Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use

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Contents

Preface

Bruce Aylward
Assistant Director-General of the Universal Health Coverage,
Life Course Division

"Antimicrobial resistance (AMR) has become one of the most urgent health threats of our time, undermining the efficacy of life-saving drugs and threatening the gains we have made in controlling infectious diseases. Vaccines play a pivotal role in our strategy to combat AMR by preventing infections, reducing the need for antibiotics and helping to curb the spread of resistant strains. It is imperative that we not only accelerate the development of new vaccines but also maximize the use of existing ones to protect global health and safeguard future generations. The time to act is now, leveraging every available tool to mitigate this looming crisis."

Yukiko Nakatani
Assistant Director-General,
Antimicrobial Resistance, WHO

"To effectively combat AMR, we must adopt a holistic approach that integrates vaccines into a comprehensive package of AMR interventions. Vaccines are a powerful tool in our arsenal, capable of preventing infections and reducing the reliance on antibiotics, which in turn slows the spread of resistance. However, vaccines must be part of a broader strategy that includes improved infection prevention, access to essential health services, accurate diagnosis and appropriate treatment. By combining these efforts, we can build a resilient health care system that is capable of addressing the multifaceted challenge of AMR and ensuring a healthier future for all."

Jeremy Farrar
Chief Scientist,
Science Division, WHO

"Addressing the immediate and increasing impact of AMR requires an urgent and unwavering commitment to research and innovation. The development of new vaccines and the optimization of existing ones are critical components in our strategy to combat AMR. Comprehensive surveillance and data analysis enables us to understand the evolving landscape of resistance, identify the most pressing and emerging threats, and measure the impact of our interventions. But surveillance is not enough. We must then have the tools to act on those data to prevent and treat infections. That will take an increased and sustained commitment to research and development, to allow us to innovate and advance vaccine and other technologies as we seek to get ahead of resistant pathogens. Our collective efforts in data-driven research will pave the way for new and improved vaccines, which we must ensure are equitably available to all, thereby securing a future free from the devastating impact of untreatable infections."

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Abbreviations and acronyms

ACT	artemisinin-based combination therapy
ALRI	acute lower respiratory infection
AMR	antimicrobial resistance
ARI	antibiotic-treated respiratory infection
CDC	United States Centers for Disease Control and Prevention
CHAMPS	Child Health and Mortality Prevention Surveillance
CHOICE	Choosing Interventions that are Cost-Effective
CI	confidence interval
DALY	disability-adjusted life year
DDD	defined daily dose
ECVP	Evidence Consideration for Vaccine Policy
ETEC	enterotoxigenic *Escherichia coli*
ExPEC	extraintestinal pathogenic *Escherichia coli*
GAS	Group A *Streptococcus*
GBD	Global Burden of Disease
GBS	Group B *Streptococcus*
GDP	gross domestic product
GLASS	Global Antimicrobial Resistance Surveillance System
HIV	human immunodeficiency virus
IA2030	Immunization Agenda 2030
IHME	Institute for Health Metrics and Evaluation
IPC	infection prevention and control
IVB	Immunization, Vaccines and Biologicals
LMIC	low- and middle-income countries
mAb	monoclonal antibody
MDR	multidrug resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
NG	*Neisseria gonorrhoeae*
NIS	national immunization strategies
NTS	nontyphoidal *Salmonella*
PA	*Pseudomonas aeruginosa*
PCV	pneumococcal conjugate vaccine
PDR	pan-drug resistant
PI	prediction interval
PPC	preferred product characteristic
PPS	point prevalence survey
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
R&D	research and development
RNA	ribonucleic acid

RR	rifampin-resistant
SPara	*Salmonella* Paratyphi A
ST	*Salmonella* Typhi
TB	tuberculosis
TCV	typhoid conjugate vaccine
TPP	target product profile
UCR	Unit Cost Repository
UI	uncertainty interval
UN	United Nations
UNICEF	United Nations Children's Fund
US	United States
UTI	urinary tract infection
WHO	World Health Organization
WOAH	World Organization for Animal Health
WUENIC	WHO/United Nations Children's Fund Estimates of National Immunization Coverage
XDR	extensively drug resistant

Organisms

A. baumannii	*Acinetobacter baumannii*
C. difficile	*Clostridioides difficile*
C. jejuni	*Campylobacter jejuni*
E. coli	*Escherichia coli*
E. faecium	*Enterococcus faecium*
Hib	*Haemophilus influenzae* type b
H. influenzae	*Haemophilus influenzae*
H. pylori	*Helicobacter pylori*
K. pneumoniae	*Klebsiella pneumoniae*
M. tuberculosis	*Mycobacterium tuberculosis*
N. gonorrhoeae	*Neisseria gonorrhoeae*
P. aeruginosa	*Pseudomonas aeruginosa*
P. falciparum	*Plasmodium falciparum*
RSV	respiratory syncytial virus
S. aureus	*Staphylococcus aureus*
S. enterica	*Salmonella enterica*
***S.* Paratyphi**	*Salmonella* Paratyphi
S. pneumoniae	*Streptococcus pneumoniae*
S. pyogenes	*Streptococcus pyogenes*
***S.* Typhi**	*Salmonella* Typhi

Report summary

Key messages

- Antimicrobial resistance (AMR) is one of the most important global public health and development threats.
- In 2019, an estimated 5 million lives globally were lost as a result of AMR. Vaccines have the potential to avert an estimated 515 000 of these deaths each year by reducing incidence of infections, transmission of pathogens, antibiotic use, and subsequently, evolution of resistant genes.
- The role of vaccines in reducing AMR has been underrecognized, yet vaccines have the power to train the immune system to mount a defence against various pathogens before an infection starts or becomes severe. Vaccinated people will have fewer infections and thus will also be protected against potential complications from secondary infections that may trigger the use of antimicrobials or require admission to hospital.
- This report focuses on 24 pathogens and 44 vaccines (either licensed by national regulatory agencies, in clinical development or hypothetical). By combining the knowledge of international experts with data and a robust methodology, the report aims to quantify the potential for these vaccines to reduce AMR, its effects and antibiotic use.
- Existing vaccines could avert annually up to 106 000 deaths, 9.1 million disability-adjusted life years (DALYs), US$ 861 million in hospital costs and US$ 5.9 billion in productivity losses, all associated with AMR. These vaccines could also reduce antibiotic use by 142 million defined daily doses (DDDs) annually. For example, achieving the target from the Immunization Agenda 2030 (IA2030) and World Health Organization (WHO) for global coverage of *Streptococcus pneumoniae* vaccines in children (of 90%) and in elderly people could avert an additional 27 100 deaths per year and 1.5 million DALYs, and prevent US$ 507 million in hospital costs and US$ 879 million in productivity losses annually, all associated with AMR.
- Vaccines in late-stage clinical development could avert annually up to 135 000 deaths, 5.0 million DALYs, US$ 1.2 billion in hospital costs and US$ 2.2 billion in productivity losses, all associated with AMR. They could also reduce antimicrobial use by 1.9 billion DDDs annually. For example, a vaccine against *Mycobacterium tuberculosis* administered to adolescents to prevent the progression of latent infection to active disease could prevent significant AMR burdens annually: 71 000 deaths and 2.6 million DALYs associated with AMR, and 1.2 billion DDDs of antimicrobials.
- Vaccines in early clinical development could avert annually up to 408 000 deaths, 23.0 million DALYs, US$ 30.0 billion in hospital costs and US$ 17.7 billion in productivity losses, all associated with AMR. They could also reduce antimicrobial use by 548 million DDDs annually. For example, a maternal vaccine targeting *Klebsiella pneumoniae* aimed at safeguarding neonates from bloodstream infections could prevent an estimated 27 000 deaths, 2.4 million DALYs, US$ 280 million in hospital costs and US$ 2.5 billion in productivity losses annually, all linked to AMR.
- Vaccines are critical in the fight against AMR, and must be integrated in national and global AMR mitigation strategies, and in decision-making about vaccine development, introduction and use.

Key recommendations

The recommendations given below summarize the full recommendations given in Chapter 5.

- The impact of vaccines in reducing AMR needs to be recognized by stakeholders in AMR and immunization. Global, regional and national AMR and immunization strategies and implementation frameworks should include vaccines as interventions to reduce AMR, advocating for their broader implementation and integration.

- The introduction of existing vaccines should be accelerated and their coverage increased. All existing paediatric vaccines should reach the immunization targets of IA2030, and the use of vaccines in older age groups should be considered. The impact of existing vaccines on AMR should be monitored to inform policy decisions.

- To prepare for the introduction of newly developed vaccines, the impact of vaccines on AMR should be systematically evaluated and embedded into existing decision frameworks, including regulatory and policy frameworks, cost–effectiveness studies and national immunization strategies.

- To enable vaccine development, delivery and implementation to combat AMR, it is necessary to include AMR endpoints in clinical trials, develop preferred product characteristics (PPCs) for impactful vaccines, create research roadmaps for challenging vaccines, ensure access to vaccines for high-risk populations, engage with regulatory agencies, consider synergistic combination vaccines, and target non-human reservoirs through One Health approaches.

- To implement comprehensive AMR containment strategies, it is necessary to make use of alternative interventions, enhance surveillance platforms, raise awareness of resistant pathogens, and assess the health and economic burden of AMR. Also needed is the collection of data on the impact of vaccines on the prevalence of AMR and antibiotic use, and the preparation of comprehensive value assessments for vaccines in development, considering their broader impacts on equity and health care.

