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REVIEW

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Economic and cost-effectiveness aspects of vaccines in combating antibiotic resistance

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ABSTRACT
Antimicrobial resistance (AMR) is a global public health threat causing substantial morbidity and mortality as well as significant economic costs. Vaccines can contribute to combating antimicrobial resistance by reducing the incidence of resistant disease cases and lowering overall antibiotic use. Greater utilization and investments in vaccines as a tool for combating AMR might be hampered by limited economic evidence demonstrating the AMR-related value of vaccines. We reviewed the existing literature to assess the state of evidence. We found two modeling studies that provided estimates of AMR-related costs averted by pneumococcal vaccination and a few cost-effectiveness studies that exclusively focused on serotype replacement effects on overall vaccine cost-effectiveness. We did not find any cost-effectiveness studies that directly examined the cost-effectiveness of vaccines in slowing the development of AMR. Further evidence on the cost-effectiveness and economic value of vaccines in controlling AMR can help inform resource allocation decisions and guide development priorities.

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Introduction

Antimicrobial resistance (AMR), which occurs when bacteria, viruses, fungi, and parasites no longer respond to available treatments, has been classified as one of the top 10 global public health threats by the World Health Organization (WHO).[1,2] AMR leads to prolonged illnesses and deaths when existing treatments are no longer effective and results in substantial costs from reduced productivity among patients and caregivers, as well as health system costs associated with more expensive, extensive, and longer treatments.[2,3] In 2019, approximately 4.95 million deaths globally were associated with resistant bacterial infections, with 1.27 million deaths attributed directly to AMR.[4] Rapid spread of multidrug resistant (MDR) bacteria has raised concerns about common infections becoming more difficult to treat.[5] There is growing evidence that vaccines can contribute to combating antimicrobial resistance, with multiple pathways in which vaccination reduces the incidence of resistant disease cases and lowers overall antibiotic use.[6–10]

Despite the evidence on the utility of vaccines in combating AMR, greater utilization of vaccines as a tool for combating AMR might be hampered by limited economic evidence demonstrating the AMR-related value of vaccines. Existing economic evaluations of vaccines have largely omitted AMR-related value of vaccines in their analyses, and there have been calls for greater inclusion of AMR in economic evaluations of vaccines.[11–14] Exclusion of the AMR-related value of vaccines in economic analyses can lead to underestimation of the cost-effectiveness and economic value of vaccines as an intervention to reduce AMR, where policymakers may under-invest in vaccines when allocating resources to address AMR.[11,14] Evidence on the economic and cost-effectiveness aspects of vaccines in an AMR context can help influence country decisions to introduce and maintain vaccines on immunization schedules and help decision-makers assess the full value of vaccines in combating AMR.

We conducted a desk review of existing literature to assess the state of evidence on the economic and cost-effectiveness aspects of vaccines in the context of AMR. We searched for literature in PubMed for vaccines that were both in development and under license on June 1, 2022, in a two-stage process. First, we conducted a general search using variations of search terms for "vaccination" or "vaccines" and search term variations for "AMR." We then conducted a second targeted search that combined search terms for vaccination and AMR with additional search term variations for "cost-effectiveness," "costs averted," "resource utilization," and "economic evaluation" (see appendix for search terms). Merging the search results across the two stages yielded 184 records, and we reviewed the abstracts and full-texts for inclusion of relevant studies. We reviewed the references of prior literature reviews captured in our search and assessed them for potential inclusion.

We included studies that reported estimates of economic costs or resource utilization due to AMR averted by vaccination or studies that performed cost-effectiveness analyses of vaccination in the context of AMR. We outline the methods and key findings of the studies we found and highlight the evidence gaps in the current literature that can be addressed by future research.

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Economic evidence

We identified two studies that demonstrate the economic value of vaccines in combating AMR by estimating AMR-related costs averted due to pneumococcal vaccination.[15,16] Both studies utilized agent-based modeling of vaccination coverage, disease incidence, care seeking, and antibiotic use to estimate AMR-related costs that could be averted by vaccination in Ethiopia and China. The two studies modeled the change of AMR through the mechanism of different probabilities of survival for resistant and susceptible strains under antibiotic exposure, presented by heterogeneous minimum inhibitory concentrations (MICs) of the bacterial agents. The study on Ethiopia estimated that pneumococcal vaccination had resulted in U $32.7 million savings between 2011 and 2017 due to averted antibiotic treatment failures and AMR-related deaths.[16] Further, maintaining pneumococcal vaccination at 68% coverage would result in annual AMR-related cost savings of $7.67 million over a 5-year period, while scaling up vaccination coverage to 85% would result in annual savings of $11.43 million.[16]

