Centre on Global Health Security
Meeting Summary

CHATHAM HOUSE
The Royal Institute of International Affairs

The Value of Vaccines in the Avoidance of Antimicrobial Resistance

Royal Society

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Introduction

Antimicrobial resistance (AMR) – a phenomenon whereby an antimicrobial such as an antibiotic ceases to be effective against the infection it is used to treat because the pathogen develops resistance to the drug – is widely understood to be one of the most significant threats to global health. AMR has resulted in profound challenges for the treatment of infectious disease in low- and middle-income countries (LMICs) particularly, as evidenced by the emergence of antibiotic-resistant typhoid infections. All countries are experiencing growth in the emergence of resistant organisms, making the treatment of infections – especially those that are acquired in hospital settings – very difficult.

Using vaccines not only prevents cases of infectious disease and averts long-term disability and death, but it is also a powerful tool for reducing the use of antibiotics and thereby retarding the emergence of resistance. Although vaccines were acknowledged as part of the solution in the recent UN declaration on AMR and in other reports, such as (Lord) Jim O'Neill's AMR review, the potential health and economic benefits they could bring to the effort to reduce AMR have not been sufficiently explored.

On 29–30 March 2017 the Centre on Global Health Security at Chatham House convened a meeting, held at the Royal Society in London, of vaccine experts, representatives of international and regional organizations with an interest in AMR and vaccines, economists, modellers and scientists from the vaccine industry. The purpose of the meeting was to review current knowledge and action on the role of vaccines in combating AMR, and to consider the issues involved in modelling how their value for this purpose could be established. This was with a view, in particular, to ensuring that national and international policies on their use, and support for R&D efforts, properly recognize the contribution that vaccines can make in mitigating the growth of AMR.

The meeting was held mostly under the Chatham House rule,[1] with the exception of the initial addresses.

Opening session: Overview

In his overview, Chatham House associate fellow David Salisbury reviewed the plethora of recent reports and declarations on the issue of AMR, arguing that these consistently underplay the important role that vaccines can play in reducing the growth of AMR. He noted that the challenge in gaining greater acknowledgment of the potential that vaccines hold for combating AMR is to find ways to put a value on this role and to present evidence on the cost-effectiveness to policymakers responsible for deciding how funds for addressing AMR should be allocated. He proposed that there is a need to develop and promote a strategy for the recognition of vaccination as a means of slowing the evolution and reducing the spread of AMR.

In his keynote address, Seth Berkley, CEO of Gavi, the Vaccine Alliance, noted that the vaccines being rolled out with the support of Gavi are already having an impact on AMR by preventing bacterial and viral infections not only in those vaccinated but also in those not vaccinated, through herd immunity, thereby reducing the use and misuse of antibiotics. For instance, universal coverage of pneumococcal conjugate vaccines (PCVs) has been estimated to prevent 11.4 million days of antibiotic use in children under five years of age in 75 LMICs. Meanwhile, Haemophilus influenzae type b (Hib) vaccine, now used in all 73 Gavi countries, has had a considerable impact on antibiotic use.

1 When a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.

He argued that developing more effective influenza vaccines that could be available more quickly in flu seasons is also a priority. In the US, the Centers for Disease Control and Prevention (CDC) has estimated that approximately 50 per cent of antibiotic use is inappropriate – a proportion likely to be much higher in LMICs. He also favoured the development of a vaccine for Group A Streptococcus, which causes about half a million premature deaths a year, particularly from consequent rheumatic heart disease. This has not been seen as a priority by industrialized countries, where the disease has largely disappeared. Such a vaccine could avert the global need for 6.15 billion doses of antibiotics annually.

Finding vaccines for HIV, tuberculosis (TB) and malaria remains a priority, although the results to date have been disappointing. Although the World Health Organization (WHO) has recently produced a list of priority pathogens to guide antibiotic development, an equivalent list of priorities to guide R&D on new vaccines to combat AMR is needed. Gavi itself is now embarking on a new vaccine investment strategy, which, apart from using the usual health and economic indicators, ideally requires valuing the impact on AMR of different vaccines so that this can influence the ranking of vaccines. But it is not clear at this stage how this could be done.

In addition, he thought that the value of increasing the use of vaccines in animal production has been underrepresented in the discussion to date.

A developing issue is the increasing use of antibiotics in the growing elderly population: globally, there are now more people aged over 65 than there are children under five. Should the wider use of vaccines in this group be seriously considered? A similar issue pertains to the rapid growth of urbanization, with more concentrated populations facilitating the spread of infectious diseases and increasing the demand for antibiotics. Should one think of a multiple-target ‘slum vaccine’?

Newer antibiotics are clearly needed, but so are more vaccines that target priority diseases and those that would most alleviate the growth of AMR. While new vaccines continue to be developed, the development of new classes of antibiotic has flatlined over the last 25 years. He argued for the need to address how to measure the AMR value of vaccines, but also to consider the best financial structures for incentivizing the development of needed vaccines. And if the market does not provide these incentives, who will provide them and how?