Introduction

It is estimated that, in 2019, 7.7 million deaths were associated with 33 different bacterial infections *(1)*, with almost 5 million of these deaths being associated with AMR. Vaccines can play an important role in lowering the AMR burden by reducing the incidence of both drug-sensitive and drug-resistant infections, antibiotic use, and the opportunities for evolution and transmission of resistant genes and pathogens. However, the specific role for current and future vaccines in reducing AMR has not been systematically evaluated and quantified.

This report presents a thorough evaluation of the role of vaccines in reducing AMR; it also provides associated recommendations for enhancing the impact of vaccines on AMR. It covers 44 distinct vaccines targeting 24 pathogens: 19 bacteria, four viruses and one parasite. Infections can result in multiple syndromes and vary across age groups; thus, for any given pathogen, in several cases more than one vaccine was evaluated for its impact on AMR. The characteristics of each vaccine (e.g. efficacy, coverage, length of protection, target population and type of infection or disease prevented) were drawn from various sources, including published PPCs, modelling studies, clinical trials and expert consultations.

Vaccine experts classified the feasibility of developing and delivering vaccines with specific characteristics by pathogen, based on biological feasibility, product development feasibility, and access and implementation feasibility, according to predefined criteria and thresholds.

The potential impact of vaccines in reducing AMR was evaluated across three criteria:

- the AMR-related health burden – measured by the reduction in deaths and DALYs associated with AMR;
- antibiotic use (or antimicrobial use in the case of *Mycobacterium tuberculosis*); and
- the economic burden of AMR, including hospital costs and productivity losses (additional data on bed-averted days are included in the data on the WHO website *(2)*).

A static proportional model was used to calculate annual vaccine impact on AMR for 2019 across these three criteria. For each vaccine, its corresponding characteristics were applied to data from a study on the global burden of diseases associated with AMR, to calculate the AMR health burden that is averted through vaccines *(3)*. Literature reviews were conducted and data modelled to understand antibiotic use associated with treating each pathogen, as well as hospital costs associated with treating pathogens that are associated with AMR, and the loss of productivity due to an early death resulting from an AMR infection. These results were triangulated with the vaccine-averted AMR health burden data to estimate the vaccine-averted economic burden associated with AMR. For each of the three criteria the potential impact of each vaccine on AMR was categorized as low, moderate or high, according to predefined criteria.

The value estimates in this report will be useful for vaccine and AMR stakeholders (e.g. funders, vaccine developers, researchers, country, regional and global decision-makers, health workers, civil society organizations and regulators), guiding them to prioritize and channel their efforts effectively for maximum global impact against AMR.

Summary of results: the estimated impact on AMR of vaccines with a high feasibility of development and implementation

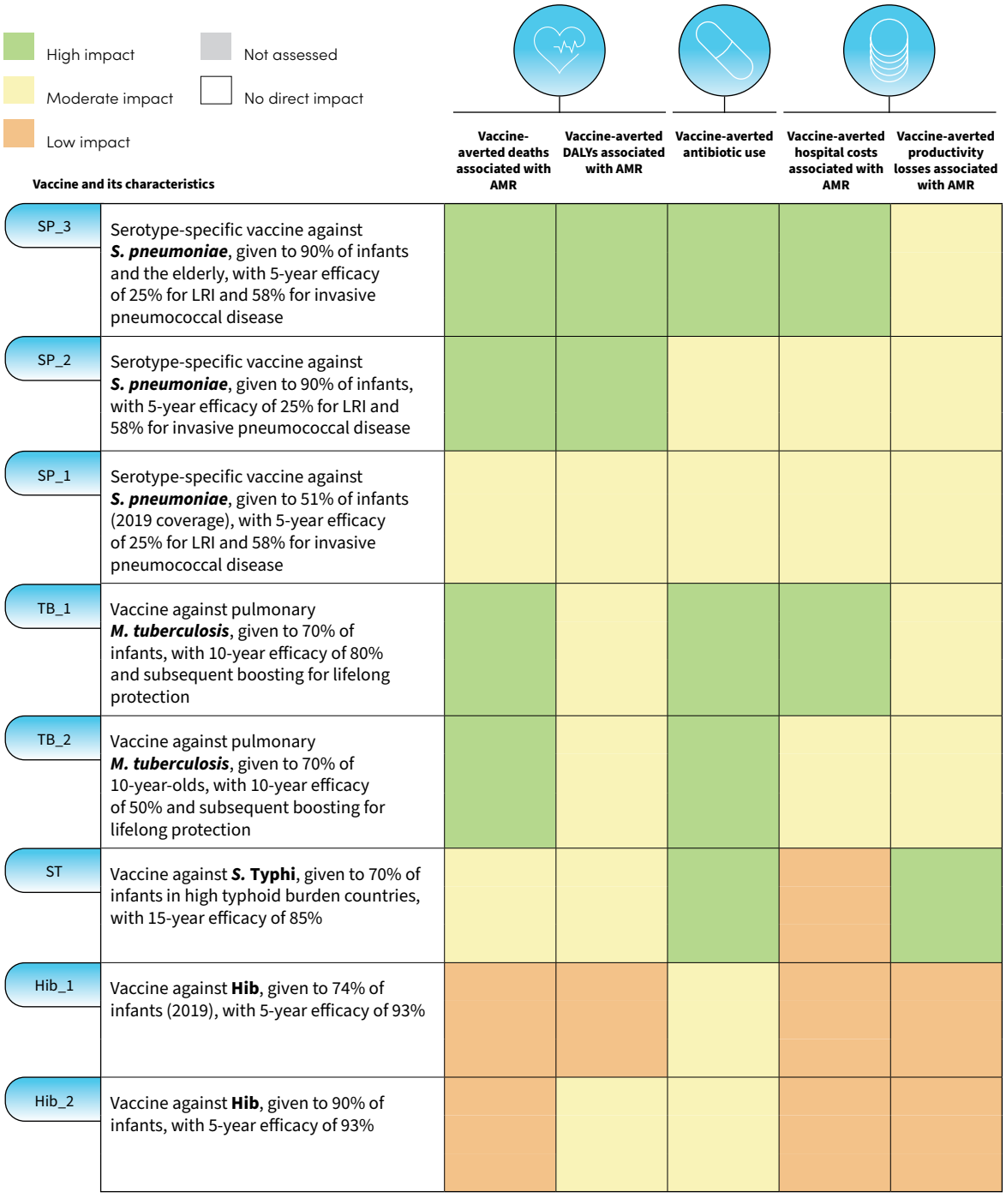
Several vaccines have a high feasibility of development and implementation, and are either already licensed or in Phase 3 of clinical development (Fig. A). Some of these vaccines are already reducing AMR, but their impact could be amplified if vaccine coverage were to increase or additional populations were to be vaccinated. For instance, vaccines against *Streptococcus pneumoniae* [SP_1] already have a moderate-to-high impact on AMR, and this could be increased by achieving the IA2030 and WHO's target global coverage of *S. pneumoniae* vaccines in children (of 90%) and in elderly people [SP_3]. Compared with the 2019 global coverage of *S. pneumoniae* vaccines [SP_1], such extended use could avert an additional 27 100 deaths per year and 1.5 million DALYs, and prevent US$ 507 million in hospital costs and US$ 879 million in productivity losses annually, all associated with AMR; it could also further reduce global antibiotic use by an estimated 10 million DDDs per year [SP_3]. Similarly, introducing the *Salmonella* Typhi vaccine [ST] in regions with a high burden of typhoid could prevent an estimated 45 million DDDs of antibiotics and US$ 2.3 billion in productivity losses linked to AMR each year, primarily by averting deaths in young children and adolescents.

