ONE HEALTH TRUST

THE VALUE OF VACCINES TO MITIGATE ANTIMICROBIAL RESISTANCE

Evidence from Low- and Middle-Income Countries

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Related research and additional information on access to antibiotics and antibiotic use and resistance are available at onehealthtrust.org

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Acronyms and Abbreviations

AOM	acute otitis media
AMR	antimicrobial resistance
ARI	acute respiratory infection
DALYs	disability-adjusted life years
DDD	defined daily doses
DREAMR	Dynamic Representation of Economics of AMR
GAVI	Global Alliance for Vaccines and Immunization (GAVI)
GoC	grade of confidence
Hib vaccines	*Haemophilus influenzae* type B vaccines
IPD	invasive pneumococcal disease
JRF	WHO-UNICEF Joint Reporting Form
Lao PDR	Lao People's Democratic Republic
LMICs	low- and middle-income countries
MCV	measles antigen-containing vaccine
MDR	multidrug-resistant
PCV	pneumococcal conjugate vaccine
S. pneumoniae	*Streptococcus pneumoniae*
S.Typhi	*Salmonella Typhi*
TCV	typhoid conjugate vaccine
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization
WUENIC	WHO-UNICEF Estimates of National Immunization Coverage
XDR	extensively drug-resistant

Glossary

Acute otitis media: Acute otitis media is an infection of the middle ear. It is caused by bacteria or viruses and is one of the most common infections in pediatric populations.

Agent-based model: An agent-based model is a computational model for simulating the actions and interactions of autonomous agents to understand the behavior of a system.

Antigen: Antigens are substances that can stimulate the immune system to produce antibodies. Antigens act as "markers" and are found in viruses, bacteria, tumors, and normal cells.

Catch-up campaign: A catch-up campaign refers to the vaccination of individuals who have not yet received the doses of vaccines in the immunization program for which they are eligible.

Conjugate vaccines: Conjugate vaccines are constructed by coupling a surface carbohydrate from bacteria (polysaccharides) to a protein carrier which makes the former more immunogenic and amplifies the immune response. Conjugate vaccines are especially effective in children under two years.

Herd immunity: Herd immunity occurs when a sufficient percentage of the population becomes immune to an infection (through vaccination or previous infection) and significantly reduces the risk of spreading the infection to those who are unvaccinated and susceptible to the infection.

Secondary infection: A secondary infection occurs during or following the onset of a different infection (a primary infection). An example of a secondary infection is pneumonia caused by bacteria following a viral respiratory infection.

Selection pressure: Selected pressure exerted by the environment impacts traits that enable an organism to survive.

Executive Summary

Accumulating evidence of the devastating health and economic consequences of antimicrobial resistance (AMR) calls for urgent action to address this global health threat through current and innovative health countermeasures. Vaccines represent a valuable health intervention for AMR mitigation. Through infection prevention or reduction of disease severity, vaccines limit the transmission of susceptible and drug-resistant strains and reduce the need for antimicrobial use, simultaneously addressing several factors that drive the emergence and spread of AMR. Although the impact of vaccines on AMR is well established, there is a need to utilize quantitative, country-specific evidence to raise awareness and inform immunization and AMR policies at the national level. With many countries reviewing their national strategies for AMR, there is an opportunity to fill this evidence and awareness gap and introduce measurable indicators that can monitor the impact of vaccination on AMR mitigation. Improving the coverage of vaccines within national immunization programs and introducing new vaccines with a significant impact on infectious disease burden and AMR comprise essential interventions that can be implemented in the short term. The impact of vaccines on the epidemiology of infectious diseases has been studied extensively; however, in this report, we highlight evidence that provides a quantitative assessment of the impact of available vaccines on AMR. Against the backdrop of stagnating and declining vaccine coverage and the re-emergence of vaccine-preventable disease, this evidence can strengthen the vaccine investment case and inform measurable targets for their uptake.

In this report, we summarize recent work that aims to quantify the impact of vaccines on the health and economic burden attributed to drug-resistant infections. In this context, we highlight estimates that quantify morbidity, mortality, and antibiotic use averted by vaccines in 13 countries: Kenya, South Africa, Viet Nam, Mozambique, Nepal, India, The United Republic of Tanzania, Uganda, Bangladesh, Lao People's Democratic Republic, Pakistan, Zimbabwe, and Nigeria.

Highlights

- The COVID-19 pandemic led to further declines in national coverage rates for vaccines that can address AMR: the *Haemophilus influenzae* type B (Hib) vaccine, the measles antigen-containing vaccine (MCV), the pneumococcal conjugate vaccine (PCV), the rotavirus vaccine, and the typhoid conjugate vaccine (TCV).
- The impact of vaccines on AMR is quantified through economic and health indicators such as a reduction in drug-resistant infections and treatment failures; a reduction in cumulative costs due to drug-resistant infections; averted AMR incidence; and a reduction in antibiotic use, among others.
- Introducing an infant TCV program with a catch-up campaign could prevent approximately 53.5 million cases of drug-resistant typhoid fever in 73 low- and middle-income countries (LMICs) over 10 years.
- Children between 6-11 weeks old in countries in sub-Saharan Africa and South Asia have the highest proportion of diarrheal cases treated with antibiotics (12.2 episodes per 100 children each year); rotavirus infections are responsible for almost one-third of the antibiotic-treated diarrhea cases in children under five.

Highlights

- Rotavirus vaccines at 77 percent coverage in children under two years old in 18 LMICs could avert 13.6 million (31 percent) episodes of antibiotic-treated diarrhea annually.

- PCVs have reduced the proportion of circulating pneumococci resistant to antibiotic treatment globally between 2000-2020.

Overview

This report summarizes recent evidence highlighting the value of vaccines in mitigating antimicrobial resistance. In addition, it provides country-specific estimates that can inform immunization policies related to antimicrobial resistance mitigation in low- and middle-income countries, where the high prevalence of infectious diseases is estimated to result in a higher vaccination impact. The role of vaccines in the reduction of infectious diseases has been studied extensively; however, this report focuses on studies that, in addition, provide a quantitative assessment of the vaccines' impact on AMR. Findings from this report have been informed by peer-reviewed research articles, organizational reports, and global health databases of immunization coverage and infectious disease trends.

Background

Antimicrobial resistance (AMR) is a global public health threat with a significant health and economic burden worldwide. In 2019, an estimated 4.95 million deaths were associated with, and 1.27 million deaths were attributable to bacterial drug-resistant infections globally (Murray et al. 2022). However, despite being a global phenomenon, the burden of AMR varies across countries due to driving factors such as inappropriate antibiotic consumption; lack of access to clean water and adequate sanitation; poor infection prevention control measures; low vaccination coverage; lack of access to quality healthcare services, including diagnostic and laboratory services; and lack of access to high-quality, and clinically appropriate antimicrobials (Frost et al. 2019).

Immunization is a critical health intervention that saves countless lives every year. Vaccines targeting viral or bacterial pathogens are estimated to have averted 37 million deaths between 2000 and 2019 (Li et al. 2021), and the measles vaccine alone is estimated to have prevented 56 million deaths between 2000 and 2021 (WHO 2023b). However, vaccination rates have stagnated or declined in recent years, and the COVID-19 pandemic-associated health system challenges and disruptions have further exacerbated the situation. Estimates suggest that 21.9 million children under 1 year did not receive the first dose of the measles vaccine in 2022, compared to 19.2 million in 2019 (WHO 2023b).

Beyond infection prevention, vaccines' less acknowledged but valuable impact lies in their ability to mitigate AMR and address its driving factors (Vekemans et al. 2021). By preventing infections, vaccines limit the transmission and emergence of susceptible and drug-resistant strains. Furthermore, they lower the risk of secondary infections and reduce the need for antimicrobial use (Figure 1). For example, the introduction of the pneumococcal conjugate vaccine (PCV) reduced rates of drug-resistant and multidrug-resistant (MDR) pneumococcal strains by more than half between 1999 and 2004 in the United States (Kyaw et al. 2006). In the context of preventing secondary infections and associated antibiotic use, the influenza vaccine was shown to reduce antibiotic prescribing in a population-level study in the United States (Klein et al. 2020) and among children between two and three years old in the United Kingdom (Muller-Pebody et al. 2021).

While the reduction in antibiotic use contributes to the preservation of antibiotic effectiveness, it also reduces their inappropriate use, which is a critical driver of AMR. In 2020, The World Health Organization (WHO) outlined an action framework highlighting the importance of vaccines in reducing the incidence of drug-resistant infections (WHO 2020). The framework emphasizes that increasing vaccine uptake, particularly in countries with a high disease burden, would not only prevent infections but also limit the need for treatment and inappropriate use, reducing the pressure for selecting resistant phenotypes and preserving the efficacy of antimicrobials. An added benefit of high vaccination coverage is the development of herd immunity which protects unvaccinated individuals from resistant infections (Micoli et al. 2021).