Discussion included the following points:

- The WHO priority pathogen list contains few pathogens where vaccines could play a part in their control (e.g. HIV, TB, malaria). A list focused on reducing transmission would be quite different, taking account of disease burdens in the population.
- How should vaccines be prioritized for investment? For example, between a TB and a typhoid vaccine, the former would have a bigger effect but is far from being available. whereas the latter is more achievable but would have a lower impact.

Session 2: Perspectives on AMR

It was noted that one problem with antibiotics is that they are used mostly to treat symptoms when the underlying causative organism is unknown, and could often be viral. This makes it very difficult to know whether a vaccine for a particular symptom complex would be effective in reducing antibiotic use. Thus, significantly curtailing the use of antibiotics for the treatment of undiagnosed fevers may require the use of several vaccines in order to cover the many different possible causes of non-specific symptoms such as fever. This observation supports the need for investment in point-of-care rapid diagnostics that would

reduce inappropriate antibiotic use. For example, A typhoid vaccine might have a very specific effect on the degree of resistance to fluoroquinolones, but cases of diarrhoea would still likely be treated inappropriately with antibiotics.

The WHO priority pathogen list takes no account of specific disease burdens. Given the difficulties surrounding generating support for new vaccine development, it was considered not feasible to think of developing vaccines against organisms such as *Acinetobacter* or *Klebsiella*, which do not affect large numbers of people. Criteria are needed to help vaccine development priority-setting, for example when comparing a disease that has a high burden but little evidence of resistance with a disease where resistance is high but the burden is lower. Moreover, if much antibiotic use is now in the elderly, should they be a more prominent focus for vaccination? Where the strains they are infected with are the same as those in children, the benefit is clearly much greater, but immunosenescence (age-related deterioration of the immune system) has to be considered when prioritizing vaccines for older people.

Many issues require addressing, including:

- Developing a research agenda for the use of vaccines to reduce AMR;
- Gathering evidence (e.g. incorporating AMR data into disease surveillance and vaccine impact data);
- Promoting R&D for new vaccines that could reduce use of antibiotics;
- Promoting R&D for vaccines against pathogens for which antibiotics are no longer working effectively, e.g. TB, typhoid;
- Considering combining prophylactic and therapeutic vaccines with antimicrobials.

A representative of the Bill & Melinda Gates Foundation noted that the Foundation focuses primarily on reducing child mortality, especially in newborns. Antibiotics have a major role to play in saving lives in the most vulnerable communities, and underuse because of unaffordability is a problem in many of these communities. The key question, in that light, is what impact AMR has on mortality in LMICs. More data are needed to answer that question, and the Foundation expressed interest in funding such work. The core of the Foundation's strategy on AMR would be to support vaccines that would have a major impact on reducing mortality – not to play a role in fighting AMR in general. Thus, it has major programmes for HIV, TB and malaria, and is supporting the only current phase III trial of a vaccine against Respiratory Syncytial Virus (RSV) as well as the development of vaccines against Group B streptococcus (GBS). Vaccines for typhoid, shigella and cholera, where AMR is an issue, are also being supported. And it is a priority for the Foundation to increase the coverage of PCV through Gavi and encourage its use in large countries where it is still to be rolled out.

A speaker from the Wellcome Trust noted that the organization had identified both vaccines and AMR as priority areas for the next five years. She noted that, in general, the AMR and vaccine communities operated separately and argued there is a need to bring the two together.

Other points made in the session included:

- There is a need to determine how best to tackle the growing problem of 'vaccine hesitancy'.
- A vaccine priority list is needed. It was noted that the World Organisation for Animal Health (OIE) has produced such a list for animals, but that there is a need for a better evidence base to produce a credible list for humans.
- Consideration should be given to the possibility of vaccines against *Klebsiella*.

- A vaccine targeting multiple winter respiratory tract infections could make a real impact on antibiotic use and AMR.
- There is a real problem of affordability in extending PCV to middle-income countries.
- In diseases where there is the development of resistance (e.g. gonorrhea), investing in new drugs that will then also fail cannot be the only answer. A more holistic approach, including vaccines, is required to address issues such as the control of sexually transmitted infections (STIs).
- The US Biomedical Advanced Research and Development Authority (BARDA) regards AMR as an 'emerging infectious disease' with enormous health and economic implications. In response to the US National Action Plan on AMR, CARB-X was created (with other partners including the Wellcome Trust). Its initial focus is on the development of antibiotics for gram-negative bacteria, but from next year it will incorporate vaccine development in its portfolio.
- In India, consumption of antibiotics peaks in each monsoon season, which is when infectious disease transmission is highest. Compared with many other countries, India uses a much smaller proportion of penicillins and a correspondingly higher proportion of more 'advanced' antibiotics. This has important consequences for the promotion of AMR.

