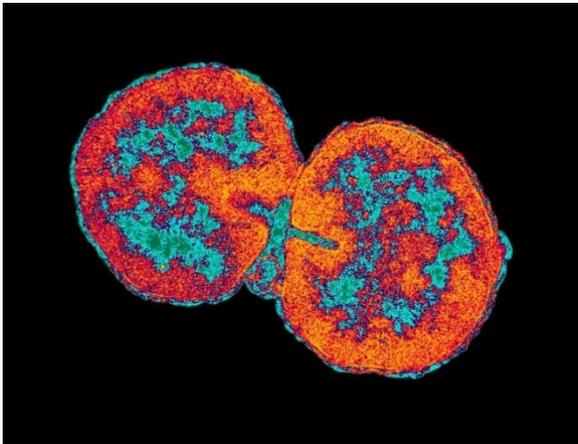


Antimicrobial Resistance and Immunisation



Antimicrobial resistance (AMR) is an urgent global health threat that, if left unchecked, could account for an estimated 10 million deaths per year by 2050.¹ Immunisation is one potential way of reducing AMR. This POSTnote describes the role for immunisation in tackling AMR, both globally and in the UK, the use of existing vaccines and how vaccine development aligns with public health priorities.

Background

Antimicrobial drugs kill or inhibit the growth of microbes (for example, bacteria, viruses and fungi). Microbes adapt by developing or acquiring traits that make them resistant to these drugs. This process is accelerated by widespread (including inappropriate) use of antimicrobials in humans and animals.^{2,3} When resistance occurs in microbes capable of causing disease (pathogens), treatment options become limited. There are ~700,000 deaths globally every year from drug-resistant infections.⁴ AMR poses a significant health and economic burden, and is a priority for the UN General Assembly.⁵ Plans to tackle AMR recognise the need for multiple approaches, including immunisation and improved sanitation, but the focus has tended to be on more careful use of existing drugs and the development of new ones.⁴⁻⁸ In 2014, the UK Government commissioned the (O'Neill) Review on AMR, to assess the global burden of resistance and make recommendations. It concluded that vaccines have been overlooked as a tool to reduce AMR and should be an investment focus.⁹

Immunisation as an AMR intervention

Immunisation confers protection from infection by introducing a non-harmful form or component of the pathogen in a vaccine. The body develops an immune response (such as antibodies) without disease. For many

Overview

- Antimicrobial resistance (AMR) has reached a point where some infections may become untreatable.
- Immunisation is one strategy to tackle AMR, by decreasing rates of infection and thereby antibiotic use and preventing the development of resistant infections.
- The World Health Organization has developed a list of pathogens where AMR is of most concern and new antibiotics are needed; there is no equivalent for vaccines.
- Quantifying the impact of immunisation on AMR and incorporating this into calculating the cost-effectiveness of vaccines is still an area of ongoing research.
- Using immunisation to tackle AMR depends on wider use and increased uptake of existing vaccines, and increasing the development of new ones.

vaccines, high uptake in a population generates herd immunity. Non-immunised people are indirectly protected by being surrounded by immunised people who do not transmit the infection.¹⁰ Some bacteria are naturally carried in or on the body, and often beneficially, but can be transmitted to and lead to disease in susceptible people.¹¹ Immunisation can prevent carriage, thereby reducing transmission to non-immunised people.¹² Mass immunisation programmes save ~2.5 million lives a year, globally.¹³

Immunisation can reduce the AMR burden through two main mechanisms. Firstly, it prevents infections (including resistant ones), disease and deaths, and negates the need for expensive, more complex drugs to treat resistant infections.^{14,15} Secondly, preventing infection avoids the need for treatment, so antimicrobial use is reduced, in humans and animals.¹⁶⁻¹⁸ One study estimated increasing uptake of the pneumococcal conjugate vaccine (PCV) could reduce antibiotic (antimicrobials for bacteria) use for pneumococcal pneumonia in children aged under 5 years by 47%.¹⁹ Antibiotic use is linked to the development of AMR; as use decreases, so too the pressure for resistance to develop in the pathogen.^{2,20,21}

