QUANTIFYING THE BENEFITS OF VACCINES IN COMBATING ANTIMICROBIAL RESISTANCE

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Summary: Vaccination is one of the most effective measures to reduce antimicrobial resistance. As vaccines are highly specific to their targeted pathogens, they are less likely to induce resistance compared to antibiotics. Their impact on resistance or antibiotic prescriptions has already been demonstrated for vaccines against pathogens such as *Streptococcus pneumonia* and influenza, but greater investment and development is needed for vaccines which target pathogens such as *Vibrio cholerae*, *Salmonella typhi*, *Escherichia coli*, common health care-associated infections and respiratory and diarrhoeal viruses. To value vaccines correctly, economic evaluations need to take account of multiple health system, ecological and epidemiological pathways through which vaccination affects antimicrobial resistance and use.

Keywords: Vaccines, Economic Evaluation, Antimicrobial Resistance

Introduction

The development and use of vaccines is a key strategy to combat antimicrobial resistance (AMR). A recently published chapter “The role of vaccines in combating antimicrobial resistance” within the book; *Challenges in Tackling Antimicrobial Resistance: Economics and Policy Responses* offers a comprehensive review of this summary. In this article we provide an overview of the key issues discussed in the chapter.

Vaccines have a number of characteristics which make them particularly effective at combating AMR. First, vaccines usually have little effect on the evolution of microorganisms besides the targeted strains. This is because vaccines work by enabling the immune system to recognise antigens that are highly specific to their targeted pathogens. In contrast, antibiotics can impose selective pressure on both targeted and non-targeted microorganisms to develop resistance. Second, due to the specific nature of vaccines, vaccines can be developed that target specific strains of a pathogen that are most pathogenic or prone to developing resistance. This has been the case with pneumococcal conjugate vaccines, where the serotypes selected for vaccine development were generally the ones most likely to cause invasive disease. Thirdly, vaccines and antimicrobials can work in a synergistic fashion – vaccines can reduce the rate
not targeted by the vaccine, such as commensal bacterial pathogens, as a result of reduced antibiotic selection pressure. For example, since influenza infections are frequently treated with antibiotics (either inappropriately for the primary viral infection, or for a secondary bacterial infection), an effective and widely used vaccine that reduces the number of influenza infections should result in population-wide reductions in antibiotic use.

Pathway 3: Infection severity effects
Vaccines that reduce the risk of symptomatic infection without reducing the risk of carriage/asymptomatic infection can lead to reductions in the proportion of infections which are treated with antimicrobials and therefore a reduction in the selection pressure for resistant phenotypes.

Pathway 4: Subtype selection effects
Some vaccines may target subtypes of a pathogen population which are more likely to be resistant. As a result, overall resistance may decrease. However, it is also possible that vaccines may target subtypes which are less likely to be resistant. In these circumstances, overall resistance may increase.

Pathway 5: Interspecific effects
Bacteria and viruses interact in complex ways. For example, influenza or respiratory syncytial virus (RSV) infections may increase the risk of secondary bacterial infections and patients with certain viral infections may transmit more bacterial pathogens. Vaccination against one organism could therefore reduce transmission of another, leading to declines in both resistant and sensitive phenotypes.

Pathway 6: Selective targeting effects
Interventions, such as hygiene improvements or vaccination, could lead to differential effects if targeted to certain population groups. For example, if a resistant strain of a given pathogen transmits preferentially in hospitals (where antibiotic use is high), targeting the hospital population with a vaccine could have a greater overall effect on the resistant strain, leading to declines in resistance in both hospitals and the community.

Priorities for vaccine investment and development to tackle AMR
Vaccines are already used effectively to tackle AMR in many countries. In the United States, the introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) was associated with an 84% reduction in multidrug-resistant invasive pneumococcal disease. In the Canadian province of Ontario, the introduction of a universal influenza immunisation programme was associated with reductions in prescriptions of antimicrobials for respiratory tract infections. However, to fully capitalise on the benefits of vaccines to tackle AMR there are a number of vaccine investment and development needs which need to be prioritised.

Vibrio cholerae
Resistant and multi-resistant cholera is a significant issue for many health care systems. An oral cholera vaccine which is effective at preventing medically-attended cholera already exists. Use of this vaccine clearly has the potential to reduce AMR through its direct effect on cholera; however, there is a need for greater investment to increase access to this vaccine, particularly in low and middle income countries (LMICs).

Salmonella typhi
A ciprofloxacin-resistant lineage of Salmonella typhi infection has emerged in many countries. Two vaccines have been available since the 1990s and are recommended by the World Health Organization (WHO): the live Ty21a vaccine and the Vi-polysaccharide vaccine. While they are both effective, their protection is partial and relatively short-lived, typically up to two years. However, there are several promising next-generation conjugate vaccines in development, including two vaccine candidates having received licensure in India. Gavi, the Vaccine Alliance, has opened a funding window for this vaccine, which will help increase access to these vaccines in LMICs.
Escherichia coli
Infections caused by E. coli are a major cause of morbidity and associated antibiotic use. In particular, enterotoxigenic E. coli (ETEC) is a leading cause of diarrhoea in children in developing countries. Ciprofloxacin-resistant ETEC strains represent a major challenge for ETEC treatment strategies in some parts of the world. While there are no licensed vaccines for ETEC, vaccine development for ETEC is a WHO priority. There are a number of ETEC vaccine candidates in development and currently undergoing phase II trials. The introduction of an ETEC vaccine could play an important role in reducing resistance primarily through its impact on reduced antibiotic consumption but also through reduced bystander selection.