Session 3: Case studies 1

Pneumococcus

The introduction of the conjugate PCV7 vaccine in 2000 in the US produced a very significant reduction in the incidence of invasive pneumococcal disease (IPD) both among vaccinated children and in the elderly through indirect protection. However, it contributed to the expansion of new serotypes not covered by PCV7 that filled an ecological niche, notably 19A, which is also increasingly resistant to penicillin. The introduction of PCV13, which covers 19A, resulted in similar declines in IPD in both resistant and non-resistant strains in the US. Similar trends were documented in South Africa and France, and in Kenya where PCV10 has been introduced. In Germany, there was a cumulative reduction of 539,000 prescriptions for treatment of pneumonia in children under 10 between 2007 and 2014, although a slightly worrying upturn occurred in 2014. The picture for the impact of PCV on mitigating AMR was considered encouraging, but there is now a growth in the US in other resistant strains (e.g. serotypes 35B, 15B and 23A). Similar trends are evident in other countries for different serotypes. It was proposed that, to make a sustainable impact on AMR, vaccines that target all pneumococcal serotypes need to be considered.

Influenza

Evidence from the UK and US demonstrates the complex clinical matrix linking influenza and bacterial pneumonia. Influenza is an important cause of community-acquired pneumonia and is also associated with bacterial co-infection, and bacterial infections are associated with severe and fatal pneumonia. This means that antibiotics are used both appropriately and inappropriately for influenza in community, outpatient and hospital settings. But given the association between influenza and more dangerous bacterial infections, it will be difficult to bring about a large reduction in inappropriate use in clinical practice without a major advance in affordable, rapid point-of-care diagnostics. Therefore, the emphasis must be on averting cases of influenza, recognizing that influenza represents a relatively small part of the broad clinical presentation of acute respiratory infections (ARIs).

A study in Ontario found that prescribing of antibiotics fell by 64 per cent as a result of a flu vaccination programme. Other studies confirm that vaccination can have an effect beyond the targeted child

population. In a UK study of the roll-out of live attenuated influenza vaccine in primary and secondary schools, hospital admission rates for adults fell. Higher vaccination coverage in children could help reduce the incidence in the adult population, especially in those people whose conditions put them at elevated risk from influenza. The challenge for influenza is that the vaccine may not be very effective. In addition, typically, even in the peak of the flu season, fewer than 50 per cent of ARIs are caused by flu. Using RSV vaccines now in development alongside flu vaccines could have a huge impact. It was also noted that there is a lack of data on the burden of flu in LMICs, which inhibits the expanded use of vaccines, for instance through their inclusion in Gavi's portfolio.

Group B Streptococcus (GBS)

GBS is a common colonizer of the gut, from which it can seed infection/ colonization of the urinary or genital tracts (20–30 per cent carriage). It causes a number of diseases in humans, including meningitis, bacteraemia, pneumonia, soft-tissue infection and osteomyelitis. It has been recognized as a cause of peripartum sepsis since it was first characterized in the 1930s, and it is thought to have emerged as neonatal pathogen during 1960s–70s. In the UK, reported cases have more than doubled in the last 25 years. GBS transmission from mother to child during childbirth can result in severe neonatal infection – it is the most common cause of neonatal sepsis, meningitis and infectious death in the UK. Prevention is currently through intravenous antibiotic administration during labour. Most countries base their policies on screening in late pregnancy. In the US, 32 per cent of pregnant women receive antibiotics on that basis and there has been a marked drop in GBS infections. If the UK screened as the US does, then about 150,000 women would receive antibiotics. The UK adopted a risk-based approach, but early- and late-onset infant GBS has risen over the last 25 years. The evidence suggests that 40–60 per cent of infants with GBS are born to mothers with no risk factors. Cases of maternal sepsis are also a significant cause of illness, particularly associated with emergency caesarean sections and an elevated rate of premature and stillborn births.

Another clear trend in the UK is the rapid increase in adult GBS infections – 70 per cent of all disease is now in adults, particularly marked for the over-75s, in whom the case-fatality rate is more than 15 per cent. However, the reasons for this are not well understood.

A vaccine for GBS could have a large impact in averting infections in mothers and children, and in adults, and in reducing AMR. There are just 10 capsular serotypes for GBS, and five of these are responsible for 95 per cent of the disease: this is very different from pneumococcus. Serotype V shows macrolide resistance, so it is essential that the vaccine incorporates it; otherwise, the vaccine would actually drive AMR as type V is selected.