The study on China simulated three pneumococcal vaccination scenarios over a 5-year period from 2021 to 2026: (1) a status quo of maintaining current vaccination coverage of 4.74%; (2) a scaled scenario of steadily increasing vaccination coverage to 99% over the 5-year period; and (3) an accelerated scenario of increasing coverage to 85% in the first 2 years and further increasing coverage to 99% over the remaining 3 years.[15] AMR-related costs averted by pneumococcal vaccination were estimated using the cost-of-illness method and included direct medical and non-medical costs, productivity losses for caregivers, and productivity losses due to death and disability. Pneumococcal vaccination averted $371 million in AMR-related costs to patients and caregivers under the scaled scenario and averted $586 million under the accelerated scenario.[15] When accounting for AMR-related productivity losses due to death and disability, pneumococcal vaccination averted an additional $37 million in the scaled vaccination coverage scenario and $67 million in the accelerated scenario.[15]

Cost-effectiveness evidence

The literature we found addressing cost-effectiveness aspects of vaccines relevant to antibiotic resistance focused on the impact of serotype replacement on vaccine cost-effectiveness.[17–28] Serotype replacement refers to an increase in circulation of non-vaccine serotypes following introduction of a vaccine.[29–31] Serotype replacement has been linked with an increase in antibiotic resistance attributed to the emergence of drug-resistant non-vaccine serotypes, particularly in the context of pneumococcal vaccines.[32–35] Hence, evidence on the cost-effectiveness of vaccines accounting for serotype replacement can help inform the value of vaccines in combating antibiotic resistance.

All identified cost-effectiveness studies examined serotype replacement associated with the pneumococcal vaccine and incorporated these effects in the disease models or as a scenario in sensitivity analyses.[17–28] Most of the studies found that pneumococcal vaccination remained cost-effective even when accounting for the effects of serotype replacement. In the few instances where vaccination was not cost-effective, other factors such as prices of the vaccines were major driving factors of cost-effectiveness, rather than the serotype replacement effects.[22,28] One study, a multi-county analysis of cost-effectiveness of pneumococcal vaccination across middle-income countries, found that even with serotype replacement effects the 7-valent pneumococcal vaccine would be highly cost-effective for 53 of the 77 countries.[24] In this study, only one country, Seychelles, was found to have a negative cost-effectiveness ratio where disability-adjusted life-years (DALYs) due to serotype replacement effects were greater than the DALYs averted through direct protection and herd protection from vaccination.[24]

Evidence gaps

Evidence on AMR-related economic costs averted by vaccination is extremely limited, with only two such studies identified in our review. These existing studies have several limitations, primarily related to the lack of availability of data inputs for the modeling studies, which leads to use of assumptions and extrapolations from other contexts. Overall evidence gaps are noted such as limited longitudinal AMR data and antibiotic utilization data specific to vaccine-preventable diseases. Other gaps and limitations of the studies relate to the modeling of AMR and the study populations. For example, neither study incorporated serotype replacement effects nor included fitness costs in the models due to sparcity of data, and both studies only focused on impacts on children under age five. Spontaneous mutations or acquisition of resistance-related genes through horizontal gene transfer from other resistant bacteria were not included in the models due to lack of availability of such data. Additionally, the general burden and cost-of-illness due to AMR of a specific pathogen is usually underreported, therefore hindering the estimation of the economic impact of vaccines on AMR. More country-specific primary studies on the epidemiology of AMR and data on antibiotic utilization are needed to improve the quality of inputs into studies modeling the health and economic impacts of vaccines in controlling AMR.

Literature on AMR-related cost-effectiveness of vaccines was limited to literature assessing the effects of serotype replacement on the cost-effectiveness. The effects of serotype replacement were often examined in scenario analyses, and in some instances, the effects were lumped together with other indirect effects, such as the herd effect. A significant gap in the cost-effectiveness literature is the lack of any studies directly examining the cost-effectiveness of vaccines in controlling the development of AMR, beyond serotype replacement.

Methodology for estimating the economic costs of AMR

A possible barrier to greater inclusion of AMR in cost-effectiveness studies and economic analyses could be availability of evidence on AMR costs or challenges with conceptualizing how to measure costs of AMR and incorporate the costs into evaluations of AMR interventions. A 2018 systematic review on the burden of AMR conducted by Naylor et al. suggested considerable variations in reported burden estimates across studies and found that the economic burden due to AMR was underreported in most studies.[36] However, we identified some literature that have worked on developing the methodologies for estimating the costs of AMR. One study sought to estimate the costs of AMR in order to inform evaluations of interventions that impact antibiotic use, such as vaccination.[37] The study estimated the costs of AMR in Thailand and the United States across five pathogens and a range of antibiotic classes, including direct costs for treating resistant infections and indirect costs of productivity losses from premature mortality.[37] This study estimated direct costs of AMR infections using data from the Medical Expenditure Panel Survey (MEPS) and hospital data from Thailand, while indirect costs were estimated using the human capital approach and mortality data were converted to productivity losses.[37] The total economic costs attributed to AMR across the five pathogens was $0.5 billion in Thailand and $2.9 billion in the United States.[37]