Vaccines offer long-term protection from infection in contrast to antibiotics, and many vaccines still effective today were

introduced decades ago.²² However, if a pathogen undergoes high rates of mutation, the vaccine will need to be changed, such as for influenza.²³ Furthermore, if a vaccine only covers some strains of a pathogen, infections caused by other strains can occur or increase.^{24,25}

Priority Infections

The World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) have priority lists of bacterial pathogens of most concern, due to risk of resistance (Box 1).^{26,27} The O'Neill Review identified key contexts where immunisation could reduce AMR. This includes vaccinating against: infections acquired in hospital or the community; viral infections, for which antibiotics are ineffective but may be prescribed for symptoms of, or to prevent (secondary) bacterial infections.⁹

Box 1. Antibiotic Resistant Priority Pathogens

There is no specific list of the most important resistant pathogens for the UK but lists have been developed by CDC and WHO, focusing on bacteria. Many pathogens are on both lists and categorised by threat level; the most urgent/critical threats are described here. In 2013, CDC identified the most urgent threats for the US as *Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae* and *Neisseria gonorrhoeae*.²⁷ In 2017, WHO identified pathogens for which research and development of new antibiotics was most needed (*Mycobacterium tuberculosis* has a dedicated programme). Critical threats include:²⁶

- *Acinetobacter baumannii* that are resistant to carbapenem drugs
- *Pseudomonas aeruginosa* that are carbapenem-resistant
- *Enterobacteriaceae* that are carbapenem-resistant and/or resistant to 3rd generation cephalosporin drugs.
- Carbapenem resistance is an issue as this is a "last resort" class of antibiotic, used for treatment when other options have failed.²⁸ There are no licensed vaccines for any of the pathogens listed above, although some are currently in development.²⁹

The Global Context

The burden of disease and AMR varies considerably across the world. Many serious infections disproportionately affect low- and middle-income countries (LMICs).³⁰⁻³² HIV, tuberculosis and malaria are the "big three" infections, so-called because of the health burden they pose. Resistance is an issue for treatment of all three.³³⁻³⁶ Vaccine development for each is ongoing; there is no HIV vaccine and the major vaccine in development for malaria and the only available vaccine for tuberculosis provide a sub-optimal level of protection.^{29,37,38}

There are a number of infections where new vaccines or increased uptake of existing ones could reduce mortality and/or antibiotic use, such as those caused by group A streptococci, pneumococci, influenza and respiratory syncytial virus (RSV).^{19,39-43} In 2016, there was an outbreak of typhoid fever in Pakistan, resistant to multiple antibiotics.⁴⁴ A new typhoid vaccine has been recommended, with higher efficacy than previous vaccines.⁴⁵⁻⁴⁷

The UK Context

Many infections that present a global problem are also an issue in the UK. Vaccines could be a useful tool in managing infections where antibiotic treatment is undermined by resistance, such as gonorrhoea (Box 2).

Cases of gonorrhoea have increased since 2008 and many antibiotics are no longer recommended for routine use due to the emergence of resistance. A recent case of gonorrhoea in the UK was resistant to both current primary recommended treatments.^{51,48-50}

Box 2. Gonorrhoea

Gonorrhoea is a common bacterial sexually transmitted infection and can result in infertility if left untreated. Antibiotic treatment options are limited by high levels of AMR.^{51,52} There is no vaccine currently available.²⁹ Data from New Zealand show that a vaccine against meningitis B had an estimated 31% efficacy against gonorrhoea. The bacteria causing meningitis B and gonorrhoea are related. This has led to suggestions of optimising the next generation of this vaccine to prevent gonorrhoea.⁵³ In 2015, the UK became the first country to offer routine meningitis B immunisation, using a vaccine which shares a component with the vaccine used in New Zealand.⁵⁴

Healthcare-associated infections (HAIs)

HAIs incur significant costs to the NHS and can result in severe outcomes, such as blood-stream infections (BSIs).⁵⁵⁻⁵⁷ *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA) infections remain a burden in healthcare settings, but have decreased substantially in recent years (due to better infection prevention and control, and reduced prescribing). Between 2007/08 and 2017/18, there was a 76.1% decrease in *C. difficile* infections and 81% decrease in MRSA BSIs.⁵⁸ Another cause of HAIs are the "Gram-negative" class of bacteria, where resistance is significant.^{55,59} Most Gram-negative BSIs are caused by *Escherichia coli*, *Klebsiella* and *Pseudomonas aeruginosa*.⁵⁵ Almost half of *E. coli*-BSIs are resistant to co-amoxiclav, a routinely used antibiotic, and resistance to carbapenem antibiotics (Box 1) is low but increasing annually.⁵⁵ The Government has a target to reduce the incidence of Gram-negative BSIs by 50% by 2021, through improved infection prevention and control.⁵⁵