Session 4: Manufacturers' forum

Points made in this session included:

- Live Attenuated Influenza Vaccine (LAIV) is a quadrivalent vaccine applied nasally, which makes it likely to be more protective than injected vaccines.
- Flu vaccination of children can also reduce exacerbation of non-communicable diseases in their family members and communities as a result of flu (e.g. stroke, heart attack or lung disease).
- In New Zealand, an outer membrane vesicle (OMV) vaccine was used to vaccinate all young people against meningococcus B with great success. Later analysis revealed that the incidence of gonococcus has also fallen by 31 per cent in the vaccinated population, but the incidence of

chlamydia has not changed, which points to a protective effect of meningococcus B vaccine against gonococcus.

- *E. coli* is growing in importance as a principal cause of bloodstream infections and related complications in the US, particularly among the elderly, and antibiotic resistance is increasingly seen in cases. A biconjugate vaccine is being developed (Phase 1) against four serotypes covering about 50 per cent of the *E. coli* strains causing bloodstream infections, but about 70 per cent of those that are becoming resistant. If developed successfully it raises similar questions about the feasibility of vaccinating older population groups who would be among those most likely to benefit (as well as addressing neonatal sepsis, where *E. coli* is a leading cause).
- A new PCV15 is under development (Phase 2 completed), targeting 22F and 33F in addition to the strains in PCV13.
- Resistance is detected almost on introduction of a new antibiotic. This is in comparison with earlier antibiotics, when it took years or decades for resistance to be detected.
- Market-based incentives for new vaccines work if there is the prospect of a strong market. For *C. difficile*, *S. aureus* and GBS there is this prospect, but for others, such as Group A streptococcus, market prospects alone are insufficient without monetization of possible AMR benefits.
- While the introduction of PCV7 and PCV13 in paediatric vaccination programmes has had a positive impact on reducing vaccine-type IPD in adults via herd immunity, the risk of IPD and pneumococcal pneumonia, including PCV13-type disease, persists in older adults. There is biological plausibility that PCV13 use in adults has the potential to reduce AMR. However, challenges remain in measuring its impact on AMR reduction and in practical application. There is a lack of adult disease data and vaccine-impact surveillance, of medical/scientific recommendations and of reimbursement arrangements, and there is insufficient infrastructure in some places to support adult vaccination programmes.
- A mix of complementary incentives is needed to encourage increased AMR-focused vaccine R&D, e.g. priority review vouchers, transferable regulatory vouchers, extended marketing exclusivity and R&D tax credits.

Session 5: Case studies 2

Typhoid

The global emergence of multiple antibiotic resistance in *Salmonella* Typhi is compromising treatment. Because it is restricted to the human population, it is possible to conceive of eliminating the disease from parts of the world. In addition, antimicrobial treatment is remodelling the landscape of the disease, for instance with the emergence of the globally distributed lineage H58, which is associated with resistance to multiple antibiotics. A novel ciprofloxacin-resistant subclade of H58 is associated with fluoroquinolone treatment failure. These organisms are evolving and, as more selective pressure is put on them, different types of pathogens are emerging. Vaccination offers a way to stop this process and control typhoid. AMR can be considered infectious as it can be transmitted between organisms, mediated by, for example, *Klebsiella*.

A study in Nepal showed that typhoid was the most common cause of fever in hospitalized children under five years of age. In Bangladesh, another study showed that the majority of families go to the local pharmacy when their child has a fever and receive antibiotics without a clinical or microbiological diagnosis. As a result, AMR is growing: in Nepal, fluoroquinolone resistance has become widespread, from being very low in 2005, while resistance to cephalosporin is also growing. Regarding vaccines, the

Vi polysaccharide vaccine has limitations, in that its efficacy declines after three years and it cannot be used in very young children. The roll-out of VIi conjugate vaccine has been very slow: one is only just now going through WHO prequalification, which is expected within the year. A challenge study recently completed showed 82 per cent efficacy. In Nepal, the government is proposing to ask Gavi to include a typhoid vaccine in its portfolio, not because of AMR but because of *S. typhi*'s prevalence in the region. Nevertheless, this could have a significant impact on AMR within a relatively short space of time.

Gonococcal infection

There are no vaccines against bacterial STIs at the moment. Research is still at the preclinical stage of trying to determine which antigens should be included. *Neisseria gonorrhoeae* is, like typhoid, exclusively found in humans and is very transmissible, including to newborns. It resides in several anatomical niches, such as the throat, and has important implications for AMR. It also facilitates the transmission of HIV. There are an estimated 78 million new cases every year in 14–59-year-olds. But the surveillance data are very poor, including those indicating the degree of AMR. Over the course of nearly 100 years, resistance has developed to each successive class of antibiotics, so that there are now no available effective antibiotics against some gonorrhoeal infections.