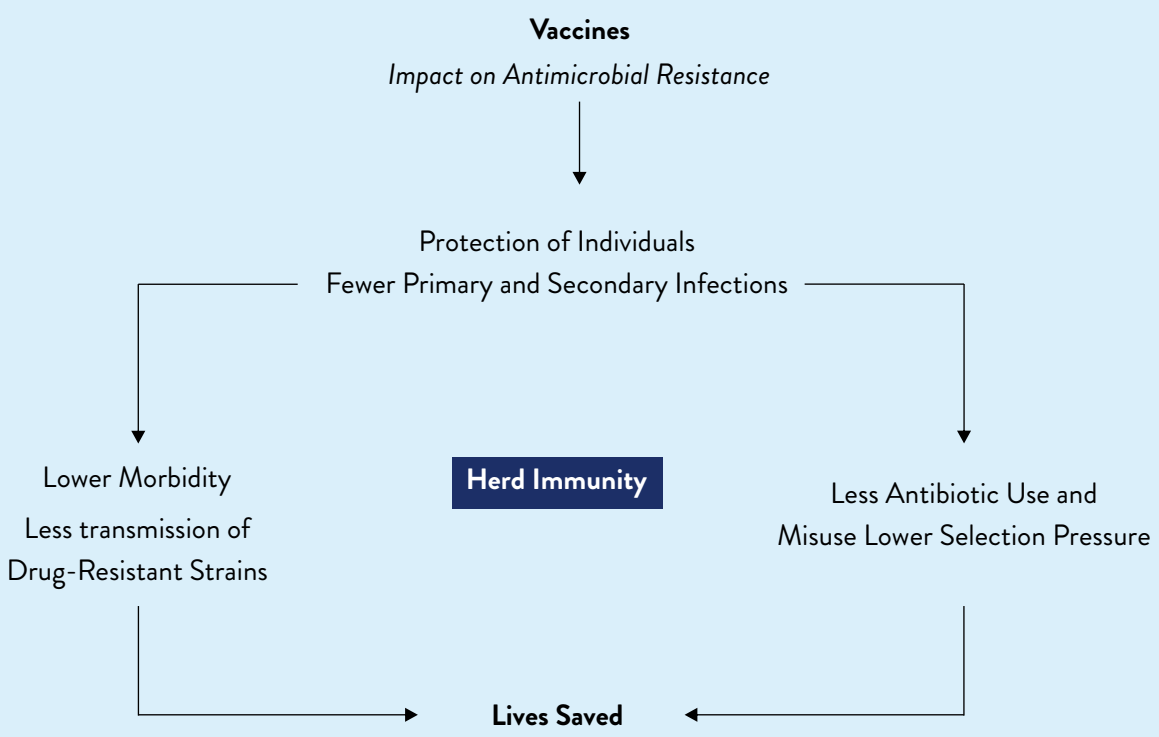

Figure 1. The value of vaccines in AMR mitigation

Building upon the WHO assessment of priority bacterial pathogens requiring urgent antibiotic development to contain AMR (Tacconelli et al. 2018), the action framework recommends "increased uptake" of currently available vaccines with an impact on drug-resistant pathogens from primary or secondary infections. Among the vaccines in this category are the *Haemophilus influenzae* type B (Hib) vaccine, the influenza vaccine, the measles antigen-containing vaccine (MCV), the pneumococcal conjugate vaccine (PCV), the rotavirus vaccine, and typhoid conjugate vaccine (TCV).

Introduction or coverage expansion of already available and effective vaccines represents short-term and cost-effective solutions to slow the spread of AMR. However, implementing these recommendations necessitates that the countries better understand the role vaccines have in mitigating the impact of AMR on health and the economy in their contexts.

Studies quantifying the value of vaccines

In recent years, the evidence quantifying the impact of vaccines on the AMR burden has accumulated. Several studies highlight the added value of immunization using economic, health, and AMR-related indicators, including averted health burden, such as reduction in antibiotic-resistant disease and treatment failures due to AMR; averted economic burden, such as reduction in cumulative costs due to antibiotic-resistant infections; averted AMR incidence; and averted antibiotic use, such as reduction in the number of patients prescribed antibiotics (Table 1).

Averted health burden

Studies based on modelling estimates or clinical trial data have quantified averted AMR-related health burden from the rollout of PCV, TCV, Hib, and influenza vaccines using indicators such as reductions in the incidence of antimicrobial-resistant disease, reduction in the number of deaths, reduction in the number of AMR chronic carriers, and treatment failure attributed to AMR. Other health indicators include reductions in medical visits, parent absenteeism from work, and disability-adjusted life years (DALYs) (Table 1).

Using an agent-based model, Dynamic Representation of Economics of AMR (DREAMR), Bui and colleagues forecast the potential AMR-related health burden that could be averted by scaling up PCV coverage. Their results project that 7.31 percent of antibiotic treatment failures and 11.2 percent of childhood mortality among Indonesian children under five could be averted by PCV at a 95 percent coverage over five years (Bui et al. 2021). Another study using a similar methodology reveals that an accelerated scenario (for example, reaching 85 percent PCV coverage over two years, followed by 99 percent coverage over 3 years) could potentially avert antibiotic treatment failures by up to 13.8 percent versus a scaled scenario (for example, reaching 99 percent PCV coverage in 5 years) which was estimated to avert 8.8 percent of antibiotic treatment failures (Lu et al. 2021). Other studies indicate that high disease-burden areas in Africa may benefit from increased vaccination uptake. For example, an early-2000s clinical trial in South Africa stipulates that following the introduction of PCV9, the incidence of invasive pneumococcal disease caused by penicillin-resistant strains of *Streptococcus pneumoniae* (*S. pneumoniae*) was reduced by up to 67 percent (Klugman et al. 2003). Similarly, a recent modelling study from Ethiopia estimates that increased PCV coverage has averted approximately 718,100 treatment failures, resulting in a 27.8 percent reduction in AMR-related deaths between 2011 to 2017 (Ozawa et al. 2021). Globally, the roll-out and increased coverage of PCV have resulted in an overall decrease in the proportion of non-susceptible pneumococci resistant to first-line antibiotics (Andrejko et al. 2021). In addition, proportional impact modelling of potential deaths and DALYs that could be averted following PCV, TCV, and Hib uptake in global populations predict that Africa and south-east Asia would have the highest avertable AMR disease burden among all six WHO regions (Kim et al. 2022).

Regarding the impact of TCV rollout, a modelling study in 73 countries supported by the Global Alliance for Vaccines and Immunization (GAVI) suggests that 21.2 million cases of MDR typhoid fever, 826,000 deaths, and 44.4 million DALYs could be averted in children over a 10 year period following the introduction of TCV with a catch-up campaign for children up to 15 years (Birger et al. 2022). Furthermore, in Pakistan, a country dealing with rising levels of extensively drug-resistant (XDR) typhoid cases, a census survey cohort study shows that TCV is over 90 percent effective in protecting against XDR *Salmonella Typhi* (*S.* Typhi) in young children (Yousafzai et al. 2021). Finally, a transmission modelling study indicates that increased TCV coverage globally could modestly reduce the

prevalence of AMR chronic carriers (from 2.6 to 2.2 percent), resulting in a lower transmission rate for antibiotic-resistant strains of *S.* Typhi (Kaufhold et al. 2019).

Table. 1 Summary of studies measuring the impact of vaccination on AMR

Country/ Region	Vaccine	Type of study	Indicator	Reference
Averted Health Burden				
Global	PCV	systematic review	reduction in antibiotic-resistant disease in children	Andrejko et al. 2021
Global	TCV	modelling study	reduction in antibiotic-resistant disease, DALYs, and deaths	Birger et al. 2022
Indonesia	PCV	modelling study	reduction in treatment failure	Bui et al. 2021
Global	TCV	modelling study	reduction in AMR chronic carriers	Kaufhold et al. 2019
Global	PCV	modelling study	reduction in antibiotic-resistant disease, DALYs, and deaths	Kim et al. 2022
South Africa	PCV, TCV, Hib	double-blind, randomized trial	reduction in antibiotic-resistant disease in children	Klugman et al. 2003
China	PCV	modelling study	reduction in treatment failure	Lu et al. 2021
Ethiopia	PCV	modelling study	reduction in treatment failure, deaths	Ozawa et al. 2021
Global	Influenza	randomized placebo-controlled trial	reduction in medical visits, parent absenteeism from work	Pepin et al. 2019
Pakistan	TCV	census survey cohort study	reduction in antibiotic-resistant disease in children	Yousafzai et al. 2021
Averted Economic Burden				
Global	TCV	modelling study	reduction in cumulative costs due to typhoid infection with an AMR strain	Bilcke et al. 2019
Indonesia	PCV	modelling study	reduction in cumulative costs due to AMR (medical costs and productivity losses)	Bui et al. 2021
China	PCV	modelling study	reduction in cumulative costs due to pneumoccocal infection with an AMR strain (productivity losses)	Lu et al. 2021
Ethiopia	PCV	modelling study	reductions in cumulative costs due to pneumoccocal infection with an AMR strain (deaths and treatment failures)	Ozawa et al. 2021

Averted Antimicrobial Resistance				
Nigeria	PCV	cross-sectional survey study	reduction in AMR incidence (coverage of serotypes)	Adetifa et al. 2012
Indonesia	PCV	modelling study	reduction in AMR incidence	Bui et al. 2021
The United Republic of Tanzania	PCV	cross-sectional survey study	reduction in AMR incidence (carriage of pneumococci with reduced susceptibility to penicillin among non-PCV13 serotypes)	Emgård et al. 2019
Global	TCV	modelling study	reduction in AMR incidence	Kaufhold et al. 2019
China	PCV	modelling study	reduction in AMR incidence	Lu et al. 2021
Ethiopia	PCV	modelling study	reduction in AMR incidence	Ozawa et al. 2021
Averted Antibiotic Use				
Indonesia	PCV	modelling study	reduction in AMR incidence	Ozawa et al. 2021
Global	Influenza	randomized controlled trial	reduction in number of children prescribed antibiotics	Dbaibo et al. 2020
USA	Rotavirus	retrospective cohort study	reduction in number of children prescribed antibiotics	Hall et al. 2022
USA	Influenza	retrospective ecological study	reduction in antibiotics prescribed per 1,000 individuals	Klein et al. 2020
Sub-Saharan Africa	Influenza	estimation study	reduction in antibiotic use per 100,000 individuals	Knight et al. 2018
Canada	Influenza	ecological study	reduction in antibiotics prescribed per 1,000 individuals	Kwong et al. 2009
Sub-Saharan Africa	Rotavirus	case-control study	incidence of antibiotic-treated rotavirus, incidence of inappropriate antibiotic treatment	Lewnard et al. 2020 (a)
Global	PCV, Rotavirus	estimation study	reduction in pathogen-specific incidence of antibiotic-treated PCV and rotavirus in children	Lewnard et al. 2020 (b)
Global	Influenza	clinical trial study	reduction in antibiotic use	Pepin et al. 2019
Nepal	Measles	cross-sectional survey study	reduction in number of children prescribed antibiotics	Zheng et al. 2021