There are no licensed vaccines for any of these infections.²⁹ It is suggested that these vaccines could be targeted to people with an increased risk of infection, such as those with planned surgical procedures.^{9,60,61} Vaccines are in development for MRSA and *C. difficile* and three *E. coli* vaccines are in early trials, but there are no candidates in trials for *P. aeruginosa* or *Klebsiella*.²⁹ Although Gram-negative bacteria can cause serious infections at certain sites in the body, many normally live in the gut of healthy people.⁶²⁻⁶⁴ It is unclear how immunisation would impact gut bacteria and consequently overall health.^{11,65}

Viral infections

Lack of rapid diagnostics for use at the time of consultation means many antibiotics are prescribed on the basis of symptoms alone, which can be caused by multiple pathogens, for example for respiratory tract infections (RTIs).⁶⁶⁻⁶⁸ This can lead to unnecessary antibiotic use for RTIs caused by viruses that can resolve without antibiotic treatment, but which are prescribed due to the risk of bacterial infection, particularly in children and the elderly.⁶⁹⁻⁷³ Vaccinating against common viral causes of RTIs, such as influenza virus, can reduce antibiotic use and acquisition of secondary bacterial infections.^{17,74,75} RSV is the most

common cause of acute lower respiratory tract infections in children under 5 years of age globally and is an issue for adults with other conditions and/or lowered immune systems.^{76,77} There is no licensed vaccine but there are many vaccine candidates in different stages of clinical trials.⁷⁸⁻⁸⁰

The influenza vaccine is offered to all over 65s, at-risk groups (including pregnant women), and more recently to children, to provide protection from infection and to decrease transmission from children to vulnerable older individuals.⁸¹ Vaccine uptake in the UK varies between groups but is high (>70%) for over 65s.⁸² Variations in the circulating strains causing infections each season can lead to mismatches, where the available vaccine does not fully target the current strain. There is ongoing research in developing a vaccine that covers all strains, to reduce influenza infections⁸³⁻⁸⁶ and with further benefits of reduced antibiotic use and secondary ear infections.⁸⁷⁻⁸⁹ Population-wide influenza vaccination in Ontario was associated with a 64% decrease in influenza-associated respiratory antibiotic prescriptions.¹⁷ Research by Public Health England (PHE) is assessing any changes in antibiotic prescribing and secondary lower respiratory tract infections in the context of the influenza immunisation programme in England.⁹⁰

Decisions about Vaccine Use

There are two main approaches to reducing AMR using immunisation: maximising the utility of existing vaccines by ensuring good uptake and offering them more widely as appropriate, and making decisions about which vaccines should be developed and introduced and when and where to use them most efficiently.⁹ Decisions about choices for national immunisation programmes vary between countries due to vaccine availability and affordability, disease risk, vaccine efficacy and different frameworks for advice.^{91,92}

Measuring the Impact of Vaccines on AMR

Vaccines may have several direct and indirect effects on AMR:⁹³

- preventing disease and deaths
- reducing the progression to and severity of disease
- reducing transmission of infection between people
- reducing antibiotic use and pressure for resistance
- reducing GP visits and hospital stays.

Monitoring and quantifying the effects of immunisation on AMR and assigning economic benefit to these outcomes is challenging and requires surveillance data and complex analysis (Box 3).^{7,93,94} The committee that advises the UK Government on vaccination considers AMR in its decision-making process insofar as it is able, based on the evidence (Box 4).⁹⁵

Surveillance and Data Collection

Understanding disease burden and the proportion that is resistant is important in informing design and use of AMR interventions, including vaccines.^{4,96-98} The UK has