There are few estimates of the economic and health costs of gonorrhoea. Using US-based findings, it was crudely estimated in 2005 that the global costs of resistance in this disease were $500 million per annum. Men who have sex with men (MSM) who are taking pre-exposure prophylaxis (PrEP) for HIV are particularly vulnerable to gonorrhoea, and similar increases have been found for syphilis and chlamydia. Also, MSM are much more likely than heterosexuals are to be infected with resistant strains. The oro-pharynx is an ideal niche for genetic exchange of AMR determinants between commensal bacteria and gonococci as oro-pharyngeal antibiotic concentrations are also lower, leading to AMR and treatment failure. The current dual therapy for gonorrhoea is cephalosporin and azithromycin, and the first dual therapy failure was documented recently. In resource-poor settings, dual therapy may not be possible.

Gonorrhoea is now on the CDC and WHO priority pathogen lists for AMR-related antibiotic development. But, for several reasons, the prospects of a new antibiotic becoming available soon to tackle the urgent AMR threat in gonorrhoea seem poor, and the current pipeline of three antibiotics in Phase 2 is not very promising. Therefore, a vaccine is needed to control the disease. However, there is a long way to go in developing one; the few previous attempts to produce a vaccine have failed. In spite of the findings from New Zealand of the effect of meningococcal vaccination on gonorrhoea, there is a long list of technical challenges to be overcome if a vaccine is to be developed. But if a vaccine with high efficacy can be developed, the disease could be nearly eliminated in 15 years. If substantial resources can be made available for investment, and the technical challenges can be overcome, development of a gonococcal vaccine would be a major advance for global health.

Tuberculosis (TB)

WHO estimates that TB now kills more people than any other pathogen. There were 10.4 million new cases and 1.8 million deaths in 2015. AMR is a very significant problem in both primary and secondary TB, and there is extensive multi-drug resistance (MDR). The two antibiotics now affected by MDR were developed 60 years ago, and the two antibiotics recently introduced to supplement them are already encountering resistance. There are also extensively drug-resistant (XDR) strains, where there is resistance to a second-line injectable antibiotic and treatment success is less than 30 per cent. In 2015 only approximately one-quarter of the 500,000 people experiencing MDR TB actually received treatment. In addition, because TB treatment duration ranges from six months (when there is no resistance) to 18–20

months (for XDR TB), there are compliance problems that exacerbate the AMR problem. Generating new antibiotics is not necessarily going to be the answer here. Attaining the SDG goal of ending the TB epidemic requires new tools.

There are now more than a dozen TB vaccine candidates in clinical trials, whereas 14 years ago there were none. One important question is what type of vaccine is required for which target populations? Prophylactic vaccines could be targeted at infants and uninfected adolescents or young adults, the latter being the main group responsible for transmission. Meanwhile, post-exposure vaccines could be used for latently infected people to prevent the reactivation of the disease, or even to eradicate the latent infection. Therapeutic vaccines could be used as an adjunct to chemotherapy, particularly with a view to shortening treatment duration, especially for MDR/XDR cases.

As with gonorrhoea, there are many challenges in vaccine development. The four animal models used are not necessarily relevant to human disease, and there is no immunological correlate to guide vaccine development. Furthermore, disease incidence and the lack of site infrastructure present challenges for mounting efficacy trials.

For therapeutic vaccines, the end points need to be identified. An improved rate of microbiological cure, a reduced time to achieve it, and a shortening of the time it takes for a sputum smear test to turn negative would have an impact on transmission. Another question is when to administer vaccines – on diagnosis, when treatment starts, or during treatment, bearing in mind the likelihood of adverse reactions depending on the phase of treatment. The development path for a therapeutic vaccine needs urgent discussion with regulators, given that phase III vaccine trials are as challenging as phase III drug trials. More collaboration is needed between the drug and vaccine fields.

Session 6: Modelling the value of vaccines against AMR

The effect of vaccine use on the development and cost of AMR should figure in decisions about allocating resources to the development and delivery of vaccines. The issues are how importantly it should figure, and what is needed to quantify, monetize and justify that allocation. There are many uncertainties and complexities. There is a heterogeneity among different and evolving pathogens, and the actual and potential vaccines and antibiotics needed to control them. There is also a diversity of stakeholders – including ministries of health and finance – with various interests. There is a distinction between the use of existing vaccines and decisions on the development of new vaccines. There are complex regulatory issues, including the timelines to deal with AMR as it evolves and the fact that AMR is driven by both humans and animals. Vaccines also affect AMR in multiple ways – not only by preventing diseases, but also by reducing the severity of disease and by reducing or eliminating the need for treatment.

Modelling the impact of vaccines on AMR is certainly an important way to analyse and increase understanding of complex processes. The key question is whether they could be sufficiently meaningful and reliable to be a useful guide to decision-making.