DALYs, disability-adjusted life years; DDD, daily defined doses; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; TCV, typhoid conjugate vaccine; Hib, Haemophilus influenzae type B

Averted economic burden

Hard-to-treat infections caused by drug-resistant strains require complex treatments and result in longer hospital stays, increasing financial costs for patients and healthcare facilities. Vaccines could contribute to reducing the additional costs associated with treating drug-resistant infections. Estimates show that PCV coverage of 50, 80, and 95 percent over 5 years in Indonesia could reduce costs related to treatment failures by US$2.1, US$4, and US$3.7 million, respectively (Bui et al. 2021). In China, cumulative costs due to AMR for patients and caretakers could be reduced by US$371 million to US$586 million over 5 years of increasing PCV coverage (Lu et al. 2021). In Ethiopia, sustained PCV coverage could reduce cumulative costs due to AMR deaths and treatment failures by US$7.67 million annually over 5 years; however, increased uptake to 85 percent would reduce these costs by US$11.43 million annually (Ozawa et al. 2021). Finally, one global study for TCV demonstrates that the optimal vaccination strategy would benefit from catch-up campaigns for children up to 15 years, citing that a reduction in circulating antibiotic-resistant strains of *S.* Typhi may reduce overall medical costs and productivity losses (Bilcke et al. 2019).

Averted antimicrobial resistance incidence

While reducing the spread of infections through increased vaccination efforts can substantially alleviate health and economic burden, reducing overall AMR incidence worldwide requires a multi-pronged approach. Developing new vaccines, expanding awareness campaigns, and leveraging existing vaccines are critical in tackling AMR persistence, especially in low- and middle-income countries (LMICs) (Vekemans et al. 2021). In addition to the health and economic benefits of increasing vaccine coverage projected in the DREAMR studies discussed earlier, the impact on AMR incidence is significant. In Indonesia, 50 and 95 percent PCV coverage is projected to reduce AMR incidence by 4 and 8 percent over 5 years (Bui et al. 2021). In China, antibiotic resistance is projected to decrease by 6 to 17 percent in the scaled and accelerated PCV uptake scenario over 5 years (Lu et al. 2021). Data on TCV suggests that while the proportion of antibiotic-resistant *S.* Typhi infections would remain the same, the number of resistant infections is projected to decrease by 44 percent over 10 years if TCV uptake is maintained at 80 percent (Kaufhold et al. 2019). In Ethiopia, researchers estimate that PCV implementation from 2011 to 2017 has resulted in approximately 15 percent fewer amoxicillin-resistant infections (Ozawa et al. 2021). However, some evidence suggests that certain PCV serotypes may be more effective at protecting against AMR than others. For example, a cross-sectional survey from Nigeria revealed that 13-valent pneumococcal conjugate vaccine (PCV13) serotypes were nearly twice as effective at reducing circulating strains of penicillin-resistant *S. pneumoniae* in children (61.7 percent) than 7-valent pneumococcal conjugate vaccine or 10-valent pneumococcal conjugate vaccine serotypes (34.8 percent) at only 62 percent coverage (Adetifa et al. 2012). Another survey study from The United Republic of Tanzania identified a 31 percent higher penicillin resistance rate in non-PCV13 serotypes of *S. pneumoniae* in children in 2015 following PCV introduction in 2013 (Emgård et al. 2019).

Averted antibiotic use

While a large body of work has primarily focused on vaccines targeting bacterial pathogens, there is considerable evidence highlighting the impact of vaccines for viral pathogens in the context of reduced antibiotic use. Rotavirus infections are estimated to be responsible for nearly 30 percent of all antibiotic-treated diarrhea in children under five in sub-Saharan Africa, and for every appropriately prescribed antibiotic to treat diarrhea, there are

approximately 12 inappropriately prescribed incidences (Lewnard et al. 2020a). Rotavirus vaccine rollout is estimated to have a considerable impact on inappropriate antibiotic use; a 77 percent coverage rate among children under two across 18 LMICs could avert 13.6 million antibiotic-treated diarrheal cases every year (Lewnard et al. 2020b). In the United States (US) it is estimated that 67,000 antibiotic prescriptions were averted following rotavirus vaccine implementation between 2007 and 2018; children who received a full rotavirus vaccination by eight months of age were less likely to switch antibiotics to treat acute gastroenteritis than children who received no vaccination (Hall et al. 2022).

Increased influenza vaccination has also been estimated to reduce antibiotic-treated acute respiratory infection (ARI) cases in children under 5 across Africa and avert approximately 24,000 antibiotic prescriptions at low (30 percent) vaccine coverage rates (Knight et al. 2018). Globally, one clinical trial study suggests that the implementation of the influenza vaccine has reduced overall influenza risk by approximately 40 percent in all age groups (Pepin et al. 2019). However, other research indicates that reduced antibiotic use is more prevalent in wealthier regions (Dbaibo et al. 2020). In the US, a 10 percent increase in influenza vaccine uptake resulted in approximately 14 fewer antibiotics prescribed per 1,000 individuals from 2010 to 2017 (Klein et al. 2020). Furthermore, one study in Canada demonstrated that antibiotic prescribing following influenza vaccine implementation resulted in approximately 10 fewer antibiotics per 1,000 individuals annually between 1997 and 2007 (Kwong et al. 2009). The significant vaccine impact on antibiotic use is not isolated to the prevention of viral infections; at a 70 percent coverage, PCV administration in children under 2 across 18 LMICs could avert 23.8 million antibiotic-treated ARIs annually (Lewnard et al. 2020b).

Coverage of available vaccines that address antimicrobial resistance

Evaluation of national vaccine coverage data can provide insights into how approved vaccines are utilized to mitigate infectious disease burden and AMR. Here we extract vaccine coverage data for selected LMICs in Africa and Asia to understand how vaccines that can mitigate AMR are utilized in different contexts. Coverage data is obtained from the WHO-UNICEF Estimates of National Immunization Coverage (WUENIC) database, which, since 1999, has monitored child immunization coverage for 14 antigens across 195 member states (WHO 2022a).

Data sources

As of 2022, vaccination coverage data stems from four main sources: national authorities, healthcare providers, household surveys, and other sources, including available literature and local authorities. Healthcare providers and national authorities supply information yearly through the WHO-UNICEF Joint Reporting Form (JRF) on Immunization (WHO 2023a). These values are country-specific ratios representing children vaccinated over the national target rate, while government-based estimates rely on this information and any additional data supplied from household surveys or local authorities (Burton et al. 2009; WHO and UNICEF 2012; WHO 2023a). Estimated coverage rates are accompanied by a grade of confidence (GoC) metric designed to account for the uncertainty inherent in gathering vaccination coverage data from multiple reporting sources (Brown et al. 2013). As vaccination coverage estimates are often limited by a lack of precise and accurate measurements, GoCs attempt to provide endorsements of national immunization coverage rather than give traditional statistical measures of uncertainty (Burton et al. 2012). Lastly, WHO estimates reveal that COVID-19 interruptions have severely reduced the number of reports submitted to the WUENIC database, with only 28 countries submitting vaccination coverage data in 2020 and even fewer in 2021 (24 countries). To account for these data gaps during COVID or when data is unavailable, WUENIC values are interpolated using data from previous years (Burton et al. 2012; WHO 2022a).

Vaccine coverage data for the years 2010 to 2022 were obtained from the WUENIC database for Kenya, South Africa, Viet Nam, Mozambique, Nepal, India, The United Republic of Tanzania, Uganda, Bangladesh, Lao People's Democratic Republic (PDR), Pakistan, Zimbabwe, and Nigeria (Annex A, Figure A1. a-m). Coverage estimates for all vaccines addressing AMR which are included in the immunization program are presented, with some exceptions: TCV is only included in the immunization schedule in Pakistan, Nepal, and Zimbabwe, and the rotavirus vaccine is included in the immunization schedules of all selected countries, except Bangladesh, Viet Nam, and Lao PDR. Regarding international target vaccine coverage, the Global Vaccine Action Plan 2011–2020 recommends coverage of 90 percent or greater for PCV, Hib, and rotavirus vaccines (Peck et al. 2019), while the WHO recommends coverage of at least 95 percent for the measles vaccine (WHO 2022b).

Pneumococcal conjugate vaccine

National coverage of the third dose of PCV is greater than 90 percent in Bangladesh (99), Kenya (91), Uganda (90), and Zimbabwe (90); however, the remaining countries fall behind the international target, with India and Nigeria reporting coverage of 66 and 60 percent, respectively (Figures A1 – b and A1 – g). Despite low values, PCV coverage in Nigeria significantly increased between 2021 and 2022, from 25 to 60 percent, respectively (Figure A1 – g).