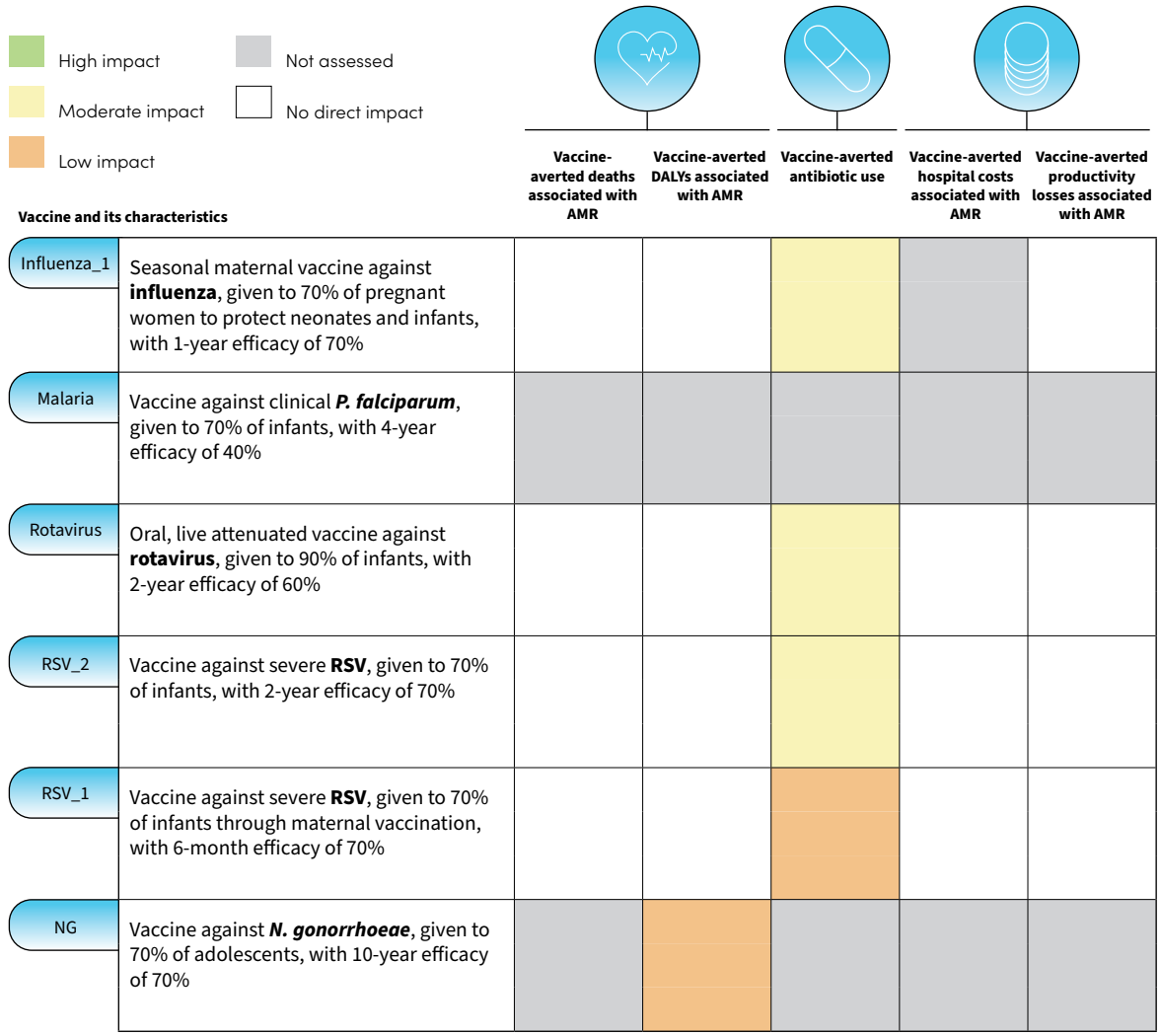
Several new vaccines against tuberculosis (TB) are under development, with approaches that include improving infant immunization, targeting adults and adolescents to prevent progression to active TB, and revaccination with bacille Calmette-Guérin (BCG) *(4)*. The potential impact of these TB vaccines on AMR was estimated. Together, a vaccine administered to infants to prevent disease [TB_1] and another given to adolescents to prevent the progression of latent infection to active disease [TB_2] could prevent significant AMR burdens annually: 71 000–118 000 deaths, 2.6–4.5 million DALYs, US$ 600 million – US$ 1.0 billion in hospital costs and US$ 1.2–2.0 billion in productivity losses. Additionally, these vaccines could prevent 1.2–1.9 billion DDDs of antimicrobials specific for the treatment of TB, a projected impact driven in part by the long course of treatment (>6 months). Other analyses presented in the WHO publication *An investment case for new tuberculosis vaccines* show that – even if the length of protection was limited to 10 years and no vaccine boosters were given – a new TB vaccine targeting adolescents

would have a significantly higher impact than a vaccine given to infants *(5)*.

Of the viral and malarial vaccines evaluated that have a high feasibility of development and implementation, most are projected by this analysis to have a moderate impact on reducing antibiotic use. Antibiotics are often prescribed empirically against syndromes that are common to infections caused by bacteria, viruses and parasites (e.g. *Plasmodium falciparum*). The vaccine-mediated reduction in antibiotic use is significant, and through the bystander effect it could drive a decrease in the prevalence of resistance in bacteria that are not directly targeted by a vaccine. Owing to a lack of data, this report did not evaluate the impact of viral and malarial vaccines on deaths, DALYs or economic burden associated with resistant secondary infections.

Fig. A. The estimated and potential vaccine impact on AMR annually for vaccines with a high feasibility of development and delivery





AMR: antimicrobial resistance; DALY: disability-adjusted life year; Hib: *Haemophilus influenzae* type b; *M. tuberculosis: Mycobacterium tuberculosis; N. gonorrhoeae: Neisseria gonorrhoeae; P. falciparum: Plasmodium falciparum;* RSV: respiratory syncytial virus; *S. pneumoniae: Streptococcus pneumoniae*; *S.* Typhi: *Salmonella* Typhi.

Categories of impact: low (orange), moderate (light green) and high (green). The categories were assigned as follows: for vaccine-averted deaths associated with AMR: low (<25 000), moderate (25 000–50 000), high (>50 000); for vaccine-averted DALYs associated with AMR: low (<1 million), moderate (1–5 million), high (>5 million); for vaccine-averted antibiotic use (DDDs): low (<10 million), moderate (10–30 million), high (>30 million); for vaccine-averted hospital costs associated with AMR (2019 US dollars): low (<US$ 250 million), moderate (US$ 250 million – US$ 1 billion), high (>US$ 1 billion); for vaccine-averted productivity losses associated with AMR (2019 US dollars): low (<US$ 1 billion), moderate (US$ 1–4 billion), high (>US$ 4 billion).

Summary of results: the estimated impact on AMR of vaccines with a medium feasibility of development and implementation

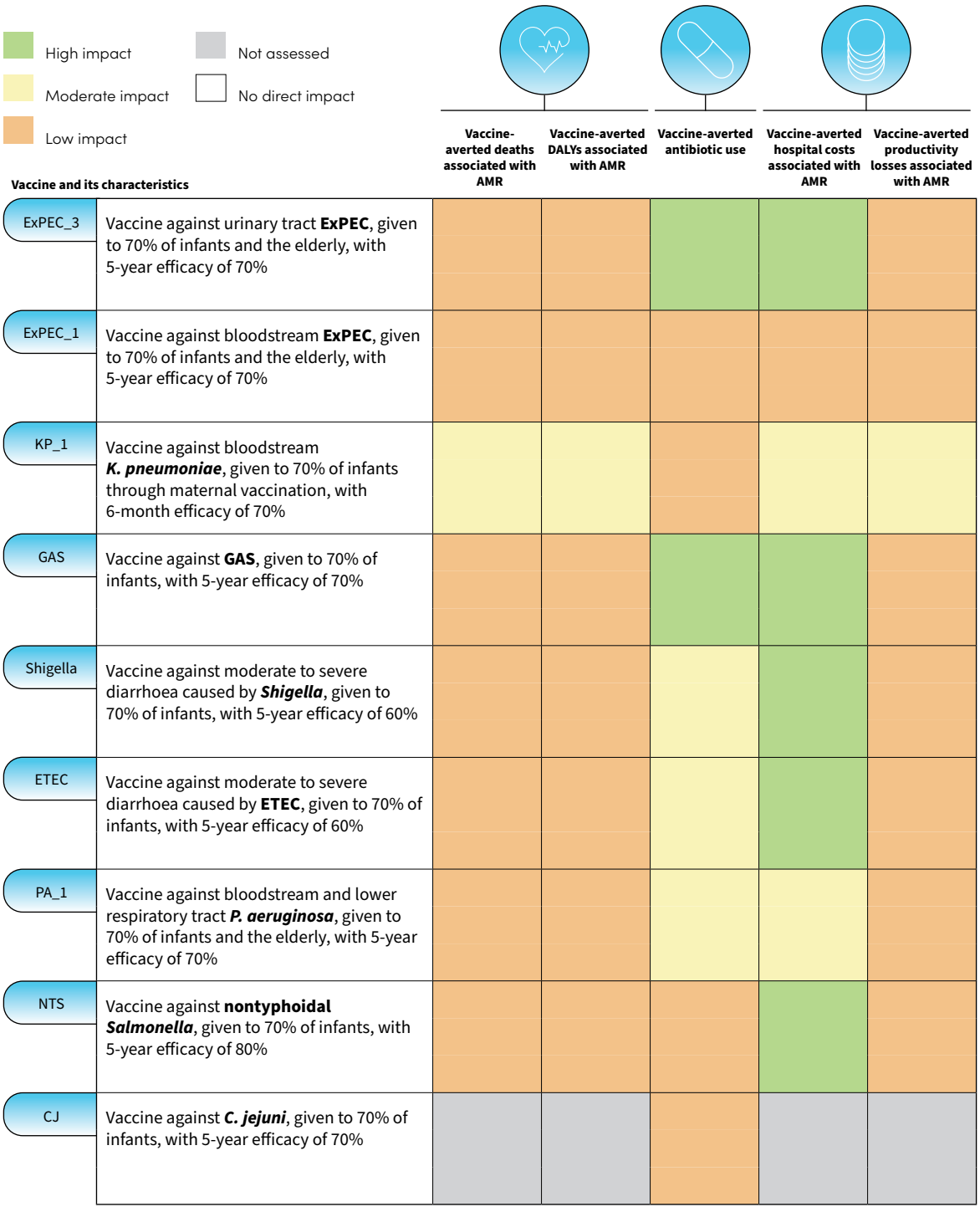
Several vaccines have a medium feasibility of development and implementation. They cover a range of pathogens; for some of these pathogens, vaccines are already under development (e.g. *Shigella* spp.), whereas for others (e.g. *Pseudomonas aeruginosa*) there are no vaccine candidates (Fig. B). Notably, a vaccine targeting urinary tract infections (UTIs) caused by extraintestinal pathogenic *Escherichia coli* (ExPEC) given to 70% of infants and elderly people could avert an estimated 96 million DDDs of antibiotics globally and US$ 6.2 billion in hospital costs associated with AMR annually [ExPEC_3]. Additionally, a maternal vaccine targeting *Klebsiella pneumoniae* aimed at safeguarding neonates from bloodstream infections could prevent an estimated 27 000 deaths, 2.4 million DALYs, US$ 280 million in hospital costs and US$ 2.5 billion in productivity losses annually, all linked to AMR [KP_1]. There is one vaccine candidate against *K. pneumoniae* in clinical development; however, its primary target population or the range of syndromes prevented is uncertain *(6)*.

