Patent Pool funded by UNITAID. Another key to global access will also lie in more and more academic teams and companies developing new products in countries where most patients live and at prices they can afford, such as India, China, Russia, Brazil or South Africa.

> *To contain the emergence of drug resistance globally, all these interventions will need to be designed to deliver access to the patients who need them, wherever they are and regardless of levels of income.*

a.

Using existing vaccines more widely in humans and animals

As we have discussed there are already vaccines available that have the potential to prevent large numbers of infections, benefitting patients directly, while also significantly reducing the amount of antibiotics used, benefitting society with lower rates of resistance. Two examples of these would be the pneumococcal and rotavirus vaccines. Improving coverage of these should be a high priority for governments, NGOs and healthcare systems working with companies to make sure that these products are available to all patients who need them, regardless of their income levels.

This will involve providing financial support in some cases, in low-income countries where the work of Gavi and UNICEF, and others, is making great headway towards better vaccine coverage, but also in some richer medium-income countries where for lack of universal coverage large portions of the population may be losing out on essential vaccinations. It will also involve action to overcome cultural inertia from both individuals and healthcare providers, through awareness campaigns and clinician training.

b.

Renewed impetus from a Global Innovation Fund to boost early-stage scientific research.

The Review has already proposed a two billion USD Global Innovation Fund to kick-start early-stage research to combat AMR. So far we have recommended that this would fund early research into new antibiotics and diagnostics, and we think it is logical that this should also include vaccines and other alternatives. This would increase the funds available for research, alongside existing funding initiatives, and should increase the supply of products in the pipelines.

This early-stage funding should be done in conjunction with building an open access evidence base that outlines both successes and failures, which is particularly important in the case of alternative therapies, to ensure that over time and with sufficient evidence we begin to narrow our focus to the most viable alternatives, or at least move away from areas which have been proved to be unfruitful. The Global Innovation Fund along with other established funding groups, such as the Biomedical Advanced Research and Development Authority (BARDA), could play a part in this. Again, this would necessitate having decision makers with an openness to and knowledge of alternative candidates and able to fund some early and higher risk avenues of research.

c.

Pull incentives for vaccines and alternatives.

While some vaccines are highly profitable and should not require public funding to support their development, others may not be attractive commercial propositions without some type of public intervention. In response to the market failures we have described, we believe there should be pull incentives for certain vaccines and alternatives that tackle drug resistance. However the optimal pull incentive would not be the same for every product, as different vaccine markets have different market failures.

All products likely to be considered would either stop people from becoming sick (preventative), help people who already are sick (therapeutic), or both. The incentives needed for these two types of products are likely to be different. Incentives that encourage wide use are well suited for preventative products because prevention is crucial in slowing the emergence of drug resistance. On the other hand, incentives that encourage wider use are not well suited to therapeutic treatments if the therapy increases the risk of drug resistance emerging: you only want these products to be used when really needed, as is the case for antibiotics.

(i)

Therapeutic treatments.

As proposed in the Review's paper in May 2015[52], we believe that there is a need to create a more predictable market for antibiotic development, through Market Entry Rewards for successful products. We proposed that about 20 billion USD would be needed to pull through 15 new antibiotics or therapeutic profiles to combat AMR over the next 10 years.

In our view, it is logical that alternative therapies that could replace use of antibiotics should be able to compete with antibiotics for these rewards on a level playing field. The key is the outcome – tackling resistance, by treating an infection, and improving health outcomes – rather than the specific method of achieving that outcome. Since any successful products would need to meet the same requirements laid out in our paper on antibiotics, in terms of treating critical infections, this would be funded from the same estimated 20 billion USD envelope that we have already proposed. In other words if one alternative were to be eligible for a Market Entry Reward, it would effectively be replacing the relevant antibiotic.

We note that, in practical terms, this would necessitate having decision makers with an openness to and knowledge of alternative candidates. However, this would be mitigated to a large extent by our recommendation that the rewards should only be paid about two years after market entry for successful products, thereby reducing the need for a global institution to 'pick winners' early.

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52 Review on AMR Securing New Drugs for Future Generations – the pipeline of antibiotics. 2015.

(ii)

Preventative measures.