Haemophilus influenzae type B

Coverage levels for the third dose of the Hib vaccine were 90 percent or greater in Bangladesh (98), India (93), Viet Nam (91), Kenya (90), Nepal (90), and Zimbabwe (90) (Figures A1 – a, b, l, c, f, m). In contrast, coverage among the other countries averages between 80 to 89 percent, except Mozambique and Nigeria, with coverages of 61 and 62 percent, respectively (Figures A1 – e and A1 – g).

Measles antigen-containing vaccine

MCV coverage is well below the international target of 95 percent in most countries. First and second-dose MCV coverages are 90 percent or above in Bangladesh and India (Figures A1 – a, b), whereas the second dose of MCV is one of the vaccine doses with the lowest coverage across all countries, with Nigeria (38 percent), Uganda (49 percent), Lao People's Democratic Republic (55 percent), and Kenya (55 percent), reporting the lowest uptake (Figures A1 – g, k, d, c).

Rotavirus vaccine

The rotavirus vaccine, one of the most recently introduced vaccines, shows significant uptake in all the countries reporting coverage data; Nigeria introduced the rotavirus vaccine in 2022 and reports vaccine coverage of 12 percent (Figure A1 – g). International target coverage for the rotavirus vaccine is achieved in India (92 percent), with other countries reporting values between 12 and 88 percent. Reductions in vaccine coverage between 2022 and 2021 were reported in The United Republic of Tanzania, Zimbabwe, and Kenya, with Kenya reporting a dramatic reduction from 91 percent in 2021 to 23 percent in 2022 (Figures A1 – j, m, c).

Typhoid conjugate vaccine

Currently, five countries (Liberia, Nepal, Pakistan, Samoa, and Zimbabwe) with high typhoid fever estimates have introduced TCV into immunization campaigns (WHO, 2022). The introduction of TCV in Malawi is scheduled for 2023 (Hancuh, 2023). According to the WUENIC database, reported TCV coverage for 2022 (administrative values) consists of 43 percent for Nepal, 77.8 percent for Pakistan, and 81.06 percent for Zimbabwe. In Pakistan, mobile vaccination campaigns for TCV have helped the country reach vaccination targets by reducing the need for families to travel long distances (UNICEF, 2021). In 2022, a similar program in Nepal established nearly 50,000 catch-up vaccination sites for TCV to reach 95 percent coverage for children aged 15 months to 15 years (OCHA 2022). However, a Global Burden of Disease study in 2019 estimates that these 5 countries represent 7 percent of the 44 sampled regions associated with high or very high disease burden, with Bangladesh, India, Kenya, Lao PDR, Mozambique, Nepal, Nigeria, The United Republic of Tanzania, Uganda, and Viet Nam currently without TCV implementation (Institute for Health Metrics 2020). According to WHO, barriers to TCV implementation include insufficient data to guide vaccine implementation and conflicting national health priorities (Hancuh, 2023).

Country-specific evidence on the impact of vaccines on antimicrobial resistance

The lack of local data and lack of their utilization challenge the setting of priorities and policy design. Here we describe country-specific evidence on the impact of four approved vaccines (PCV, TCV, rotavirus, and influenza) on AMR burden through indicators such as cases of infections, deaths, DALYs, and antibiotic use (Annex B, Tables B1 to B5). Model assumptions on parameters such as vaccine efficacy (the ability of vaccines to reduce disease in the vaccinated group compared to the non-vaccinated group in an ideal scenario), vaccine effectiveness (how the vaccine performs in "real-life"), national coverage and catchup campaigns are presented as applicable (Table B1). The evidence highlights the impact of vaccines in reducing the incidence of drug-resistant infections and the resulting loss of lives and productivity. In addition, it highlights their impact on antibiotic use due to primary and secondary infections.

PCV can lead to considerable reductions in the number of antibiotic-treated respiratory infections. For ARI attributable to the PCV 10/13 serotype *S. pneumoniae* in children aged 24-59 months, Lao PDR had the highest estimates for antibiotic-treated cases of invasive pneumococcal disease (IPD) and acute otitis media (AOM) at 24.6 cases and 35.6 cases per 100 children, respectively, and the highest number of antibiotic-treated cases preventable by the PCV serotypes 10/13 vaccine at 19.7 cases per 100 children (Lewnard et al. 2020b, Table B2). South Africa is estimated to have the lowest values for antibiotic-treated cases and those preventable by PCV (6.9 cases per 100 children) in the same age group. Similar trends are observed for the 0-59-month age group; estimates for vaccine-averted antibiotic-treated cases for ARI are once again highest in Lao PDR (9.8 cases per 100 children), Uganda (8.4 per 100), and Nepal (8 per 100) and lowest in South Africa (3.6 per 100) (Lewnard et al. 2020b, Table B2).

Averted multidrug-resistant (MDR) typhoid fever cases, deaths, and DALYs from TCV immunization in children between 9 months and 15 years are estimated in another modeling study by Birger and colleagues in all but 1 of the 13 countries (South Africa) (Birger et al. 2022, Table B3). Over 10 years, Uganda shows the highest estimated proportion of MDR cases averted by TCV (76 percent), followed by Kenya (75 percent) and The United Republic of Tanzania and Mozambique (both 74 percent). The lowest proportions of MDR cases averted are estimated in India (58 percent) and Pakistan (57 percent). Zimbabwe has the greatest proportion of estimated averted MDR deaths (76 percent), followed by The United Republic of Tanzania and Mozambique (75 percent) and Kenya and Uganda (73 percent). Averted MDR DALYs range from 2,000 (Nepal) to nearly 4,000,000 (Nigeria) (Birger et al. 2022, Table B3).

Averted antibiotic-treated cases of diarrhea attributed to rotavirus in children aged 0-23 months are estimated in all 13 countries (Lewnard et al. 2020a, Table 4A). Viet Nam (17.6), Nigeria (17), and India (14.5) show the highest number of antibiotic-treated cases per 100 children, while The United Republic of Tanzania (10.8), Nepal (10.6), and South Africa (8.1) display the lowest number. The number of antibiotic-treated cases of diarrhea preventable by the rotavirus vaccine ranges from 5.4 cases per 100 children in South Africa to 11.8 per 100 in Viet Nam (Lewnard et al. 2020a, Table B4).

Estimates for averted antibiotic prescriptions among children and adults in Kenya and South Africa from influenza vaccination show that, on average, adults aged 65 and older in South Africa have the highest total number of averted antibiotic prescriptions per year (over 11,000), followed by children under five years of age in Kenya (9,400) (Knight et al. 2018, Table B5).

Conclusion

This report highlights the impact of vaccines in reducing infectious disease burden, the need for treatment, and the health and economic consequences resulting from the treatment of complex and hard-to-treat infections. While much effort has been spent on quantifying this impact with measurable health and economic indicators, there is a need for additional population-based cohort studies to better quantify this impact and inform policies at the national level. At the same time, there is a need to utilize recently generated country-specific evidence to inform immunization and AMR strategies at the national level. Despite evidence quantifying the value of vaccines in preventing infectious diseases for which treatment is becoming increasingly ineffective, the national coverage data summarized in this report reveals significant coverage gaps for vaccines in routine immunization programs. The impact on AMR is an important metric that must be considered in the investment case for vaccines. Available evidence suggests opportunities for interventions to sustain or increase current vaccine coverage for all vaccines in the routine immunization schedule and introduce the rotavirus and typhoid vaccines in the immunization schedules in countries where it is currently lacking.

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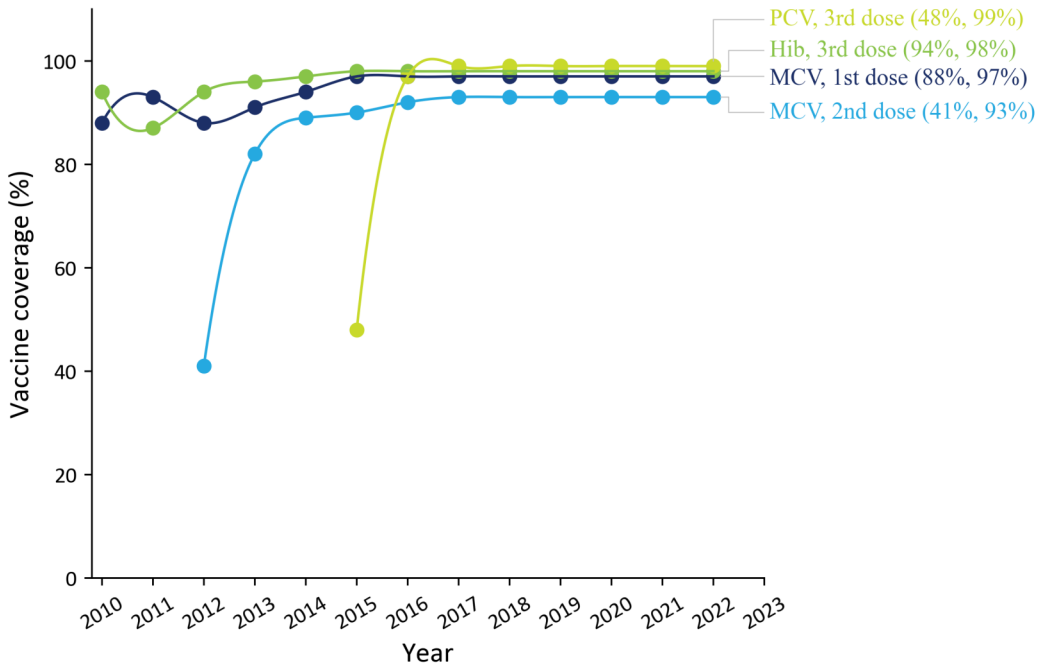
Annex A