Box 3. Mathematical Modelling and Cost-Effectiveness Analysis

Mathematical modelling of the impact of a vaccine on a target population and cost-effectiveness evaluations are an important part of decision-making about vaccines in the UK. This is a statutory requirement before a vaccine can be recommended to Ministers.⁹² Modelling of immunisation and AMR is a useful tool to increase understanding and predict impact but its utility in informing public health strategies is restricted by the complexity in modelling this relationship.⁹³ For example, although antibiotic use has accelerated development of AMR, this can vary depending on the drug, pathogen and host setting.⁹⁴ Furthermore, antibiotic use can also pressure the bacteria carried in the body of healthy people to develop resistance.⁹⁹ Existing studies aiming to model AMR in the context of immunisation are restricted to pneumococcal and *S. aureus* infections.⁹³

separate surveillance systems to monitor disease and AMR.^{55,100} Some lower income countries, in which AMR has a disproportionate impact, do not have the capacity for detailed surveillance, which limits understanding.^{101,102} Programmes to increase surveillance in these regions include The Fleming Fund and the WHO Global AMR Surveillance System.^{103,104} Monitoring antibiotic use is one way to quantify the impact of immunisation on AMR but this is complex.¹⁰⁵⁻¹⁰⁸ The Wellcome Trust has commissioned a review of studies on immunisation and antibiotic use. It is also encouraging data collection about antibiotic use during clinical trials and post-vaccine roll out studies.¹⁰⁹

Box 4. Scientific Advice to the UK Government on Immunisation

The Government amends the national immunisation schedule on the advice of the Joint Committee on Vaccination and Immunisation (JCVI). Decision making is informed by a range of evidence including disease burden, vaccine availability, safety and efficacy and cost-effectiveness. The AMR burden for an infection is considered where possible. This is limited by the complex challenges in quantifying the impact of vaccination on the AMR burden and assigning economic benefit to this impact. Researchers are developing models to predict these complex effects. The JCVI has identified two infections for which vaccines are unavailable but could be beneficial and cost-effective, RSV and Group B *Streptococcus* (GBS).^{95,110} These could also be beneficial from an AMR standpoint as both infections lead to potentially avoidable antibiotic use. Antibiotics are ineffective against RSV but may still be prescribed, including for secondary bacterial infections.⁴¹ For GBS, there are global differences in screening practices and antibiotic use.¹¹¹⁻¹¹³

Utility of Existing Vaccines

The O'Neill Review recommended wider use of existing vaccines, such as those for pneumococcal infections.⁹ After the pneumococcal conjugate vaccine (PCV) was introduced in the UK in 2006, the incidence of disease across all age groups caused by types ("serotypes") contained in the vaccine fell by 97% by 2016, and infections resistant to a certain class of antibiotics (macrolides) also decreased (Box 5).^{25,114} Reduced prevalence of drug-resistant infections and antibiotic use through immunisation depends on achieving good vaccine uptake. There are major global disparities in uptake, as a consequence of supply and affordability, weaknesses in health systems and public attitudes.^{115,116}

Box 5. Pneumococcal Conjugate Vaccine (PCV)

Streptococcus pneumoniae can cause severe disease, including meningitis, septicaemia and pneumonia, with under 5 year-olds and the elderly most at risk.¹¹⁷ There are >100 identified serotypes that vary in their prevalence, drug-resistance and ability to cause disease^{118,119} PCV7, a vaccine covering 7 serotypes, has been linked to reduced antibiotic use and resistant infections in some regions.¹²⁰⁻¹²² A reduction in vaccine-targeted serotypes was followed by an increase in disease caused by other serotypes, known as serotype replacement.²⁵ New vaccines are required to cover serotypes arising through this process, for example PCV13 is now used in many countries, including the UK.^{25,117}

The Global Context

The effectiveness of national immunisation programmes relies on high vaccine uptake in the target populations.^{10,123} However, many countries do not have the infrastructure or means to achieve this. For example, the WHO estimates that global coverage of PCV for children under 5 is 42%.¹²⁴ Gavi is a public-private partnership that aims to increase vaccine coverage in the world's poorest countries.¹²⁵ Gavi's portfolio contains 11 vaccines,¹²⁶ and they estimate that their provision of *Haemophilus influenzae* type b, pneumococcal and meningococcal vaccines between 2001 and 2030, could mean that 500 million doses of antibiotics would not be used. AMR is a recent addition to Gavi's vaccine investment decision criteria.¹²⁷