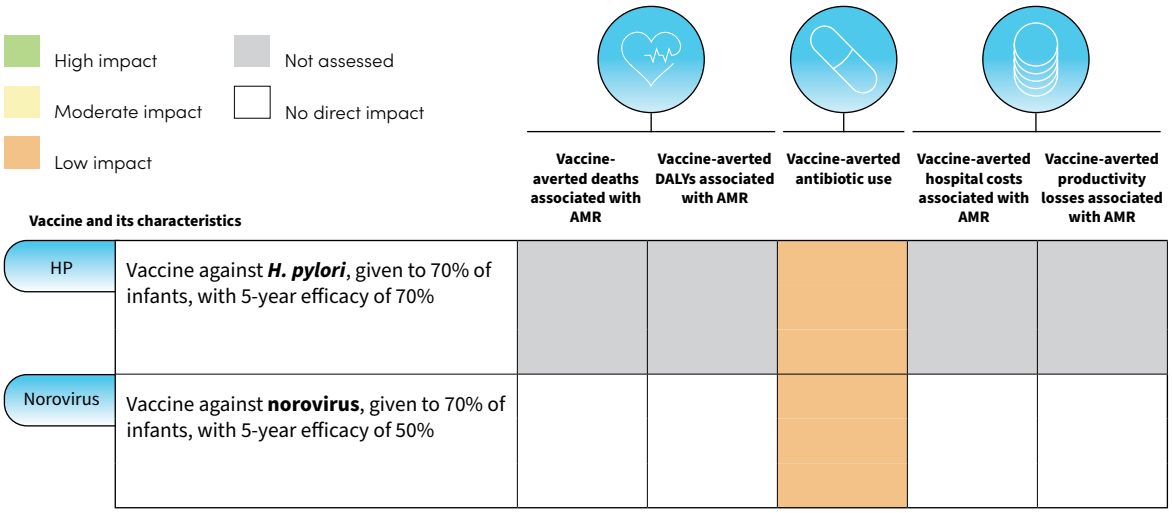
In the case of Group A *Streptococcus* (GAS), a vaccine could considerably reduce antibiotic use, averting 72 million DDDs annually; it could also substantially decrease hospital costs related to AMR by up to US$ 3.6 billion per year [GAS]. This is largely due to the high volume of antibiotics prescribed for conditions such as pharyngitis, the incidence of invasive diseases, and other GAS-related conditions requiring hospitalization. Currently, there is no available vaccine against GAS, but three candidates are in clinical development *(7)*.

Vaccines targeting diarrhoeal diseases caused by pathogens such as *Shigella* or enterotoxigenic *E. coli* (ETEC) are also noted for their potential moderate-to-high impact on antibiotic use and hospital costs associated with AMR. Diarrhoea, which is particularly prevalent in LMIC, is often linked with high antibiotic use and frequent hospitalizations. Currently, there are no licensed vaccines against ETEC and *Shigella*, but development efforts include six candidates for ETEC and eight for *Shigella (6)*.

The potential impact of vaccines against *Campylobacter jejuni* and *Helicobacter pylori*, especially in LMIC, was not evaluated because of limited data, particularly regarding criteria other than antibiotic use.

Fig. B. The estimated and potential annual impact on AMR of vaccines with medium feasibility of development and implementation





AMR: antimicrobial resistance; *C. jejuni: Campylobacter jejuni*; DALY: disability-adjusted life year; ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *Escherichia coli*; GAS: Group *A Streptococcus*; *H. pylori: Helicobacter pylori; K. pneumoniae: Klebsiella pneumoniae; P. aeruginosa: Pseudomonas aeruginosa*.

Categories of impact: low (orange), moderate (light green) and high (green). The categories of impact were assigned as follows: for vaccine-averted deaths associated with AMR: low (<25 000), moderate (25 000–50 000), high (>50 000); for vaccine-averted DALYs associated with AMR: low (<1 million), moderate (1–5 million), high (>5 million); for vaccine-averted antibiotic use (DDDs): low (<10 million), moderate (10–30 million), high (>30 million); for vaccine-averted hospital costs associated with AMR (2019 US dollars): low (<US$ 250 million), moderate (US$ 250 million – $US 1 billion), high (>US$ 1 billion); for vaccine-averted productivity losses associated with AMR (2019 US dollars): low (<US$ 1 billion), moderate (US$ 1–4 billion), high (>US$ 4 billion).

Summary of results: the estimated impact on AMR of vaccines with low feasibility of development and implementation

Certain vaccines pose significant challenges in development (e.g. a vaccine against *Staphylococcus aureus*) or delivery (e.g. a vaccine against *Acinetobacter baumannii*), or both (Fig. C). Given the challenges, the potential impact of these vaccines on AMR was evaluated across all disease syndromes and for various groups, including those at risk of infection or specific age demographics.

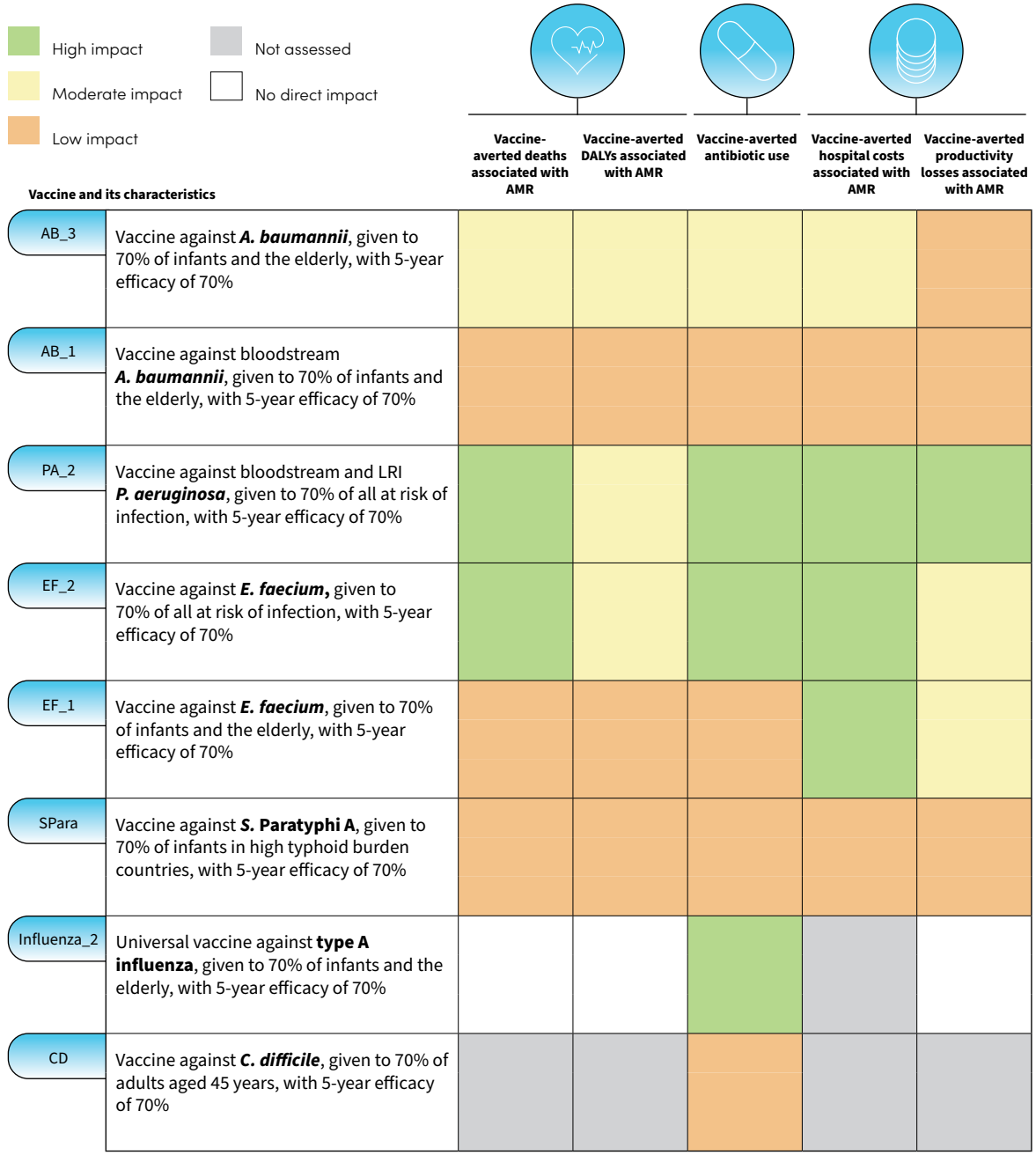
Among the vaccines with identified target populations, three show noteworthy potential. It is estimated that a vaccine against any type of ExPEC (infection), if administered to infants and elderly people, would have a high impact on AMR [ExPEC_5]. Such a vaccine could potentially avert 62 000 deaths, 2.3 million DALYs, US$ 7.2 billion in hospital costs and US$ 1.4 billion in productivity losses associated with AMR annually. Currently, there are four ExPEC vaccines in clinical development, but their efficacy in preventing various disease syndromes remains to be established *(6)*.