Mechanisms by which vaccines may reduce antimicrobial resistance

The most obvious way in which vaccines address AMR is by preventing infections and therefore associated antibiotic treatment (both appropriate and inappropriate). The impact of the pneumococcal vaccine shows this effect. A characteristic of the use of antibiotics is that they can induce selection among the many bacteria that reside in the human body, not just the pathogen against which they might be targeted. This is known as bystander selection. For example, treatment of flu with antibiotics can increase

resistance in bacterial pathogens. This complicates the measurement of the likely reduction in AMR as a result of avoided antibiotic use. It is much easier, at least in principle, to measure potential reductions in antibiotic use from a specific vaccine than it is to trace what reductions in AMR might result given the interactions with different pathogens in the human body, some of which may be causing clinical syndrome symptoms. Thus, 'avoided use' of antibiotics, although inferior to AMR reduction, might be the best end point to use in modelling the impact of vaccines. It might even be possible to include this as a secondary end point in clinical trials, or more likely in post-licensure studies, given the much larger populations under study.

Other possible mechanisms include the development of vaccines that work preferentially against resistant strains. PCV has achieved this, albeit temporarily, as non-vaccine strains exhibiting resistance are again becoming more prominent. A vaccine that targets some of the proteins that confer resistance in ways that would counteract selection for resistance (as with PCV) would be most valuable. Vaccine efficacy against resistant strains does not have to be that powerful to bring about selection in favour of drug-sensitive strains. Another possibility is that early-life infections, e.g. otitis media, may increase susceptibility in later life. Vaccination would then have a secondary effect in reducing adult proneness to infection.

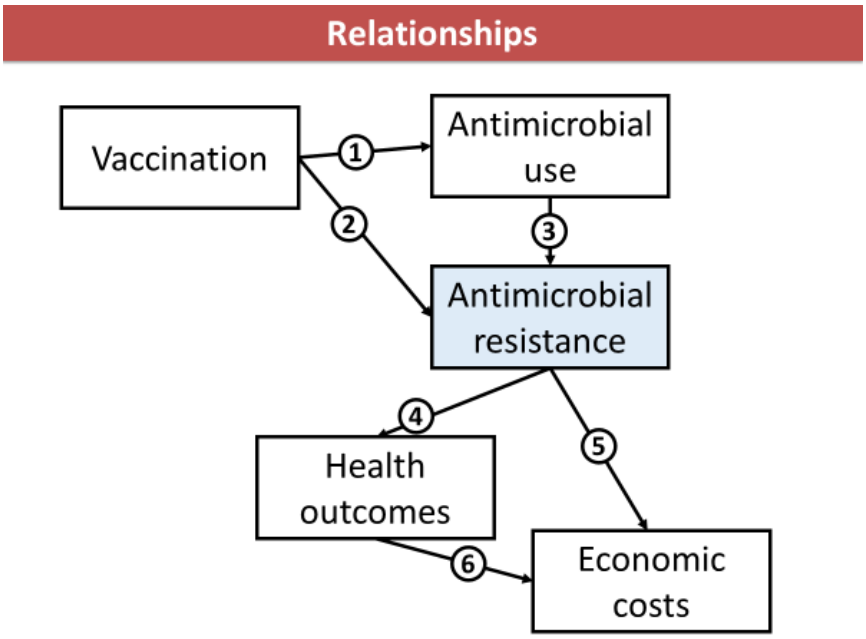
Therefore, overall, modelling the ecology of AMR and interactions between vaccine hosts and microbes will be highly complex, with limited understanding of the link between antibiotic use and AMR and of the possible importance of bystander selection. On the other hand, for those diseases where AMR is prevalent (e.g. STIs, TB, HIV and Group A streptococcus), the case for vaccines is obviously very strong.

Complications in predicting the effects of vaccines on AMR

Much selection for resistance is random, and resistance is frequently linked to other traits. Models that assume resistant strains are otherwise identical to sensitive strains may be inaccurate. Resistance evolution is unpredictable. Vaccines targeting resistance elements may lose effectiveness with time. Resistance is not always costly, and we do not fully understand what maintains resistance to begin with. It would be best if we could vaccinate against resistant elements directly, guaranteeing cost-effectiveness as opposed to hard-to-estimate indirect effects. As noted before, the bulk of many microbes' antibiotic exposures come from antibiotics used to treat other microbes. Therefore, we need to consider the vaccine's impact on total antibiotic use and the typical host/antibiotic environment experienced by each pathogen, not prescription rate per pathogen. There are probably small, but distinct, possibilities that va

Models of the impact of vaccination on development of AMR: existing work and gaps