Viral infections
Respiratory syncytial virus (RSV) is a common virus that can cause cold-like symptoms in adults and is also the causative agent for bronchiolitis in children. There is no licensed RSV vaccine, but a number are undergoing clinical trials, including vaccines that are likely to be optimal for the paediatric population as well as some that are likely to be appropriate for pregnant women and older people. Viruses are also responsible for many diarrhoeal illness, and vaccines against these viruses may also lead to reductions in antibiotic use and reduced resistance by altering bystander selection. For example, the well-established rotavirus vaccines protect against the most common cause of severe diarrhoea in young children and can prevent up to a third of severe diarrhoea cases in developing countries. Finally, a vaccine against norovirus is a priority for development. Norovirus accounts for nearly 20% of all cases of acute gastroenteritis. Two candidate vaccines have reached clinical trials and there are a number of candidates at preclinical development stages.

Quantifying the economic benefit of vaccines that prevent antimicrobial resistance
The value for money of a vaccination programme can be estimated using an economic evaluation such as a cost–effectiveness analysis, which considers the balance between the incremental costs and incremental health impacts of an intervention. As discussed throughout this article, AMR reduction is a key benefit of vaccines but a recent review of published models of the impact of vaccines on the dynamics of AMR did not find any studies that considered the economic value of this benefit.

The simplest way to estimate the benefit of vaccines that prevent AMR is to multiply the reduction in risk of acquiring a resistant strain in vaccinated individuals with the health detriment and financial cost of being infected with such a strain. However, there are several reasons why this approach may be too limited. First, as discussed, there are several other pathways by which vaccines can combat AMR, including herd immunity, bystander effects, infection severity effects, subtype effects, interspecific effects, and selective targeting effects. Therefore, the benefit of vaccination must be measured taking account of these pathways. Second, several reviews have highlighted how the wider benefits of vaccination on households and economies are often overlooked. The economic cost of AMR is substantial when considering reductions in labour productivity, the need to fund research into developing new antimicrobials, and the implications of potentially being unable to perform routine medical procedures such as surgery because of untreatable surgical site infections. Finally, it is important to consider the global nature of the benefits of vaccines that prevent AMR. AMR does not respect borders, and many countries will simultaneously benefit from effective vaccines. Economic models rarely consider this externality, which may discourage manufacturers from developing vaccines. This market failure could be addressed through mechanisms like advanced market commitments and market entry rewards, which have effectively been utilised by Gavi and others for pneumococcal vaccines.

Health care associated infections
Multi-resistant health care associated infections are a common issue across all health care systems. They are particularly prevalent in hospital settings, where antibiotics exert high selection pressure. Vaccines against some of these infections are in development. For example, there are ongoing phase II/III clinical trials for Staphylococcus aureus and Pseudomonas aeruginosa, which are opportunistic infections that are common causes of skin, respiratory and urinary tract infections. The “ESKAPE” pathogens (Enterococcus, Klebsiella, Acinetobacter, Enterobacter) are responsible for some of the most severe AMR problems. Yet, with the exception of P. aeruginosa, there is little activity in developing vaccines or other immunotherapies for these pathogens that has extended beyond animal models and it is thought unlikely that these vaccines will be available within the next 10 years. Major technical hurdles to developing vaccines for these “ESKAPE” pathogens exist such as limited understanding of pathogen biology including natural immunity, limited knowledge of vaccine targets, the existence of multiple strains and a complex epidemiology where resistance determinants frequently move between different bacterial strains and species.
Vaccines are crucial to combating AMR. However, when quantifying the economic benefit of vaccines, their impact on AMR is often ignored. Adequately valuing this benefit is important in prioritising the vaccine development pipeline, as well as choosing between alternative interventions (such as a new vaccine and a new antibiotic). To fully capture the value of vaccines in reducing AMR, three sets of pathways need to be quantified. First, the health system pathway, which governs the impact of vaccines on antimicrobial prescriptions. This will require clinical trial and surveillance data on antimicrobial prescription rates. Second, the epidemiological pathway, which governs the impact of vaccines on AMR (both directly and through reduced prescribing). This will require dynamic transmission models that capture both direct and indirect effects of vaccines. Finally, the economic pathway, which governs the value of reduced AMR. This will make use of macroeconomic models which explore the long-term consequences of alternative resistance rates on labour productivity, the need to continuously develop new antibiotics and antibiotic classes, as well as the wider health-system effects.

Conclusions

Vaccines

Vaccines are crucial to combating AMR. To fully capture the value of new vaccines in reducing AMR, three sets of pathways need to be quantified. First, the health system pathway, which governs the impact of vaccines on antimicrobial prescriptions. This will require clinical trial and surveillance data on antimicrobial prescription rates. Second, the epidemiological pathway, which governs the impact of vaccines on AMR (both directly and through reduced prescribing). This will require dynamic transmission models that capture both direct and indirect effects of vaccines. Finally, the economic pathway, which governs the value of reduced AMR. This will make use of macroeconomic models which explore the long-term consequences of alternative resistance rates on labour productivity, the need to continuously develop new antibiotics and antibiotic classes, as well as the wider health-system effects.

References