An enhanced vaccine against *S. pneumoniae* – if improved to be non-serotype-specific and to offer 50% efficacy against lower respiratory infections caused by *S. pneumoniae* and administered to infants and elderly people – could significantly impact AMR [SP_4]. Compared with the current pneumococcal vaccines with high coverage in infants and elderly people [SP_3], this enhanced vaccine could additionally avert 47 000 deaths, 3.7 million DALYs, US$ 929 million in hospital costs associated with AMR and 27 million DDDs annually. However, there are currently no vaccines in human trials that fit this profile, reflecting the low feasibility of development.

A vaccine targeting *S. aureus* for infants and elderly people could also have a high impact on AMR [SA_1]. However, the development of *S. aureus* vaccines has proven difficult, with many candidates failing during clinical trials *(6)*.

Although most vaccines in this category have a high potential impact on AMR, their development feasibility is low because of challenges in identifying and accessing vaccine target populations, and in implementing these vaccines to effectively prevent infections; the ambitious coverage target; and the long duration of protection required.

Fig. C. Estimated and potential annual impact on AMR of vaccines with a low feasibility of development and implementation



A. baumannii: Acinetobacter baumannii; AMR: antimicrobial resistance; *C. difficile: Clostridioides difficile*; DALY: disability-adjusted life year; *E. faecium: Enterococcus faecium*; ExPEC: extraintestinal pathogenic *Escherichia coli*; *K. pneumoniae: Klebsiella pneumoniae; P. aeruginosa: Pseudomonas aeruginosa; S. aureus: Staphylococcus aureus;* S. Paratyphi: *Salmonella* Paratyphi; *S. pneumoniae: Streptococcus pneumoniae*.

Categories of impact: low (orange), moderate (light green) and high (green). The categories of impact were assigned as follows: for vaccine-averted deaths associated with AMR: low (<25 000), moderate (25 000–50 000), high (>50 000); for vaccine-averted DALYs associated with AMR: low (<1 million), moderate (1–5 million), high (>5 million); for vaccine-averted antibiotic use (DDDs): low (<10 million), moderate (10–30 million), high (>30 million); for vaccine-averted hospital costs associated with AMR (2019 US dollars): low (<US$ 250 million), moderate (US$ 250 million – US$ 1 billion), high (>US$ 1 billion); for vaccine-averted productivity losses associated with AMR (2019 US dollars): low (<US$ 1 billion), moderate (US$ 1–4 billion), high (>US$ 4 billion).

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1. Introduction

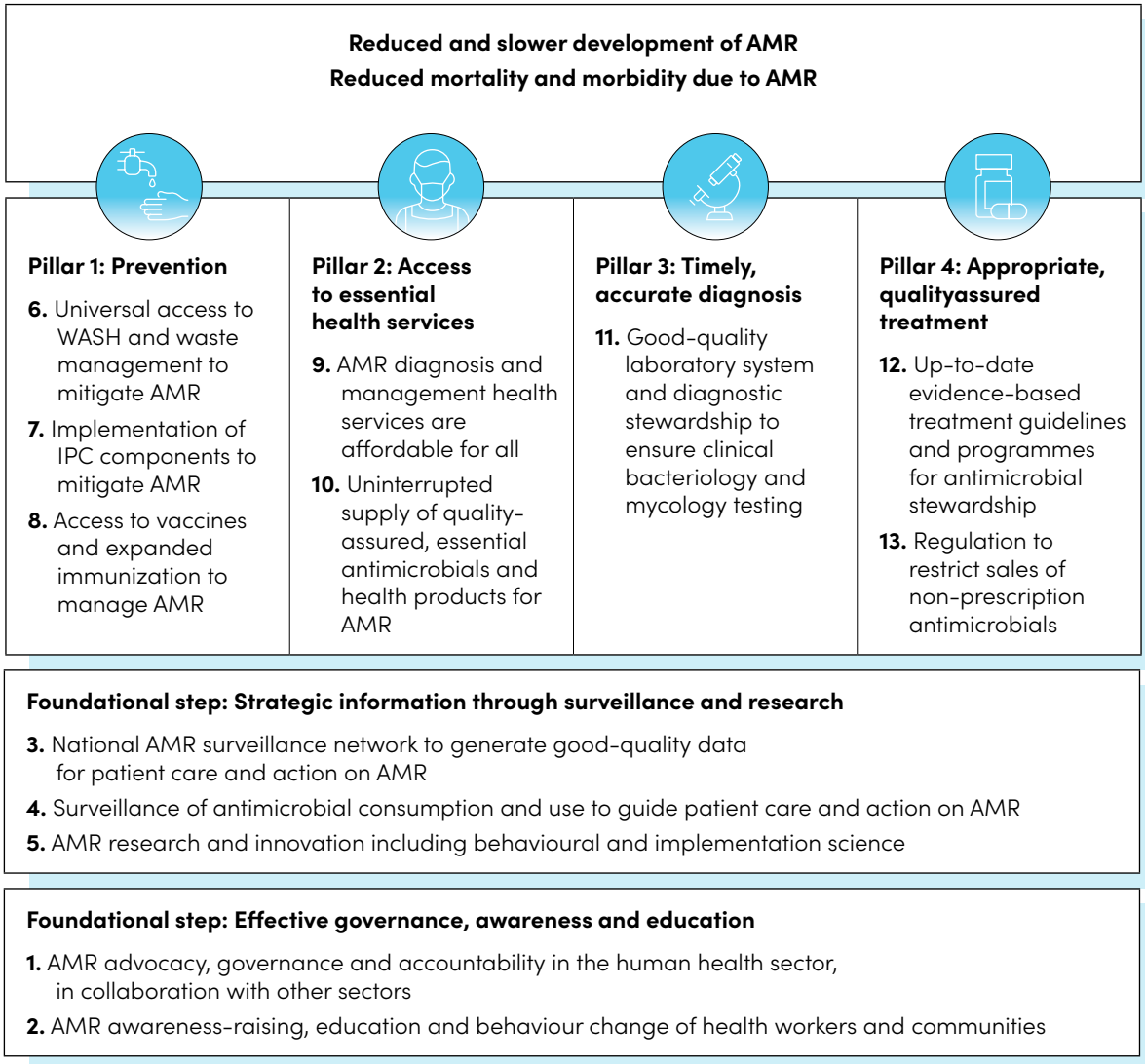
1.1 The burden of antimicrobial resistance and its challenges

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective, which in turn means that infections become difficult or impossible to treat, increasing the risk of disease spread, severe illness, disability and death. Resistant strains of pathogens (in humans, animals, plants and the environment) continue to emerge, making it more challenging to manage syndromes and diseases such as pneumonia, urinary tract infections (UTIs), typhoid fever or sexually transmitted diseases *(1)*. In 2019, an estimated 4.9 million deaths were linked to bacterial infections caused by resistant pathogens. Although the mortality burden of these drug-resistant infections is most pronounced on the African continent, followed by South-East Asia and Eastern Europe *(2)*, community mobility increases the chance of transmission of resistant pathogens to other continents. If unaddressed, AMR could impose a global cost of up to US$ 3.4 trillion annually by 2030, with the most severe impact expected in low- and middle-income countries (LMIC) *(3)*.

A key driver of AMR is the systematic misuse and overuse of antimicrobials in health care, animal health and agriculture *(1)*. The use of antimicrobial agents in animals is the largest contributor to the overall use of antimicrobials globally. The World Organisation for Animal Health (WOAH) has estimated that 84 500 tonnes of antimicrobials were used in the animal sector in 2019, but it found a 13% decrease in the use of antimicrobials in animals in 2019 compared with 2017 *(4)*. In contrast, global antibiotic consumption in humans increased by 65% from 2000 to 2015, mainly in LMIC, and is projected to triple by 2030 (when compared with 2015) without appropriate interventions *(5)*. A key challenge is ensuring improved, equitable access to antimicrobials, especially in LMIC, where people are more at risk of dying from a lack of access to appropriate antimicrobials than from resistant infections *(6)*. There is a need for strategies that enable and improve sustainable patient access to antibiotics globally, especially in areas with the highest burden of infectious disease. In addition, there is a need to tackle inappropriate antibiotic use, including in LMIC, resulting from insufficient diagnostic capabilities and health care infrastructure, sale of non-prescription antimicrobials, excessive dispensation and limited access to quality health care services and antimicrobial treatments.

AMR is a complex problem that cannot be managed in isolation. Management of AMR requires both sector-specific actions, in sectors such as human health, food production, animals and the environment, and a coordinated "One Health" approach across these sectors. The World Health Organization (WHO) has identified a core package of interventions to manage AMR in human health by putting people and their needs at the centre of the AMR response *(7)* (Fig. 1.1). The proposed interventions are embedded into four pillars: prevention of infections, including access to vaccines and expanded immunization; access to essential health services; timely, accurate diagnosis; and appropriate, quality-assured treatment. To effectively introduce these interventions, two foundational steps are critical: effective governance, awareness and education; and strategic information obtained through surveillance and research. These steps are needed to overcome barriers that people and health systems face in dealing with AMR.

Fig. 1.1. The WHO core package of interventions to manage AMR in human health



AMR: antimicrobial resistance; IPC: infection prevention and control; WASH: water, sanitation and hygiene; WHO: World Health Organization.

Source: Reproduced with permission from WHO, 2023 *(7)*.