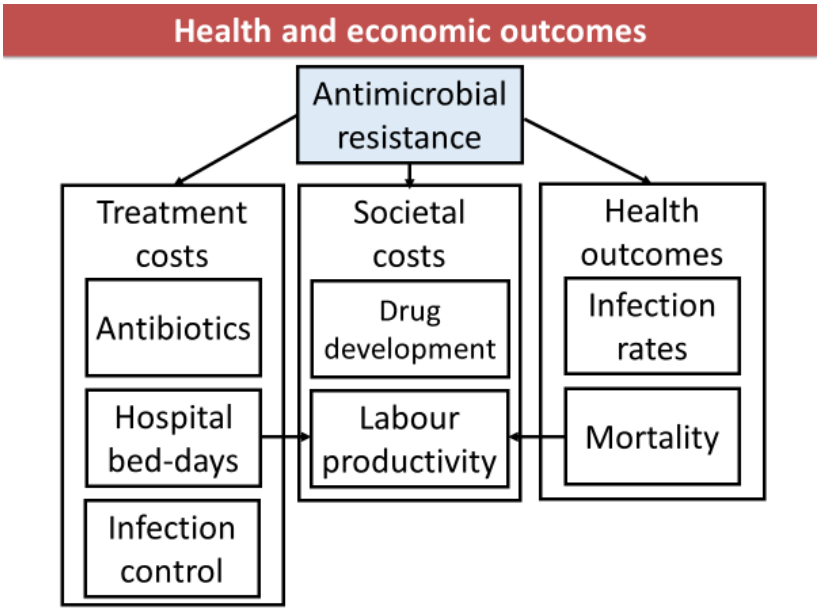
The central issue is whether models can address a decision-maker's question about whether to invest in one vaccine rather than another. These are the relationships of concern:



The problem from the modelling point of view is that working out these relationships involves three groups that normally work separately – those modelling antibiotic stewardship and AMR in general, vaccination modellers, and those modelling health and economic outcomes.

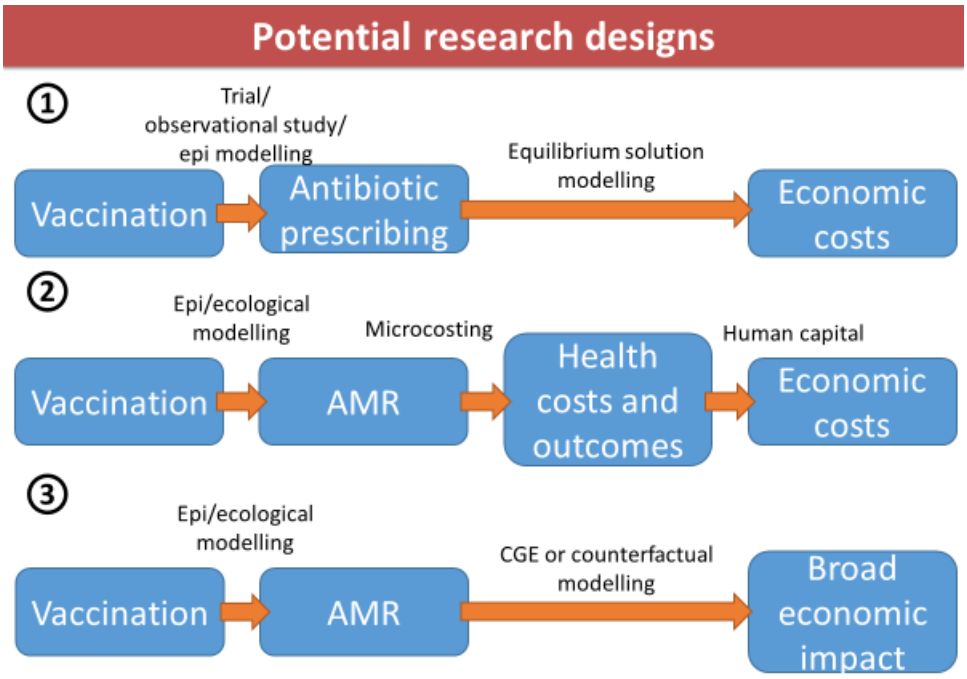
There is very little literature in this area, and most focuses on pneumonia. Although those publications consider the different pathways by which vaccines could affect AMR, they do not include the bystander effect. In addition, there is a complexity introduced because the pathways are not independent.

There are also multiple health and economic costs associated with AMR whose values and relationships need to be quantified:



There are about five different approaches that have been adopted to address these elements. The simplest one is to compare, for instance, the costs of hospitalization for patients with or without resistant strains. Other approaches involve several assumptions that are open to question. Furthermore, if the impact of AMR is very large, then it has health and economic consequences that are very difficult to model.

There are three possible ways to approach vaccine and AMR modelling:



The first approach is the most feasible with current knowledge and data, but it depends on strong assumptions that may not be realistic. The other two approaches involve trying to model the dynamic effects of AMR, both in terms of epidemiology and ecology; and in the third case the dynamic economic effects are modelled as well.

What is known about the health and economic burden of AMR?

The burden of AMR cannot be considered in the same terms as the burden of, say, cardiovascular disease. In the case of AMR, the burden reflects how we have used antibiotics in the past. This is not only difficult to measure with any accuracy, but it also reflects the extent to which we have not used other means of preventing infection that would obviate the need for antibiotics, such as vaccines or improved water and sanitation.