A 2020 study by Jit et al. documented the state of the literature estimating the cost of AMR and proposed a conceptual framework and recommendations for how to improve methodologies for estimating the costs of AMR.[38] The study found 110 studies providing estimates of costs of AMR; however, most of the studies were in high-income country settings and were hospital-based studies.[38] Moreover, most studies did not take broad societal perspectives when estimating the costs, instead taking a payer or health provider perspective.[38] The authors propose a framework for advancing the methodologies for estimating the cost of AMR, which includes extending the scope of studies to include societal and national production perspectives, forecasting future scenarios, shifting from individual level analysis to the community or ecosystem level, and moving beyond single hospital-based studies to national or global studies.[38] In addition to these methodological improvements, the study also calls for greater investments in data collection and consideration of confounders and biases.[38]

Conclusion

Despite calls over the last few years to incorporate the economic value of vaccines in addressing AMR in analyses,[11–14] our review found very few such studies. We found two modeling studies that provided estimates of AMR-related costs averted by vaccination and a few cost-effectiveness studies that exclusively focused on serotype replacement effects on overall vaccine cost-effectiveness. We did not find any cost-effectiveness studies that directly examined the cost-effectiveness of vaccines in preventing AMR. Future studies should start incorporating AMR related costs in their analysis of vaccines. The few existing studies are hampered by limited availability of country-specific primary data inputs, and all studies focused on the pneumococcal vaccine only. More primary data collection is needed to address these gaps, and future studies should also examine the economic benefits and cost-effectiveness of other existing vaccines that target pathogens that have been classified as priority pathogens for AMR, such as *Salmonella enterica ser. Typhi*, *Streptococcus pneumoniae*, *Haemophilus influenzae type b (Hib)*, and *Mycobacterium tuberculosis*.[39]

As vaccine-preventable disease prevalence decreases, the benefits of vaccination become less apparent, leading to vaccine complacency.[40] Therefore, demonstrating the full value of vaccines, including capturing the benefits of vaccines in combating AMR, is essential for countries to continue to invest in vaccines. Vaccines are an important tool for tackling AMR, where there are recent calls for greater utilization of existing vaccines, accelerated development of candidate vaccines targeting MDR pathogens, and investments in vaccine discovery for pathogens on the WHO priority list with no vaccines in the pipeline.[39] Economic analyses on the value of vaccines in combating AMR can help inform investment decisions by governments, donor agencies, and other stakeholders in the global effort to combat AMR.[41] Policymakers deciding on interventions to combat AMR have to consider other interventions besides vaccines, such as investing in new classes of medicines and diagnostic tools. Evidence on the cost-effectiveness of vaccines in combating AMR can illuminate tradeoffs and optimization choices among a portfolio of other AMR interventions.[41,42] Further, efforts to tackle AMR occur in the context of other national budget priorities and global development agendas such as the sustainable development goals (SDGs) which require financing.[43] Evidence on the cost-effectiveness and economic value of vaccines in preventing and slowing the development of AMR can help inform resource allocation decisions across sectors and development priorities.

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Appendix - PubMed Search Terms

Search1

(((((((vaccin*[Title/Abstract]) OR (immuniz*[Title/Abstract])) OR (immunis*[Title/Abstract])) OR ("vaccines"[Title/Abstract])) OR ("vaccination"[Title/Abstract])) OR ("immunization"[Title/Abstract])) AND ((("antibiotic resistance"[Title/Abstract]) OR ("antimicrobial resistance"[Title/Abstract])) OR ("AMR"[Title/Abstract]))) AND ((((cost-effectiveness[Title/Abstract]) OR (cost effectiveness[Title/Abstract])) OR ("costs averted"[Title/Abstract])) OR ("resource utilization"[Title/Abstract]))

Search 2

(((((((vaccin*[Title/Abstract]) OR (immuniz*[Title/Abstract])) OR (immunis*[Title/Abstract])) OR ("vaccines"[Title/Abstract])) OR ("vaccination"[Title/Abstract])) OR ("immunization"[Title/Abstract])) AND ((("antibiotic resistance"[Title/Abstract]) OR ("antimicrobial resistance"[Title/Abstract])) OR ("AMR"[Title/Abstract]))) AND (((((((cost-effectiveness[Title/Abstract]) OR (cost effectiveness[Title/Abstract])) OR ("averted costs"[Title/Abstract])) OR ("cost averted"[Title/Abstract])) OR ("resource utilization"[Title/Abstract])) OR ("economic evaluation"[Title/Abstract])) OR ("value of vaccines"[Title/Abstract]))