Numerous calls for coordinated action against AMR have led to significant global, regional and country initiatives. In 2015, the World Health Assembly adopted a global action plan to address AMR *(8)*, urging Member States to develop national action plans. Soon after, WHO published a list of priority pathogens for the discovery, research and development (R&D) of new antimicrobials, identifying key antibiotic-resistant bacteria and tuberculosis (TB) as AMR priorities *(9)*; that list has recently been updated *(10)*. In 2017, the United Nations (UN) General Assembly passed a resolution to accelerate global action on AMR *(11)*. By March 2023, 122 countries had formulated national action plans to combat AMR *(12)*.

The *Global action plan on antimicrobial resistance* emphasizes improving awareness, strengthening knowledge, reducing infections, optimizing antimicrobial use and developing sustainable investment in new medical solutions *(8)*. In 2021, WHO published the action framework *Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance (13)*. This framework calls for actions to increase the use of existing vaccines, accelerate the development of new vaccines and foster data generation and knowledge sharing. Recognizing the potential of vaccines to reduce both infections and antibiotic use, as part of the 2023 *Global research agenda for antimicrobial resistance in human health (14)*, WHO recommends assessment of the impact of vaccines on:

- preventing colonization and infection by resistant pathogens (whether specifically targeted by the vaccine or not); and
- reducing the overall use of antimicrobial medicines, health care encounters and health system costs, among adults and children and across socioeconomic settings.

1.2 The role of vaccines in reducing AMR

1.2.1 Mechanisms through which vaccines reduce AMR

Vaccines prime the immune system to recognize and respond to pathogens that cause infection, thereby saving millions of lives every year. A modelling study suggests that, since 1974, vaccination against 14 pathogens in 194 WHO Member States has averted a remarkable 154 million deaths, including 146 million deaths among children aged under 5 years *(15)*. Goals, strategies and actions for developing and using vaccines have been described in Immunization Agenda 2030 (IA2030), a global immunization strategy *(16)*.

Vaccines can reduce the number of resistant infections through several interacting mechanisms or pathways (Fig. 1.2). The supporting evidence for these mechanisms from clinical trials, observational studies and modelling analyses was recently summarized by the One Health Trust *(17)*. Vaccines directly reduce the incidence of disease caused by both resistant and susceptible target pathogens. For example, the introduction of pneumococcal conjugate vaccines (PCVs) in the United States of America in 2000 led, within 4 years, to a 57% reduction in strains of *Streptococcus pneumoniae* resistant to multiple antibiotics, significantly reducing the incidence of antibiotic-treated illnesses in children *(18)*.

Vaccinated people will have fewer infections and thus will also be protected against potential complications from secondary infections that may trigger the use of antimicrobials or require admission to hospital. For example, influenza vaccination directly protects against influenza but also indirectly protects against secondary bacterial infections such as invasive pneumococcal disease, to which patients with influenza are more susceptible *(19)*.

For some pathogens, when a sufficiently high proportion of a population is vaccinated, the protection offered by vaccination can extend even to those who are not vaccinated. This is because of herd immunity, where vaccinated individuals do not transmit a pathogen to others, reducing the overall incidence of the disease in the community *(13)*.

Another pathway by which vaccines reduce AMR is by preventing people from becoming unwell and seeking treatment, resulting in less antibiotic use. In turn, this reduces selection pressure for the emergence and transmission of resistance, not just in the target pathogen but also in bystander members of the normal bacterial flora. This pathway also

encompasses inappropriate or unnecessary use of antibiotics that are empirically prescribed for viral infections *(13)*. For example, following a universal recommendation for free influenza vaccines in Ontario, Canada, increased uptake of influenza vaccination led to fewer antibiotic prescriptions for respiratory infections, even among unvaccinated groups, through herd immunity *(20)*.

In addition to these pathways, vaccines can also reduce AMR by reducing the opportunity for bacteria to exchange genetic material, including genes that confer resistance to antibiotics, with each other (horizontal gene transfer), and by decreasing the environmental or selective pressure that often leads to the survival and dominance of resistant strains over non-resistant ones *(21)*.

In summary, the objective of vaccination is to establish a healthier state with reduced circulation of pathogens and diseases, minimizing reliance on antibiotics. This benefits vulnerable populations; it also ensures the prolonged effectiveness of antimicrobials by mitigating the development of resistance to existing and new treatments.

1.2.2 Vaccines in the context of other approaches to contain AMR

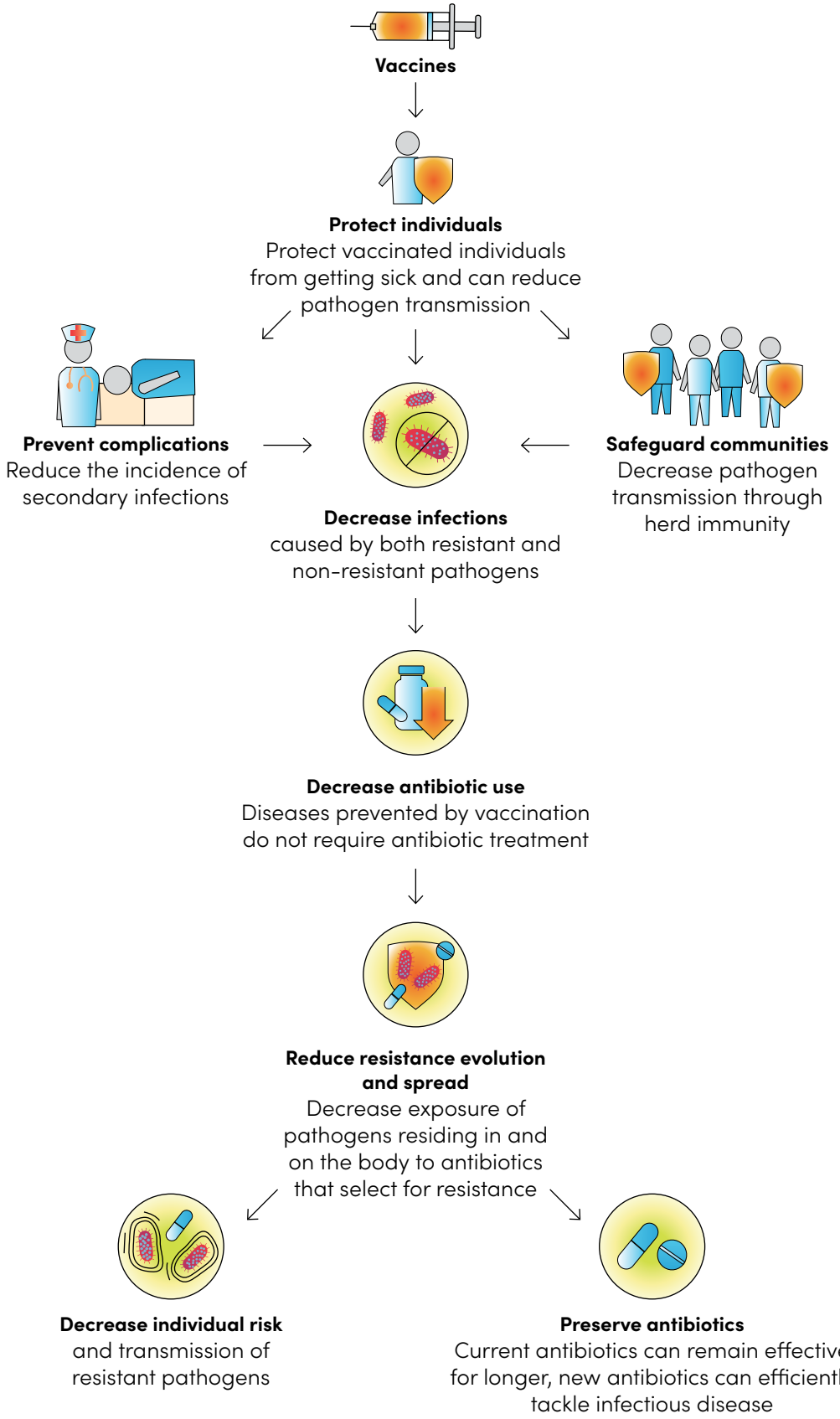
Vaccines usually prevent disease before it occurs, and typically they do this regardless of the antimicrobial susceptibility of the pathogen *(23)*. They rarely lead to resistance and, when resistance does occur, it spreads slowly. This is because vaccines are usually prophylactic, priming the immune system early and limiting pathogen replication and resistance development. Additionally, by targeting multiple antigens on distinct molecules, many of which are virulence factors in themselves, vaccines can disrupt the pathogen's ability to replicate and thrive as a virulent organism, reducing the likelihood that resistance will emerge *(24)*.

Although vaccines are important in reducing AMR, they must be integrated with other strategies, taking into account the limitations and complementary roles of each strategy. Access to vaccines and expanded use of vaccination to manage AMR is a core intervention of the prevention pillar of the people-centred approach to addressing AMR in human health *(7)*. Some pathogens cannot be tackled solely through vaccination, for various reasons: vaccines may be lacking for some pathogens; antimicrobial prescribing is often empirical; vaccine effectiveness may be limited and wane over time; and vaccine delivery and uptake can be challenging owing to individual suitability, sociocultural factors (including the values and preferences of the target population) and feasibility (including logistic requirements, such as cold chain). Therefore, vaccines need to be used together with other interventions that fall under the four pillars (prevention; access to essential health services; timely, accurate diagnosis; and appropriate, quality-assured treatment) *(7)*.