The market for products that can prevent infections, including certain vaccines and alternative approaches, may also need to be propped up as they bring benefits to society that widely exceed the sum of the private benefits to each patient. There are tried and tested ways to support such vaccines (and other preventative products), such as public vaccination campaigns delivered and procured by governments as a single purchaser and the 'Advanced Market Commitment' (AMC) secured by institutions such as Gavi, the Vaccine Alliance, where the companies would receive a top–up on the final sale price, making the development and selling of the vaccine more attractive. This principle is well established for subsidising vaccines and Gavi already operates on this principle.

It works by institutions committing to ensure that vaccines achieve a higher price than the companies would have made on the current market. This essentially creates a market for these products. For this type of intervention to work, the promise of the higher price needs to be credible and legally binding as in the Gavi model.

Patients often do not have an incentive to use treatments that prevent future illnesses or resistance in society at large, particularly when those treatments are more expensive. Changing these incentives is important and can be delivered by paying a small subsidy on top of individual treatment costs, to give incentives to patients and doctors to take actions that benefit society at large.

We will consider the benefits of vaccines for combatting AMR further, alongside the costs of interventions that might be needed, in our final report.

> *Patients often do not have an incentive to use treatments that prevent future illnesses or resistance in society at large, particularly when those treatments are more expensive.*

A PLAN TO OVERHAUL THE VACCINE AND ALTERNATIVE MARKETS FOR AMR

Increase use of existing vaccines

Global Innovation Fund to boost early stage scientific research

Strengthen the markets for vaccines and alternatives

Advance Market Commitments for preventative approaches

Market Entry Rewards for therapeutic approaches

Review on Antimicrobial Resistance
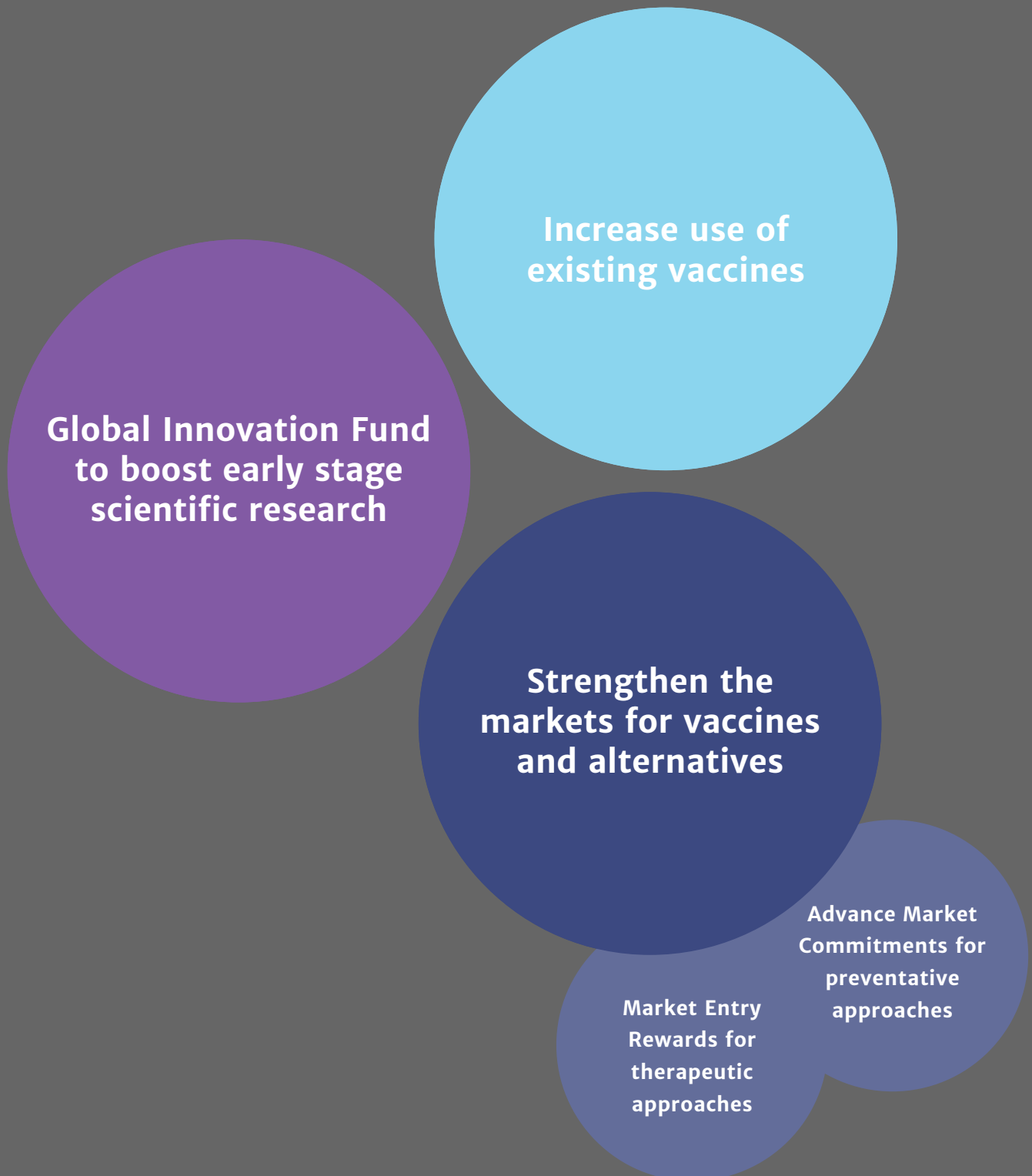
6.