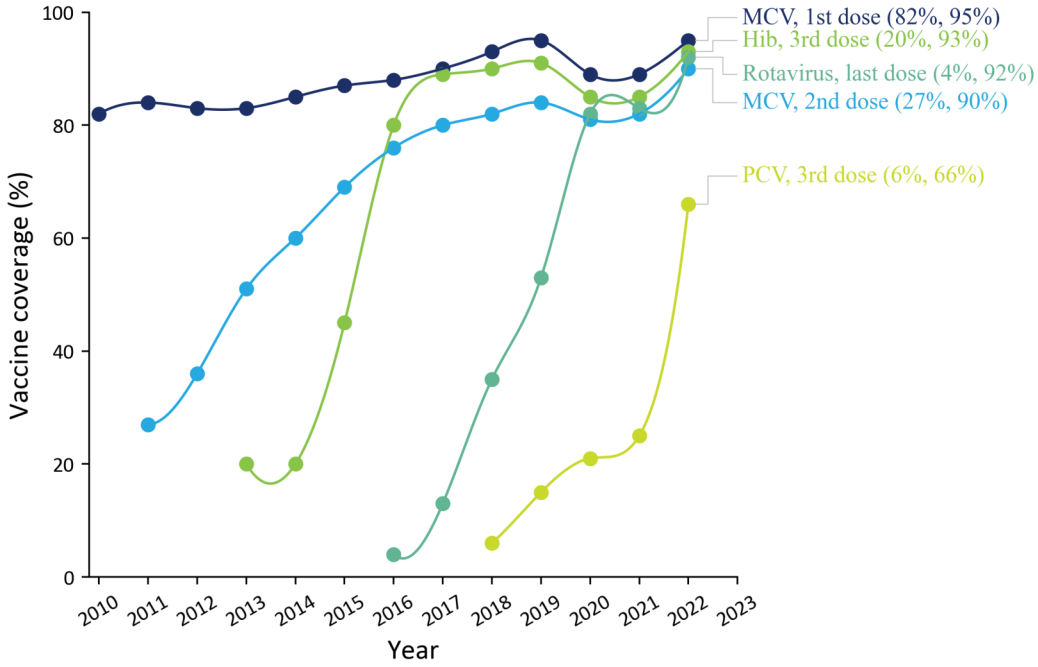
Figure A.1 (a-m). Immunization coverage (WUENIC values[1]) for 13 countries from 2010-2022

(a) Bangladesh

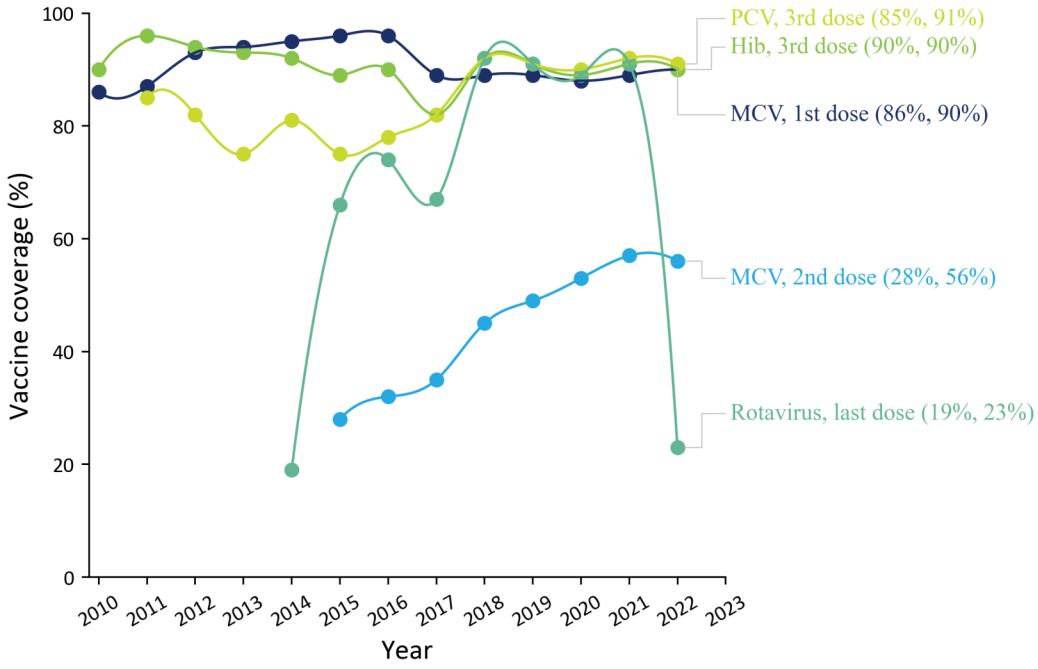


[1] All values presented here are WUENIC estimates except for coverage values for TCV which are administrative estimates.