The UK Context

The UK has one of the most comprehensive immunisation schedules and high uptake.¹²⁸ There are still inequalities in uptake in certain socioeconomic and ethnic groups, but PHE and NHS England are working to reduce them.^{129,130} Public perceptions of vaccination also influence uptake and can lead to increases in vaccine-preventable infections.^{131,132} Survey data from 2016 showed that 94% of parents in England had confidence in the immunisation programme.¹³³ This high level of confidence is not reflected worldwide, including some high income European countries.¹³⁴

Developing New Vaccines

Vaccine development requires advanced technologies, is expensive, time-consuming and subject to high attrition, so companies require markets to make research and development (R&D) commercially viable.^{9,135-136} There are a number of vaccines in development for pathogens on the WHO and CDC lists (Box 1), but some vaccines may be less attractive as they offer lower returns, such as those targeting diseases that mainly affect LMICs.^{29,137,138} A key question is how to stimulate and prioritise the development of new vaccines in the context of AMR. The O'Neill review highlighted the need to support early research and maintain a viable market.⁹ However, the majority of funding for new AMR products (excluding direct industry investment) targets development of new antibiotics.¹³⁹ Several government AMR initiatives are ongoing, including vaccine development (Box 6). Other proposed methods to encourage development include product development partnerships, market entry rewards and tax credits.^{4,40,140}

Vaccine Development and Public Health Priorities

Where collections of symptoms could be caused by several different pathogens (such as RTIs), vaccinating against many of these (such as influenza and RSV) could have a greater impact on antibiotic use, by preventing infection and reducing the need for medical intervention.^{77,40,141} It has been suggested that future research could focus on developing vaccines that preferentially target resistant pathogens or are against HCAs.^{7,40,61,142} As HCAs are more likely to affect certain groups, vaccinating the whole population may not be appropriate.^{9,143} However:

- unwell or elderly people may not be able to develop a protective immune response after vaccination^{9,143}
- identifying the target population risks missing people⁶¹
- for those entering hospitals in an emergency, there may not be time to be vaccinated and generate immunity, although treatments (monoclonal antibodies) that confer immediate, short-term immunity are being developed.¹⁴⁵

Public Health Priorities

Guidance on public health priorities can inform research and help manufacturers understand potential markets.¹⁴⁶ For example, target product profiles that outline what is expected from a vaccine can bring stakeholders together and coordinate development.^{147,148} The Wellcome Trust has commissioned work to assess vaccine development for all pathogens on the WHO priority pathogen list, including:¹⁰⁹

- R&D pipeline - past failures, existing efforts and need
- market analysis - sizing calculations and target population
- payers - who would pay or support access to vaccines
- barriers - commercial, clinical trials and delivery
- benefits for each pathogen and any cross-protection.

Vaccine Development

Various initiatives can support the pre-clinical development of promising vaccine candidates; CARB-X is a public-private partnership funding development of antimicrobial products for priority pathogens (Box 1).¹⁴⁹ The UK government funded BactiVac Network aims to accelerate development of anti-bacterial vaccines for LMICs and covers UK needs following investment from the Industry Strategy Challenge Fund.¹⁵⁰ The planned UK National Vaccine Development and Manufacturing Centre aims to support later stages of development.¹⁵¹ Medicines regulators such as the European Medicines Agency are co-operating with other bodies to discuss vaccine regulation in the context of AMR.¹⁵²

Box 6. Government AMR Strategies and Immunisation

The Department of Health and Social Care (DHSC) leads the 5-Year AMR Strategy which includes increasing uptake of immunisation and investment in new vaccines.¹⁵³ The £50 million Global AMR Innovation Fund - set up in response to the O'Neill review - funds R&D in underinvested areas.¹⁵⁴ This focuses on LMICs and includes the development of alternatives to antibiotics, such as vaccines, with investment in CARB-X.¹⁵⁵ Innovate UK works with GAMRIF and conducts other AMR and vaccine work.¹⁵¹ The Department for International Development contributes to the UK AMR Strategy and is the biggest contributor to Gavi.¹⁵⁶ The AMR Funders Forum includes research councils, government and charities and coordinates UK AMR research. This includes vaccine development and work to identify which interventions will have the most impact in different settings.¹⁵⁷

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