NEXT STEPS

This paper proposes that we need to do more to encourage the innovation and uptake of vaccines and alternatives, and value appropriately therapies that prevent, as well as treat. However, while this is an important part of the picture, if the world is to truly tackle AMR, there are further issues that we also need to consider.

Going forward, and in addition to the policy papers the Review has already published on many aspects of the AMR ecosystem, we will provide analysis and recommendations on the following:

- **Preventing and limiting the spread of infections**. Prevention removes the need for treatment, thereby reducing the need for antimicrobials 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.

Moving towards action

The battle against AMR will undoubtedly be long and for the foreseeable future we will clearly need excellent therapeutics to tackle infections as they arise. However we need to make more use of the preventative measures that vaccines, and many other alternative therapies, have the potential to provide. By reducing infections, we reduce the use of antibiotics, conserving those products for when they are really needed.

As well as incentives to encourage their innovation and uptake, as laid out in this paper, policy makers and healthcare professionals need to consider how we can begin to change our mindset and consider advancements in preventative treatments as a vital part of the strategy to combat drug resistance. We also need to ensure that access is at the top of the agenda, and that those who need these products are able to purchase them.

Incentivising further development in this area will involve an economic cost, but the economic cost of inaction, which could mean a cumulative hit to the world economy of 100 trillion USD by 2050, vastly outweighs these costs. This is without considering the millions of lives that will be lost if we do not curb resistance and find better ways of preventing and treating infections.

We were very pleased to see the declaration recently announced at the World Economic Forum in Davos, whereby 85 companies from across the pharmaceutical, diagnostic and biotech industries committed to further action to reduce the development of drug resistance, increase the investment in research and development that meets global public health needs, and improve access to high-quality antibiotics and vaccines for all. Continuing this momentum, the final paper of the Review on AMR will be published in May this year, which will cover solutions across the AMR landscape, with more detailed analysis of the costs and benefits of these interventions.

2016 is now a critical year for AMR. The G7, G20 and UN have all placed it on their agendas, and it is vital that with the current combined focus from global industry and governments, tangible agreements are reached to make real progress. We cannot let this moment of opportunity pass.

Already, over 700,000 people across the world die each year from drug-resistant infections and this figure will continue to rise until the market failures are addressed for both new therapeutics and preventative approaches, alongside reducing the unnecessary use of antibiotics in both humans and animals. However, we are confident that this picture can dramatically change through the combined efforts of governments, NGOs and industry, and this is the year to make it happen.