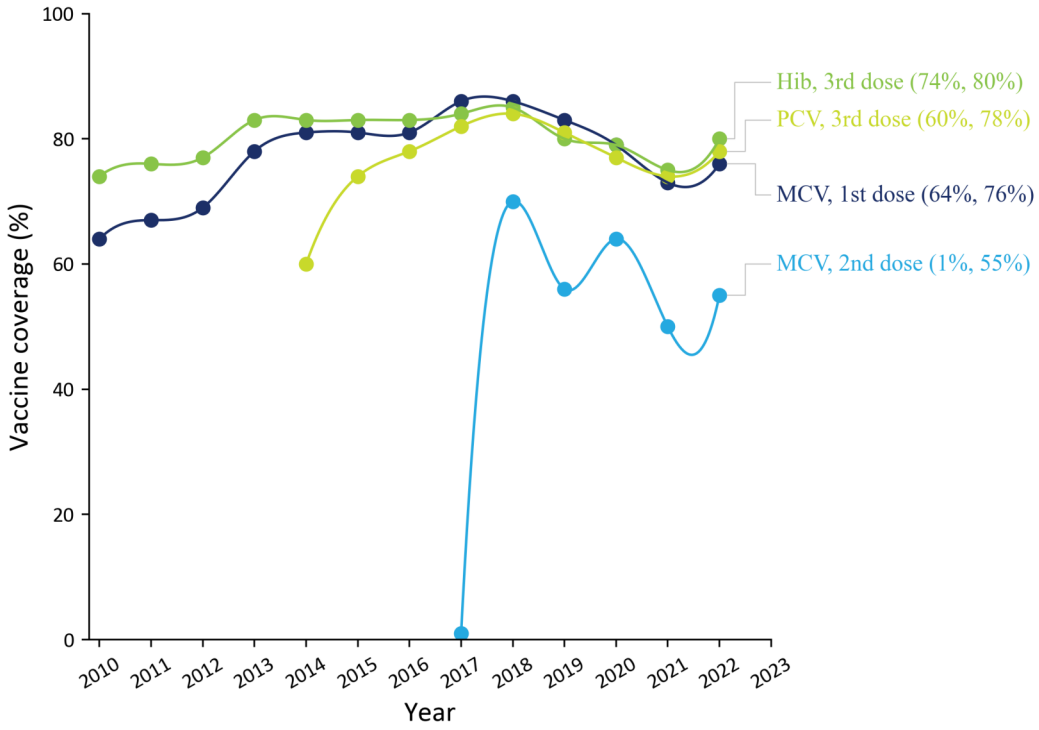
(b) India



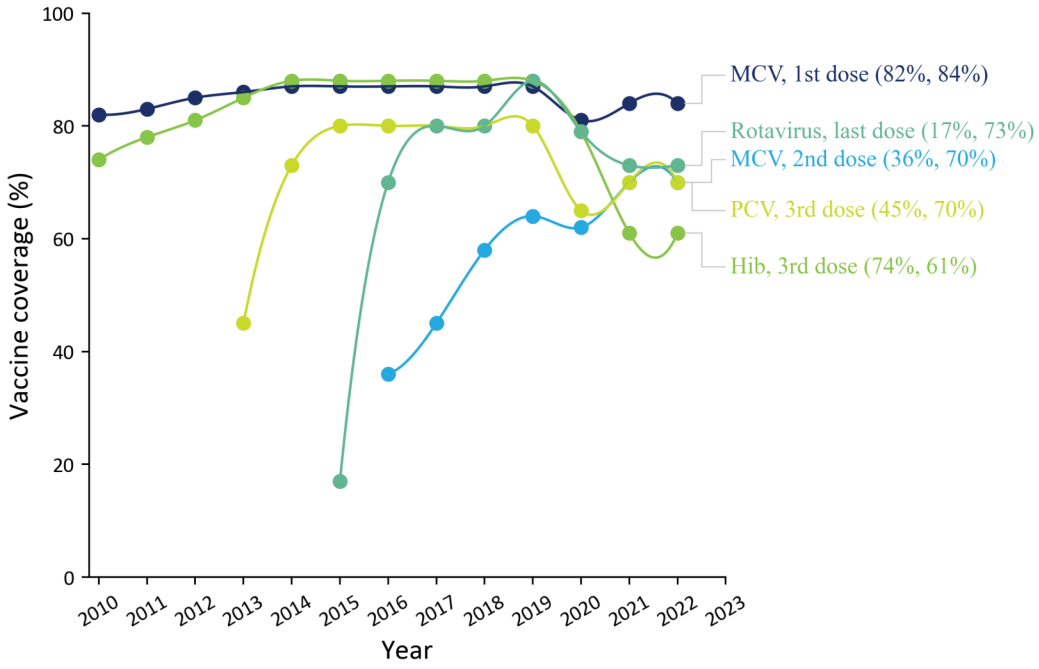
(c) Kenya



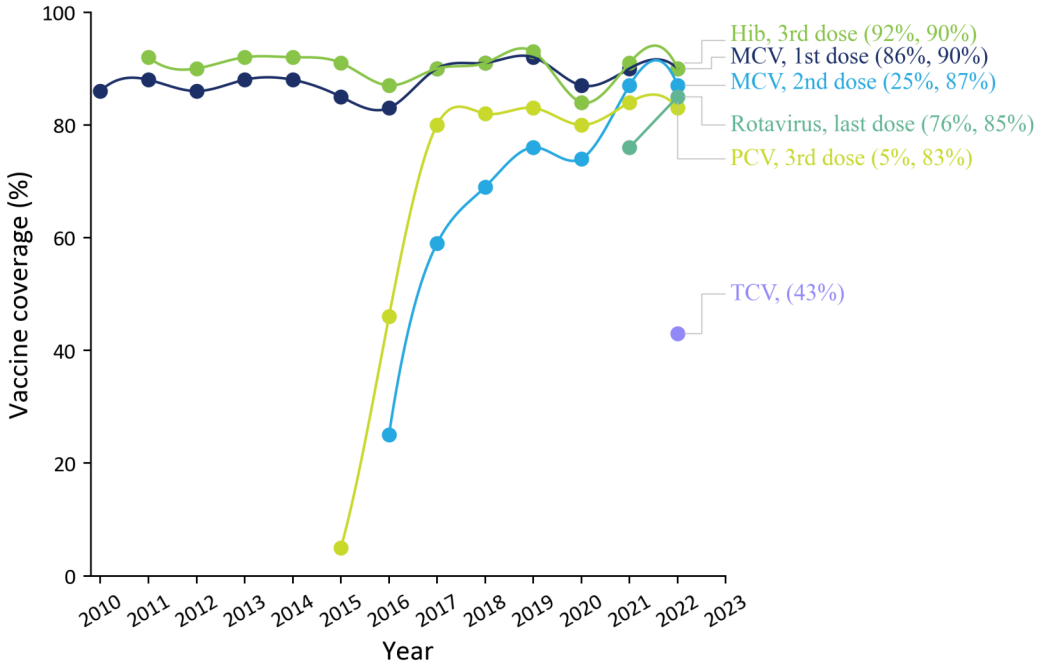
(d) Lao People's Democratic Republic



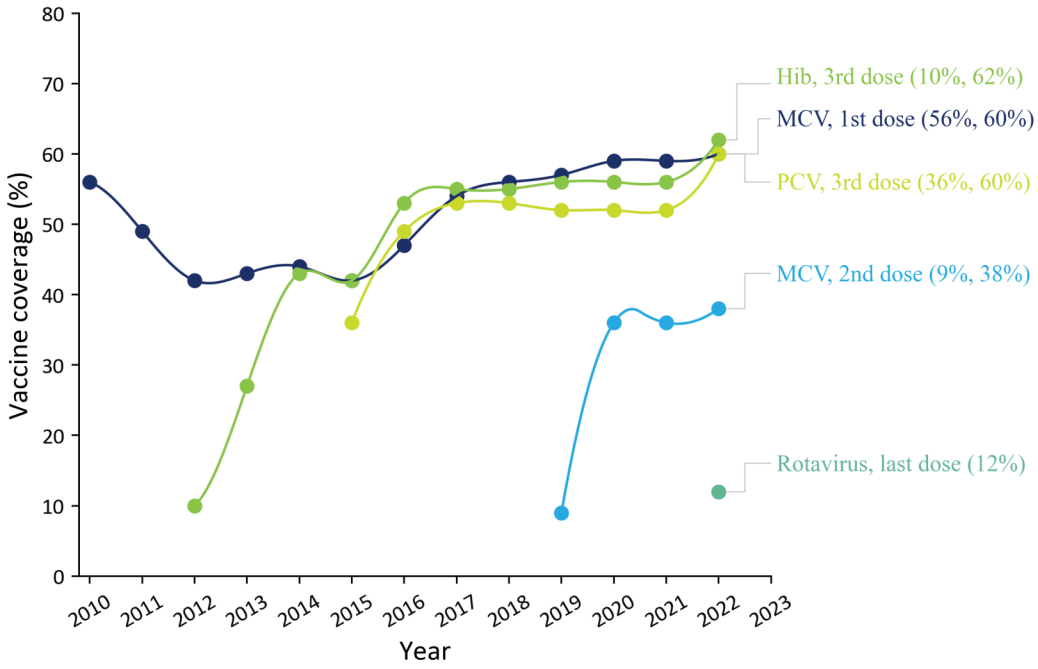
(e) Mozambique



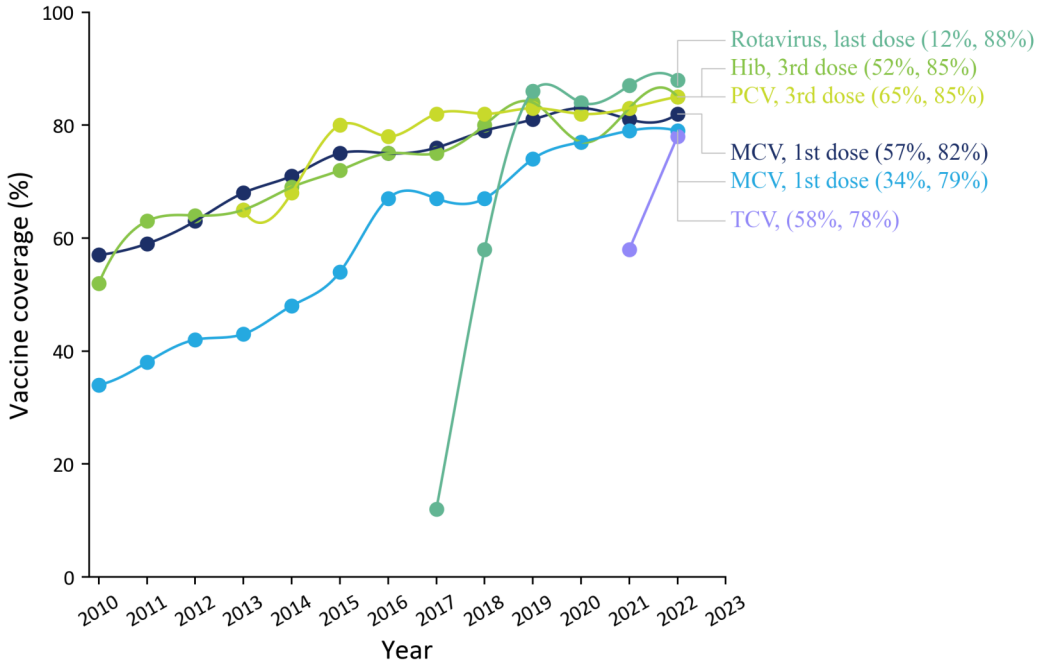
(f) Nepal



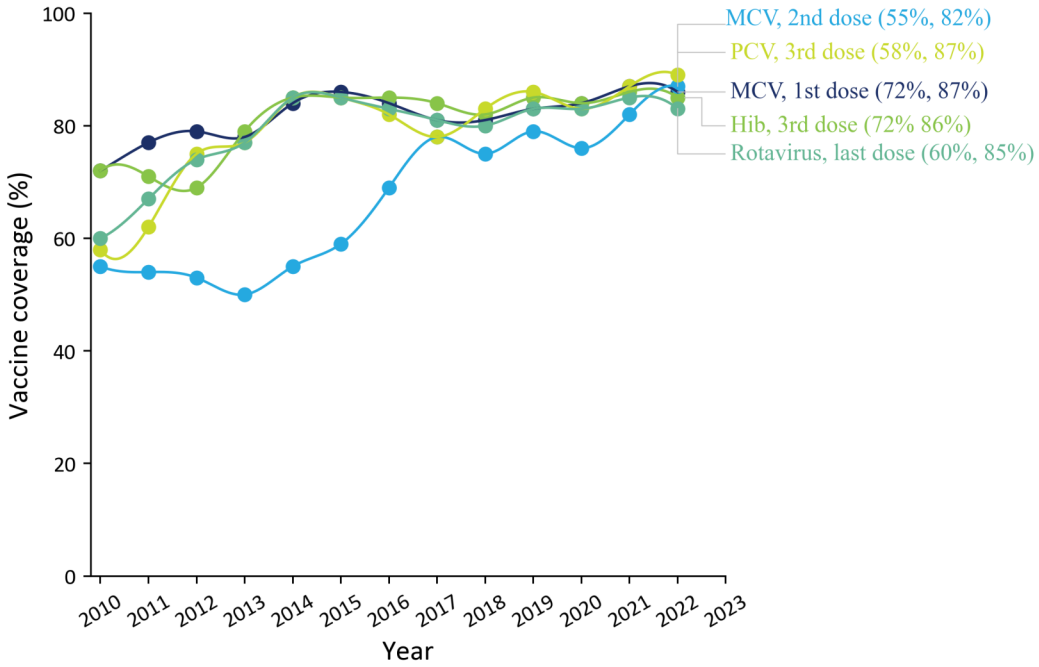
(g) Nigeria



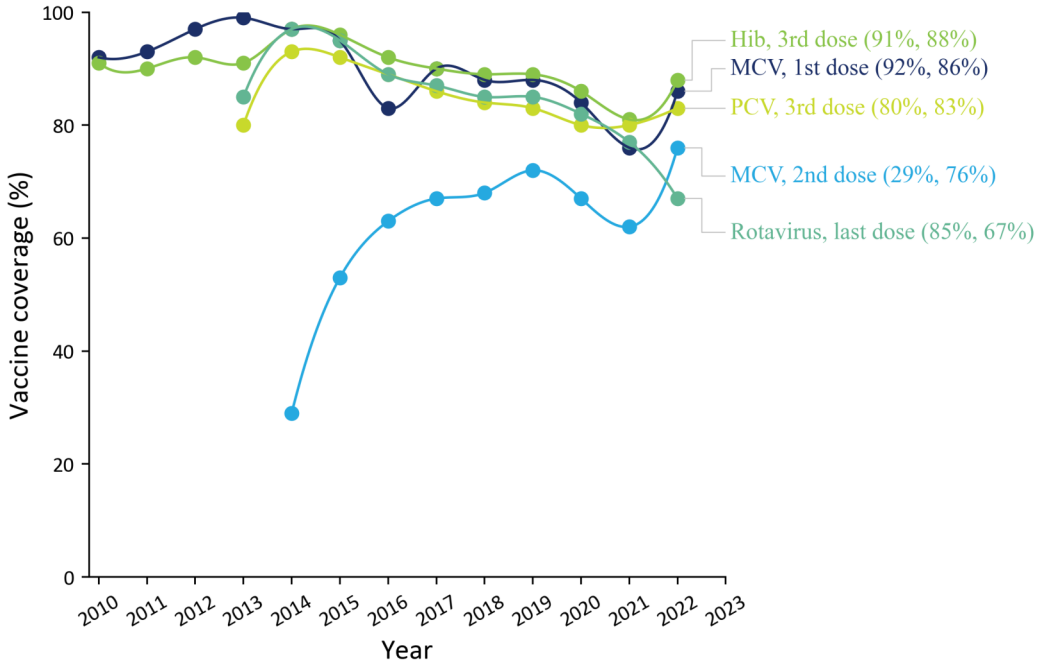
(h) Pakistan



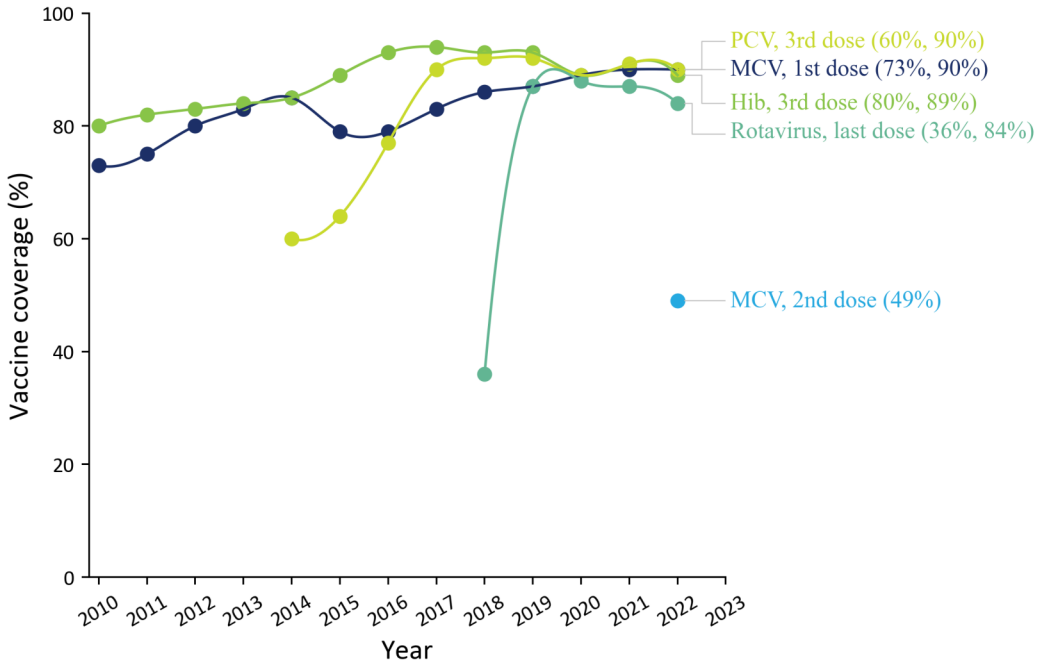
(i) South Africa



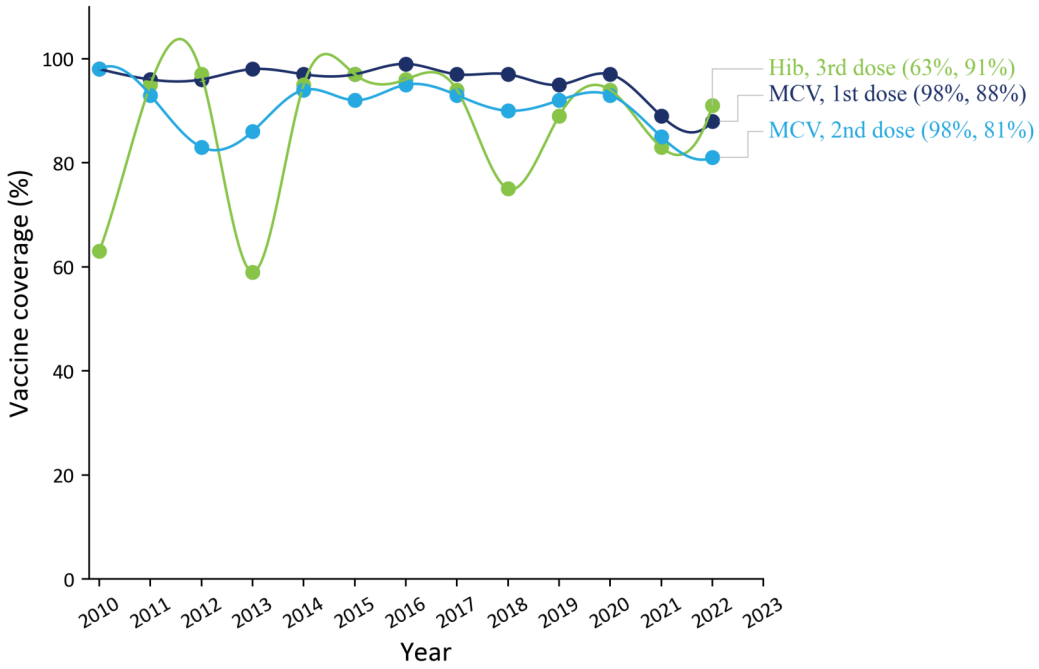
(j) The United Republic of Tanzania



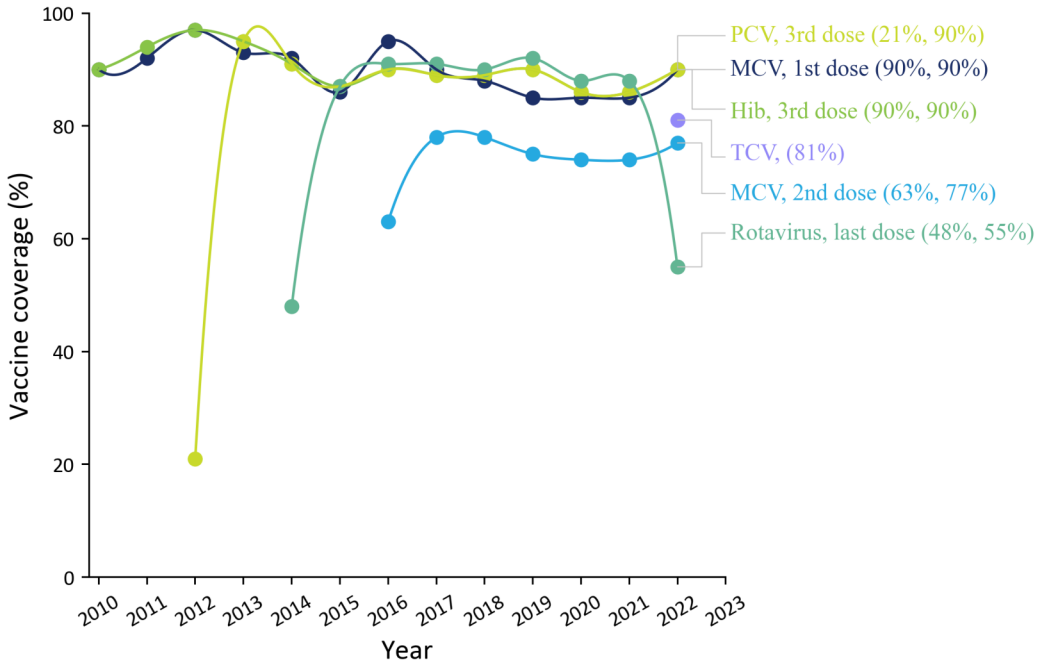
(k) Uganda



(l) Vietnam



(m) Zimbabwe



Annex B

Table B.1. Assumptions of vaccine impact projections[2]

Vaccine	Target population	Coverage %	Doses	Catch up campaign	Catch up campaign coverage %	Efficacy %	Effectiveness %	Duration of protection or rate of waning of protection
Typhoid conjugate vaccine (TCV)[3]	Infants 9 months old	Over 10 years: Bangladesh – 95% each year India – 26% increasing to 95%. Kenya – 82 % increasing to 89%. Nigeria – 34% increasing to 65%.	1	Up until age 15 years	One year over 4 weeks: Bangladesh – 90% Kenya – 90% Two years each over 4 weeks: Nigeria 45% 1st year and 44% 2nd year Four years each over 4 weeks India – 22% each year	87.5% Uniform distribution (80% - 95%) declining exponentially		0.0672 waning of vaccine induced immunity per year gamma (1.40, 0.0479)
Pneumococcal conjugate vaccine (PCV)10/13[4]	Children: 0-59 months 24-59 months	Average 66.8% in 2018 Bangladesh -99%	>=3	-	-	Invasive pneumococcal disease (vaccine stereotype)	0-59 months: 5.2% All ARI cases 8.7% Antibiotic-treated ARI	-

[2]For models estimating the impact of typhoid conjugate vaccine (TCV), pneumococcal conjugate vaccine (PCV serotypes 10/13) and rotavirus vaccine. "(-)" = no data available.