Vaccines can be integrated and work synergistically with other AMR interventions. In the context of access to essential health services, vaccines ensure healthier populations, reducing the demand for antimicrobial treatments and preserving the efficacy of those treatments. By preventing infections, vaccines indirectly support the sustainability of antimicrobial supplies, ensuring that these critical resources remain effective and accessible for future generations. In terms of diagnosis, vaccines play a supportive role by reducing the prevalence of infectious diseases that need differential diagnosis, thus possibly easing the burden on diagnostic services; in turn, this allows for more focused and efficient use of resources for AMR surveillance and management. Lastly, surveillance systems play a pivotal role in identifying and monitoring AMR trends, which can inform targeted vaccination and public health initiatives. By keeping track of resistance patterns, public health officials can prioritize the use of vaccines for pathogens that pose the greatest risk of AMR and adjust infection prevention and control (IPC) measures and stewardship guidelines accordingly.

This report focuses on vaccines intended for use in humans; however, the use of vaccines in the animal sector can also prevent infections, reduce antibiotic use and reduce selection for and spread of resistant genes. This is particularly important because most of the global antimicrobial consumption is happening in animal husbandry. To develop and effectively use vaccines to reduce antibiotic use, WOAH has identified a list of pathogens for which new or improved vaccines could have a significant impact on antibiotic use and animal health *(25)*.

Fig. 1.2. Impact of vaccines on AMR in humans: a schematic pathway



AMR: *antimicrobial resistance.*

Source: Reproduced with permission from Frost et al, 2022 *(22)*.

1.3 The need to estimate the role of vaccines in reducing AMR: a rationale for this report

So far, consideration of AMR-related value in evaluations of vaccines has been limited. Key questions that need to be answered are:

- Where do vaccines hold the greatest value in tackling AMR?
- Which vaccines should be prioritized for development, introduction and use alongside other core AMR interventions?

This report – *Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use* – is closely aligned with WHO's action framework for leveraging vaccines to reduce antibiotic use and prevent AMR *(13)*. It supports all three of the framework's priority areas by providing robust economic valuations of the potential impact of implementation or development of a range of vaccines. Further, this report addresses the broader benefits of vaccination in reducing antibiotic use and AMR, as part of assessments of the full value of vaccines *(26)*.

This report focuses on 24 pathogens and 44 vaccines that are either licensed by national regulatory agencies, in clinical development or hypothetical. By combining the knowledge of international experts with data and a robust methodology, the aim is to quantify the potential for these vaccines to reduce AMR, its effects and antibiotic use. Although this report focuses on human vaccines, similar analyses could be conducted to evaluate the role of animal vaccines in reducing and managing AMR.

Importantly, the report does not compare the relative impact across AMR interventions; rather, it considers different vaccines to identify those with the highest potential. As such, the findings will be helpful in prioritizing vaccines in terms of their impact on AMR, rather than in prioritizing different AMR interventions, including vaccines. The value estimates contained in this report will be useful for vaccine and AMR stakeholders (e.g. policy-makers, funders and researchers), guiding them to prioritize and channel their efforts effectively for maximum global impact against AMR.

1.4 Structure and audience

The structure of the report is as follows:

- methodology, including the feasibility of developing and delivering vaccines, and limitations of the methodology (Chapter 2);
- results for each of the evaluated criteria (Chapter 3);
- pathogen-specific results (Chapter 4); and
- conclusions and recommendations (Chapter 5).

The report is intended for use by funders, vaccine developers, researchers, national decision-makers, health workers, civil societies and regulators, as outlined below.

For **funders**, this report underscores the critical need to invest in vaccine R&D alongside other critical R&D needs, such as antibacterial agents and diagnostics, particularly for pathogens highly prevalent in LMIC. The report's findings highlight the substantial impact that vaccines can have on reducing the burden of AMR. Funders are encouraged to strategically allocate resources to these high-impact areas, recognizing the potential for significant health benefits and the broader global impact of reducing AMR. The report also suggests a need for diversified funding that supports both promising candidates and exploratory research for vaccines that are less developed but potentially impactful.

Vaccine developers can draw from this report a clear need to focus on pathogens with a significant threat of AMR. The report provides a roadmap for

prioritizing vaccine R&D efforts that can have the greatest impact on AMR. It also underscores the importance of considering the specific challenges in vaccine development for LMIC and adapting strategies to meet these unique needs. Thus, the report acts as a guide for directing resources and efforts for vaccine R&D in a way that aligns with global health priorities.

Researchers can interpret this report as a call to action to tackle the gaps in vaccine development for pathogens for which the feasibility of vaccine development and implementation is currently low. The report highlights the need for innovative approaches in research, such as developing new animal models and in vitro assays, and identifying correlates of protection, which are critical for advancing the field. Additionally, the report's emphasis on under-researched areas offers researchers a direction for future studies, particularly in enhancing our understanding of the broader impact of vaccines on AMR.

For **national decision-makers**, the report aims to provide valuable insights into how vaccines can be a key tool in a comprehensive strategy to combat AMR, alongside other critical interventions. It suggests a need for policies that facilitate the introduction and distribution of impactful vaccines, such as those against *Salmonella* Typhi, *S. pneumoniae*, malaria and influenza, and their integration into the broader framework of AMR mitigation strategies. The report also provides a foundation for developing or adjusting policies to optimize the impact of vaccines on reducing AMR, ensuring that policy decisions are grounded in robust evidence and strategic considerations.

Health workers can see in this report the critical role that vaccines play in reducing AMR and the important role of health workers in this process. The report underlines the need for health workers to be well informed about the latest vaccine developments and their implications for AMR, antibiotic stewardship and rational prescribing. It also suggests that health workers will be key players in administering these vaccines, monitoring their impact and educating patients about their importance, emphasizing the need for ongoing training and awareness about vaccines, as well as the comprehensive set of AMR interventions (e.g. IPC and water, sanitation and hygiene) to effectively combat AMR at the clinical level.

Civil society organizations – including patient advocacy groups, public health organizations and nongovernmental organizations (NGOs) – can use the findings of this report to advocate for greater access to and development of vaccines as a way to tackle AMR. By highlighting the potential impact of vaccines on reducing the incidence of both drug-resistant and drug-susceptible infections, civil societies can raise awareness among the public and policy-makers about the critical role vaccines play in reducing AMR. They can mobilize resources and support for vaccination campaigns, especially in LMIC where the burden of AMR is highest and vaccine access may be limited. Moreover, civil societies can leverage the report's recommendations to push for inclusive policies that ensure equitable vaccine distribution; and to foster collaborations between governments, the private sector and the international community to accelerate vaccine R&D. Through education and advocacy, civil societies can also work to dispel myths and misconceptions about vaccines, building public trust and vaccine uptake.

Regulators can use this report to make informed decisions in prioritizing vaccine approvals, especially for vaccines targeting pathogens with a significant threat of AMR. The data in this report can guide the assessment of vaccine dossiers, ensuring that considerations of vaccine impact on AMR are integral to the regulatory review process. This approach not only helps in supporting the approval of vaccines with a high potential to mitigate AMR but also in establishing criteria for clinical trial designs that include AMR-related outcomes. Additionally, regulators can use the report's findings to advocate for global harmonization in regulatory standards, speeding up access to effective vaccines worldwide. By integrating AMR considerations into their regulatory frameworks, regulatory agencies strengthen their role in public health protection, ensuring that vaccine development and approval processes contribute effectively to the global fight against AMR.

2. Methodology

2.1 How was this report developed?

This report was developed in response to the need to evaluate the contribution of various interventions, including vaccines, in reducing AMR, expressed in the Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance *(11)*. Two technical groups on vaccines and AMR were established, each with a 2-year time frame, to support and offer strategic guidance to WHO to appropriately evaluate, analyse and communicate the role of vaccines in reducing AMR. The methodologies included in the report were identified and discussed during meetings of the technical advisory groups in February 2019, December 2019, October 2020, November 2021 and January 2023. The interim results were presented and discussed in October 2020, November 2021 and January 2023. The communication strategy was discussed during the meeting in January 2023. Perspectives from industry experts were sought during a public hearing in March 2023. The report was shared with the technical advisory groups and other experts for initial review between December 2023 and January 2024, and for a second review in April 2024. All analyses and results were presented and discussed with the WHO Strategic and Technical Advisory Group for Antimicrobial Resistance in June 2023 and 2024, the Strategic Advisory Group of Experts on Immunization in September 2023, and the Product Development for Vaccines Advisory Committee in December 2022 and 2023.

2.2 Pathogen scope and assessment of feasibility to develop and deliver vaccines

The pathogens selected for evaluating the potential impact of vaccines on AMR were based on the WHO priority pathogens list for R&D of new antibiotics *(9)*, the AMR threat list published by the United States Centers for Disease Control and Prevention (CDC) *(27)* and the Indian Priority Pathogen List *(28)*. The final list of pathogens was agreed upon by the WHO Technical Advisory Group on Vaccines and AMR. Pathogens were selected based on their high incidence of resistant infections, high mortality associated with resistant infections or the high volume of antibiotics used in treating them. The final list comprised 24 pathogens: 19 bacteria, four viruses and the parasite *Plasmodium falciparum* (Table 2.1). Fungi were not included owing to a lack of data on the global burden of fungal infections, a lack of supporting data on the impact of vaccines on fungal infections and the limited number of vaccines in development for fungal infections.