> " *2016 is now a critical year for AMR. The G7, G20 and UN have all placed AMR on their agendas, and it is vital that with the current combined focus from global industry and governments, tangible agreements are reached to make real progress* "

APPENDIX A:

SUMMARY OF THE PIPELINE OF ALTERNATIVE THERAPIES[53]

	Brief description	Current pipeline	Likelihood of 1 registration by 2025	Considerations
ANTIBODIES	Bind to particular bacteria or their products, restricting their ability to cause disease	**SEVEN PRODUCTS:** *Staph. aureus* (3); *Pseudomonas aeruginosa* (3); *C. difficile* (1)	**183 PERCENT** (earliest could be 2017: *C. difficile*)	Narrow-spectrum, likely expensive
PROBIOTICS	Prevent pathogenic bacteria colonising the gut	**THREE PRODUCTS:** *C. difficile* (3)	**124 PERCENT** (earliest could be 2018: *C. difficile*)	Act in the gut only – no systemic use
PEPTIDES	Non-mammalian animals' natural defences against infection	**FIVE PRODUCTS:** *C. difficile* (2); *Pseudomonas aeruginosa* (1); *Staph. aureus* (1); UTIs (1)	**52 PERCENT** (earliest could be 2022: *P. aeruginosa* and *C. difficile*)	Perform less well than antibiotics, limited scientific and pharmacology base, poor track record to market (large players have left), high costs if target hosts not bacteria
IMMUNE STIMULATION	Products that boost the patient's natural immune system	**TWO PRODUCTS:** *C. difficile*; bacterial extracts	**43 PERCENT** (earliest could be 2021: *C. difficile*)	No evidence that effective in isolation, may be a better candidate in combination with others
LYSINS	Enzymes that directly and quickly act to kill bacteria	**TWO PRODUCTS:** *Staph. aureus* (2)	**26 PERCENT** (earliest could be 2022: *Staph. aureus*)	Narrow-spectrum, currently only against Gram-positive bacteria, resistance may emerge more slowly
WILD-TYPE AND ENGINEERED BACTERIOPHAGES	Natural or engineered viruses that attack and kill bacteria	**THREE PRODUCTS:** *C. difficile* (1); *Pseudomonas aeruginosa* (2)	**9 PERCENT** (earliest could be 2023: *C. difficile* and *Pseudomonas*)	Very specific, regulatory complexity (multiple phages per treatment, phages change in patient), not suitable for acute infections (requires patient specific testing), hyper-local manufacturing, dosing considerations

53 Adapted from: Czaplewski L, Bax R, Clokie M, et al. Alternatives to antibiotics – a pipeline portfolio review, *Lancet Infectious Diseases*, 2016, Published Online January 12, 2016, http://dx.doi.org/10.1016/ S1473-3099(15)00466-1.

N.B.– Values greater than 100 percent for a given category suggest that there are sufficient project numbers and project maturity, or both, to expect at least one product to be registered, if sufficient funding and skilled development resources are provided

APPENDIX B:

BACTERIAL ADAPTATION CAN MAKE SOME VACCINES LESS EFFECTIVE

Although bacteria do not become 'resistant' to vaccines in the same way that they do to antibiotics, there is still evolutionary selective pressure on bacteria to adapt and evade the protective immune responses that our bodies make when we are vaccinated.

Flu viruses are a good example of pathogens evolving in the context of vaccines; the composition of flu vaccines must be adjusted (and the target population re-vaccinated) annually to ensure that they offer protection against the latest circulating virus types.

Bacteria also change, albeit less quickly than viruses, and some bacterial vaccines need to be updated. Vaccines against *S. pneumoniae* (the pneumococcus) offer an example on the bacterial side. The original pneumococcal vaccines protected against types of *S. pneumoniae* most likely to cause infection at the time the vaccines were introduced, including the major types that were resistant to penicillin and/or macrolide antibiotics. However, once the vaccine was in use, other types of *S. pneumoniae* that were not covered by the vaccine became more prevalent as vaccine-susceptible strains declined; some of these emerging strains showed a likelihood of developing antibiotic resistance.

A second-generation pneumococcal vaccine with expanded coverage was necessarily developed to protect the population against infections caused by these emerging pneumococcus types. New pneumococcal vaccines are now available to cover additional pneumococcal types, not included in previous vaccines, that are causing increasing numbers of infections as they 'fill the ecological gap' opened by the success of vaccines against the targeted serotypes. This adaptation by some bacteria against some vaccines also highlights that vaccines, while a very important part of the AMR solution, are unlikely to be the only part.