[3]Birger et al. 2022

[4]Lewnard et al. 2020b

Contd.

Vaccine	Target population	Coverage %	Doses	Catch up campaign	Catch up campaign coverage %	Efficacy %	Effectiveness %	Duration of protection or rate of waning of protection
		Kenya -81% India – 44% Nigeria-58% South Africa- 83%				81.2% (63.1% - 90.5 %)	24-59 months 10% All ARI cases 19.7% antibiotic treated ARI	
Rotavirus vaccine (Human monovalent vaccine - Rotarix)[5]	Children 0-23 months	Average 77.3% in 2018 Bangladesh – Missing (assume average) Kenya – 78% India – 73% Nigeria- missing (assume average) South Africa – 80%	>=2	-	-	Rotavirus gastroenteritis (vaccine stereotype): Middle income countries 77.5% (70.3%-83.0%) Low-income countries: 49.6% (18.7% - 68.8%)	Middle income countries: 8.7% all diarrhea cases 16.6 % antibiotic treated diarrhea Low-income countries: 2.7 % all diarrhea cases 10 % antibiotic	-

[4]Lewnard et al. 2020b

Table B2 . Pneumococcal conjugate vaccine (PCV) and averted antibiotic use[6]

Country	Age (Months)	Acute Respiratory Infection attributable to PCV10/13-type *Streptococcus pneumoniae*		
		Antibiotic-treated cases, per 100		
		Invasive Pneumococcal Disease	Acute Otitis Media	Antibiotic -treated cases preventable by vaccine (direct effects, per 100)
Lao PDR	24-59	24.6 (4.2 -55.2)	35.6 (6.1-79.4)	19.7 (3.4 -43.5)
Lao PDR	0-59	12.3 (-1.8 -29.4)	17.8 (-2-42)	9.8 (-1.4 -22.6)
Nepal	24-59	19.8 (3.5 -45.1)	28.7 (6-65.2)	15.9 (2.7 -35.8)
Nepal	0-59	10.1 (-1.4 -23.8)	14.5 (-2.1-34.1)	8 (-1.1 -18.6)
Pakistan	24-59	18.8 (3.2 -40.5)	27.1 (4.6-58.7)	15 (2.6 -32.6)
Pakistan	0-59	9.6 (-1.4 -22.4)	14 (-2-32.3)	7.7 (-1.1 -17.4)
South Africa	24-59	8.6 (1.4 -20.5)	12.4 (2-29.5)	6.9 (1.1 -16)
South Africa	0-59	4.6 (-0.6 -11.3)	6.6 (-0-9-16.3)	3.6 (-0.5 -8.9)
The United Republic of Tanzania	24-59	16.6 (2.9 -37.3)	24 (4.2-53.8)	13.3 (2.4 -29.3)
The United Republic of Tanzania	0-59	8.7 (-1.3 -20.8)	12.7 (-1.8-29.9)	7 (- 1 -16.2)
Uganda	24-59	20.9 (3.8 -46.9)	30.3 (5.5-67.6)	16.8 (3 -36.8)
Uganda	0-59	10.5 (-1.5 -24.7)	15.2 (-2.2-35.4)	8.4 (-1.2 -19.2)
Zimbabwe	24-59	14.7 (2.7 -33.2)	21.3 (3.9-48)	11.8 (2.1 -26.3)
Zimbabwe	0-59	7.4 (-1.1 -17.5)	10.7 (-1.6-25)	5.9 (-0.8 -13.4)

[6] Lewnard et al. 2020b. Values extracted from
Table S11: Country-specific estimates of the incidence of ARI and antibiotic-treated ARI among children ages 24-59 months preventable by 10- and 13-valent pneumococcal conjugate vaccines.
Table S12: Country-specific estimates of the incidence of ARI and antibiotic-treated ARI among children ages 0-59 months preventable by 10- and 13- valent pneumococcal conjugate vaccines.

Table B3. Typhoid conjugate vaccine (TCV) and averted multidrug-resistant (MDR) typhoid deaths, and disability-adjusted life years (DALYs)[7]

Country	Baseline MDR cases x 1000 (95% predictio n interval)	Baseline MDR deaths (95% prediction interval)	Baseline MDR DALYs x 1000 (95% prediction interval)	Proportion MDR cases averted (%)	Proportion MDR deaths averted (%)	MDR DALYs averted x 1000 (95% prediction interval)
Bangladesh	4,176 (2,711- 5,942)	9,712 (162- 427,120)	591 (10-26,734)	67	68	435 (18-17,807)
India	925 (233-2,601)	9,353 (1,337- 60,880)	531 (74-3,375)	58	59	324 (47-2,109)
Kenya	762 (610-936)	6,379 (403- 79,116)	315 (19-3,745)	75	73	243 (17-3,053)
Lao PDR	130 (1-470)	168 (1-6,870)	9 (0.047-379)	64	63	7 (0.044-263)
Mozambique	280 (54-636)	1,427 (48- 26,222)	62 (2-1,153)	74	75	49 (2-906)
Nepal	10 (2-29)	53 (2-1,034)	3 (0.126-62)	70	66	2 (0.112-43)
Nigeria	8,325 (4,222- 13,053)	157,966 (11,355- 1,735,476)	6,251 (461- 69,265)	62	62	3,985 (341- 45,220)
Pakistan	2,071 (1,164- 3,215)	4,262 (497- 39,149)	237 (28-2,302)	57	58	150 (20-1,371)
The United Republic of Tanzania	804 (302-1,559)	4,263 (189- 72,209)	228 (10-3,755)	74	75	178 (10-2,993)
Uganda	303 (174-448)	1,693 (85- 26,336)	81 (4-1,263)	76	73	63 (4-988)
Viet Nam	311 (2-1,143)	5,975 (56- 78,733)	360 (3-4,636)	59	60	222 (2-3,113
Zimbabwe	81 (5-287)	612 (14-11,733)	28 (0.651-518)	73	76	21 (0.581-413)

[7] Birger et al. 2022. Baseline burden and vaccine impact on MDR typhoid fever. Vaccine assumptions: immunization with TCV at 9 months of age with a catch-up campaign to 15 years of age. Results are for a 10-year period.
MDR=Multidrug-resistant (typhoid fever), DALYs=Disability-life adjusted years. TCV=Typhoid conjugate vaccine

Table B4. Rotavirus and antibiotic-treated diarrheal cases preventable by the rotavirus vaccine among children under two years old.[8]

Country	Diarrhea attributable to Rotavirus	
	Antibiotic-treated case, per 100 (95% CI)	**Antibiotic-treated cases preventable by vaccine, direct effects, per 100 (95% CI)**
Bangladesh	13.5 (1.8 -27.4)	9 (1.5 -18.2)
India	14.5 (2.1 -27.9)	9.7 (1.6 -18.2)
Kenya	12.7 (1.8-24.3)	8.3 (1.3-16.4)
Lao PDR	13.9 (2 -27.6)	9.2 (1.5 -18.1)
Mozambique	12.8 (4.3-26)	7.2 (2.4-13)
Nepal	10.6 (3.5 -22.1)	5.9 (1.9 -10.9)
Nigeria	17 (2.5-33)	11.2 (1.8-21.4)
Pakistan	13.9 (2 -27)	9.2 (1.4 -18.1)
South Africa	8.1 (1.1-17)	5.4 (0.9-11.1)
The United Republic of Tanzania	10.8 (3.6 -21.3)	6 (2 -10.7)
Uganda	13.5 (4.6 -26.9)	7.6 (2.5 -13.4)
Viet Nam	17.6 (2.4-36.5)	11.8 (1.8-24)
Zimbabwe	11.1 (3.8 -22.3)	6.2 (2.1 -11.1)

[8] Lewnard et al. 2020b. Total vaccine-preventable antibiotic consumption and incidence per 100 children.
Table S13: Country-specific estimates of the incidence of diarrhea and antibiotic-treated diarrhea among children ages 0-23 months preventable by rotavirus vaccination.

Table B5. Influenza and averted antibiotic prescriptions for influenza-like illness (ILI) and severe acute respiratory infection (SARI)[9]

Country	Population (Age)	ILI	SARI	Number of antibiotic prescriptions averted per year, mean (range)		
				Total	per 100,000 population	per 10,000 vaccinations
Kenya	children under 5	x		9425 (6492–13655)	135 (93–195)	44.9 (30.9–65.1)
Kenya	children under 6 months	x	x	894 (254–3434)	128 (36–491)	42.6 (12.1–163.7)
South Africa	children under 6 months	x		1094	189	63
South Africa	adults over 65	x		11153	399	133

[9] Knight et al. 2018. Estimated number of antibiotic prescriptions that could be averted per year by the introduction of an influenza vaccine into specific high-risk groups in Africa.

ILI=Influenza-like illness, SARI=Severe Acute Respiratory Infection.

A cross ('x') indicates if the estimate came from ILI, SARI or both.

95% confidence intervals were used for South Africa, and minimum-maximum values were used for Kenya.

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