The overall effectiveness of antibiotics reflects both past use and resistance levels, and the current availability of new antibiotics. The spread of AMR also drives up the cost of new antibiotic development because of the need to address the changes in pathogens brought about by antibiotic use. It must not be forgotten that more people die because of lack of access to antibiotics than from AMR. Moreover, antibiotics are being used at high rates in low-income countries because living and environmental standards are inadequate. Infectious disease rates in the US fell dramatically prior to the first use of

penicillin as public health standards improved. Antibiotics are being used so much because the measures that prevent infection in the first place are not being implemented.

Those most at risk from the consequences of AMR are the young and the elderly. A recent study in New Delhi, for instance, showed fatality rates of newborns with sepsis as high as 69 per cent in those with resistance to cephalosporins, although even those with non-resistant strains had a fatality rate of 52 per cent. US data in the elderly suggest that antibiotic use for the 10 most common kinds of surgery reduces infection risk by between 5 percent (hip replacement) and 25 per cent (colorectal surgery). On that basis, a 30 per cent reduction in the efficacy of antibiotics in the US could result in an extra 6,000 deaths.

A study of 2000–10 data in 72 countries showed a 36 per cent increase in antibiotic consumption, of which three-quarters was accounted for just by the BRICS countries, dominated by increased hospital consumption in China and increased retail consumption in India. India is the largest consumer of antibiotics in the world, using 30 per cent more than China and double that of the US. Over the same period, however, the study showed that there were small declines in use in the US, France and Germany. In India since 2010, there has been a dramatic rise in the use of faropenem and meropenem.

The flu season is a key driver of antibiotic consumption throughout the world. The arrival of influenza in the US is nearly perfectly predicted by antibiotic sales data. Vaccines could play a major part in antibiotic avoidance by reducing the flu component of fevers in that season because these symptom presentations account for a large proportion of antibiotic consumption.

Quantifying the economic impact of AMR requires a better understanding of its health impact, and this has been difficult to ascertain. There is much to do on modelling the impact of vaccines on antibiotic use. There is a need to estimate the value of expanding access to existing vaccines, as well as the value of new vaccines (e.g. vaccines against gram-negative organisms). Many authorities have not yet identified the vaccine–AMR connection, and there is a need to provide evidence urgently.

Session 7: Conclusions and next steps

A poll was conducted in the meeting, with each participant given tokens that represented financial investments. They were asked to spend them by prioritizing between 15 possible vaccines for their impact on AMR. In order of priority, participants chose TB, typhoid, influenza, RSV, gonococcus, GBS, GAS, *S. aureus*, other (includes malaria), pseudomonas, *C. difficile*, *Klebsiella*, HIV, chlamydia and pneumococcus (last). It was pointed out that this list needed interpretation and elucidation of the criteria for prioritization. Pneumoccocus came last, but that might be because no extra incentives are needed to motivate R&D. The ability (or growing inability) to treat seemed to be a key factor, as was the feasibility of vaccine development. Beyond that, it was noted that the ability to tackle AMR had to be only one factor in decision-making about vaccine development.

Various suggestions were made as to the way forward following the meeting. These included:

- Drafting an opinion piece for the *Lancet* or other journal;
- Bringing the issue to WHO's Strategic Advisory Group of Experts (SAGE) on Immunization;
- A journal special issue on vaccines;
- Establishing a small working group to take this forward;
- Addressing the issue of vaccine use and antibiotics in animal production.

Agenda

29 March

8.30 – 9.00 Registration & coffee

9.00 – 10.00 SESSION 1 | Understanding the Landscape of Vaccines and AMR

(This session not held under the Chatham House Rule)

Welcome: David Salisbury, Associate Fellow, Centre on Global Health Security

Overview: David Salisbury, Associate Fellow, Centre on Global Health Security

Keynote Address: Seth Berkley, Chief Executive Officer, GAVI

10.00 – 13.00 SESSION 2 | Perspectives on vaccines and AMR

Panel 1: Global/Regional

10.30 – 11.00 Refreshments

Panel 2: National

Panel 3: Antibiotics and AMR

13.00 – 14.00 Lunch

14.00 – 15.30 SESSION 3 | Case studies 1

Pneumococcal vaccines

Influenza

Group B streptococcus

15.30 – 16.00 Refreshments

16.00 – 17.30 SESSION 4 | Manufacturers forum

Topics to cover include: S. aureus; GBS; C. diff; Gonococcus; RSV; Pneumococcus; Extra-Intestinal E. coli (ExPEC)

30 March

9.00 – 10.30 SESSION 5 | Case studies 2

Typhoid

Gonococcal infection

Tuberculosis

10.30 – 11.00 Refreshments

11.00 – 13.00 SESSION 6 | Modelling the value of vaccines against AMR

13.00 – 14.00 Lunch

14.00 – 15.30 SESSION 7 | Conclusions and next steps

Roundtable

Closing