So, as with new antibiotic development and the subsequent emergence of new resistance, trying to reduce AMR and drug-resistant infections with vaccines may never be absolute. Such strategies are likely to involve repeating cycles of development, followed by (perhaps short-lived) success for a few years, and with the vaccine's impact on AMR eroded in the medium to longer term.

APPENDIX C:

ADDITIONAL INTERVENTIONS THAT WE HAVE CONSIDERED

- **Mid-stage interventions – support for clinical trials.** As with drug development, the clinical trials in vaccine development is usually by far the most expensive phase. With regulatory and safety requirements for vaccines being greater than for drugs, as with vaccines the people being treated are usually not ill, the cost of clinical trials can often be prohibitive. Having governments and healthcare systems play a more central role in facilitating clinical trials would help to reduce these costs, and make it easier for firms to bring products to market. Examples of such initiatives already in existence include Open Source Drug Discovery in India, the National Institute for Health Research (NIHR) in England, the Academic and Research Libraries Group (ARLG), and several Initiatives under the European Innovative Medicines Initiative (IMI) such as COMBACTE and New Drugs for Bad Bugs, among others. Encouraging more of these initiatives would allow vaccines and alternative producers to take advantage of the infrastructure and expertise of healthcare providers.

- **Deeper collaboration in the development of alternatives between academics, biotechs, big pharma, diagnostics companies and regulators.** One improvement to the alternatives market, which should be achievable in the short-term, would be to improve collaboration across these groups, from initial scientific exploration to commercial drug development. This should include closer collaboration with diagnostic developers, particularly as many potential alternative therapies are narrow-spectrum and effective only on particular strains of particular species of bacteria. It should also include closer communication between innovators themselves in order to, as far as possible, guard against herd instinct, e.g. multiple efforts to achieve an alternative therapy for *C. difficile* and far less for other bacteria. We would also support further collaboration between alternative developers and regulators, due to the specific challenges around relatively unknown mechanisms of action that we have discussed.

- **Improved liability insurance.** The success of insurance programs such as the National Vaccine Injury Compensation Program (NVICP) in the US, in ensuring the continued supply of essential vaccines may be used as a blueprint for similar initiatives to help protect the developers of other vaccines that are not currently covered though insurance. Such an initiative could greatly enhance the attractiveness of the market from the perspective of vaccine developers, although may be seen

as representing an open-ended (and potentially high-risk) liability for the governments who underwrite them.

APPENDIX D:

LIST OF VACCINE CANDIDATES IN THE PIPELINE BASED ON THE CDC ANTIBIOTIC-RESISTANT THREAT LIST 2013

This is a list of those candidates in the pipeline for US and EU pharmaceutical and biotech companies[54]. This list does not include candidates being developed solely by government or non-profit institutes, or those outside the US and EU.

X-Indicates that there are no candidates in the pipeline.

Note: Carbapenem-resistant *E.coli* and Carbapenem-resistant *Klebsiella* are classified as Carbapenem-resistant *Enterobacteriaceae* (CRE) in the list, but are shown separately in this table to highlight the difference in vaccine pipeline for both organisms.

Target	Clinical-Stage Pipeline				Vaccine in use (Licensed by FDA)
	Phase 1	Phase 2	Phase 3	Total	
URGENT THREATS					
Neisseria gonorrhoeae	X	X	X	0	0
Clostridium difficile	X	2	1	3	0
Carbapenem-resistant *E. coli*	2	X	X	2	0
Carbapenem-resistant *Klebsiella*	X	X	X	0	0
SERIOUS THREATS					
Non-typhoidal *Salmonella*	X	X	X	0	0
Shigella	X	X	X	0	0
Acinetobacter	X	X	X	0	0
Campylobacter	X	X	X	0	0
Enterococcus	X	X	X	0	0
Candida	X	1	X	1	0
Pseudomonas aeruginosa	X	1	X	1	0
Streptococcus pneumoniae	1	3	X	4	3
Mycobacterium tuberculosis	1	4	X	5	1
Salmonella typhi	X	X	X	X	2
CONCERNING THREATS					
Group A *Streptococcus*	X	X	X	X	0
Group B *Streptococcus*	X	1	X	1	0
Staphylococcus aureus	3	1	X	4	0
TOTAL	7	13	1	21	6

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

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