For each of the 24 pathogens, a set of vaccine characteristics was identified to specify the target population, vaccine efficacy, coverage, duration of protection and disease presentation or strain prevented (Table 2.1). For the existing vaccines against *Haemophilus influenzae* type b (Hib), *S. pneumoniae* and *S.* Typhi, the analysis considered expanded coverage of the vaccines to meet the strategic priority on coverage and equity in IA2030 *(16)* or described an improved vaccine. For vaccines in development, hypothetical characteristics were identified based on preferred product characteristics (PPCs), target product profiles (TPPs), characteristics of advanced vaccine candidates, modelling studies that demonstrate vaccine impact, and expert consultations with the WHO Technical Advisory Group on Vaccines and AMR, and PATH. For pathogens with very early or no vaccine candidates in development, assumptions were made that such vaccines would reach 70% coverage, have 70% efficacy and protect for 5 years, unless experts indicated otherwise. All vaccines and their characteristics were reviewed by at least two pathogen and vaccine experts. Some pathogens have multiple disease presentations and would require different vaccines to prevent different disease presentations; for such pathogens, more than one vaccine was evaluated for its impact on AMR.

For vaccines with a highly diverse target population, or where the feasibility of reaching the target population is highly uncertain, the unrestricted use of vaccines against most of the syndromes in all individuals at risk of disease was evaluated. This was the case for seven pathogens, mostly nosocomial, for which the likeliness, feasibility and acceptability of vaccines in populations at high risk of nosocomial infections is challenging.

For each vaccine, an assessment was conducted to understand the feasibility of developing and delivering a vaccine. Three criteria were used to assess feasibility:

- Biological feasibility – Is the understanding of pathogen biology sufficient to develop a vaccine?
- Product development feasibility – Are there sufficient tools and assays to develop a vaccine?
- Access and implementation feasibility – Once developed, is there a sufficient pathway to a policy decision on the vaccine, introduction of the vaccine and sustainable financing?

For each criterion, indicators were identified with corresponding thresholds and definitions of very low, low, medium, high or very high feasibility (Fig. 2.1). The indicators and their thresholds were developed by PATH, the London School of Hygiene & Tropical Medicine and the WHO Technical Advisory Group on Vaccines and AMR. The assessments of feasibility were made by experts in the relevant pathogen. Although efforts were made to align ratings by sharing a common methodology and agreed thresholds, some subjectivity is inevitable. Different amounts of information are available for different pathogens, and challenges differ, although synergies also exist.

For each vaccine, a short name was developed; this short name, given in brackets [ ], is used consistently in graphs and tables throughout this report and in the data on the WHO website *(29)*.

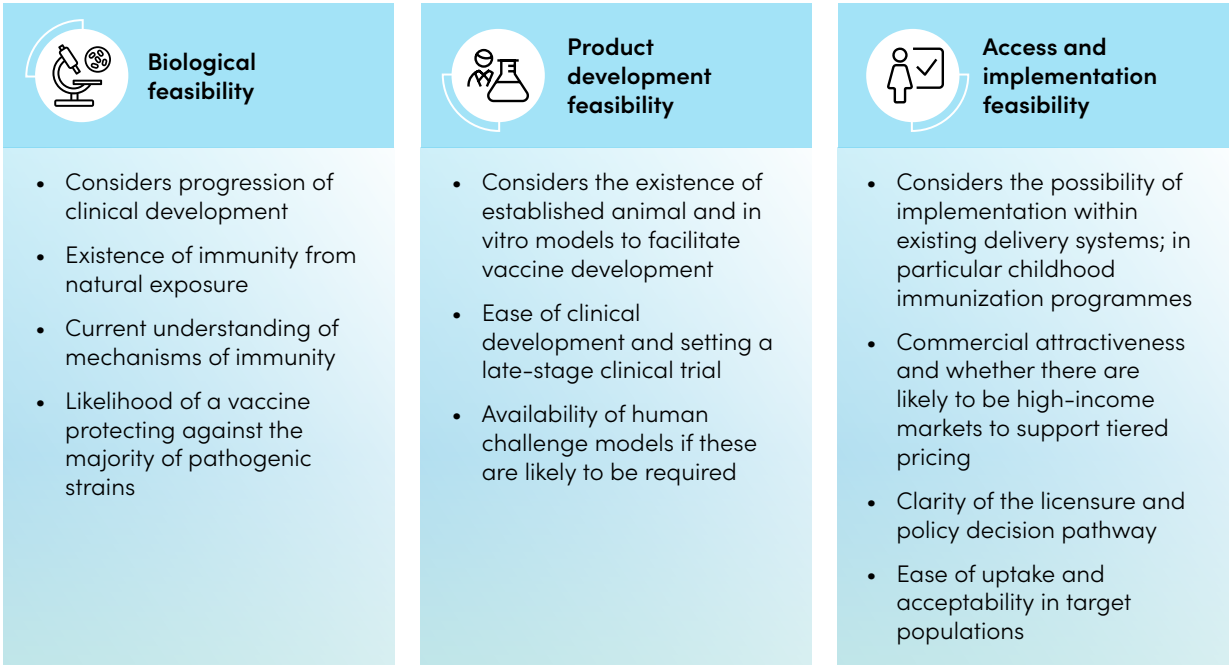
2.2.1 What was not evaluated?

The potential impact of the severe acute respiratory syndrome coronavirus 2 vaccines on antibiotic use was not evaluated owing to the dynamic nature of the virus at the time of writing, changes in treatment guidelines and dynamic changes in social behaviours that affect the spread of infection and, subsequently, antibiotic use.

The potential impact of Group B *Streptococcus* (GBS) vaccines on AMR was not evaluated because most GBS isolates remain susceptible to penicillin treatments. Although the use of penicillin treatments may have a bystander effect (i.e. increasing resistance in other bacteria), such evaluation was outside the scope of this report.

The impact of vaccines against dengue virus was not evaluated owing to limited evidence of antibiotic use associated with dengue infection and the disease burden being limited to specific regions. However, since the selection of pathogens for analysis, data have been published that demonstrate significant use of antibiotics in treating dengue infection *(30)*, modelling analyses of the impact of a dengue vaccine on AMR have been published *(31)*, and dengue disease incidence and outbreaks have increased *(32)*. Therefore, detailed analyses to understand the impact of dengue vaccines on antibiotic use and prevalence of AMR in bacteria should be conducted.

Fig. 2.1. Definition of feasibility of developing and delivering a vaccine based on biological, product development and access and implementation feasibility



Indicators and thresholds were developed for each of these criteria, and vaccines were rated from very low to very high feasibility.

Source: Reproduced with permission from WHO, 2022 *(33)*.

Table 2.1. Pathogens and their associated vaccines for which the impact on AMR was evaluated

Pathogen	Vaccine description and short name	Feasibility of vaccine development and implementation
	Bacteria	
Acinetobacter baumannii	A vaccine against **bloodstream** *A. baumannii* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [AB_1]	Low
	A vaccine against **bloodstream** *A. baumannii* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [AB_2]	Low
	A vaccine against *A. baumannii* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [AB_3]	Low
	A vaccine against *A. baumannii* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [AB_4]	Low
Campylobacter jejuni	A vaccine against *C. jejuni* infection given to 70% of infants, with 5-year efficacy of 70% [CJ]	Medium
Clostridioides difficile	A vaccine against *C. difficile* infection given to 70% of adults aged 45 years, with 5-year efficacy of 70% [CD]	Low
Enterococcus faecium	A vaccine against *E. faecium* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [EF_1]	Low
	A vaccine against *E. faecium* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [EF_2]	Low
Enterotoxigenic *Escherichia coli* (ETEC)	A vaccine against moderate to severe diarrhoea caused by ETEC infection given to 70% of infants, with 5-year efficacy of 60% [ETEC]	Medium
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	A vaccine against **bloodstream** ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_1]	Medium
	A vaccine against **bloodstream** ExPEC infection given to 70% **of all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_2]	Low
	A vaccine against **urinary tract** ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_3]	Medium
	A vaccine against **urinary tract** ExPEC infection given to 70% **of all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_4]	Low
	A vaccine against ExPEC **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_5]	Low
	A vaccine against ExPEC **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_6]	Low
Group A *Streptococcus* (GAS)	A vaccine against GAS infection given to 70% of infants, with 5-year efficacy of 70% [GAS]	Medium
Haemophilus influenzae type b (Hib)	A vaccine against Hib infection given to **74% of infants** (2019 coverage), with 5-year efficacy of 93% [Hib_1]	High
	A vaccine against Hib infection given to **90% of infants**, with 5-year efficacy of 93% [Hib_2]	High
Helicobacter pylori	A vaccine against *H. pylori* infection given to 70% of infants, with 5-year efficacy of 70% [HP]	Medium
Klebsiella pneumoniae	A vaccine against **bloodstream** *K. pneumoniae* infection given to 70% of **infants through maternal vaccination**, with 6-month efficacy of 70% [KP_1]	Medium
	A vaccine against *K. pneumoniae* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [KP_2]	Low
	A vaccine against *K. pneumoniae* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [KP_3]	Low

Pathogen	Vaccine description and short name	Feasibility of vaccine development and implementation
Mycobacterium tuberculosis	A vaccine against pulmonary *M. tuberculosis* disease given to 70% of **infants**, with 10-year **efficacy of 80%** and subsequent boosting to ensure lifelong protection [TB_1]	High
	A vaccine against pulmonary *M. tuberculosis* disease given to 70% of **children aged 10 years**, with 10-year **efficacy of 50%** and subsequent boosting to ensure lifelong protection [TB_2]	High
Neisseria gonorrhoeae	A vaccine against *N. gonorrhoeae* infection given to 70% of adolescents, with 10-year efficacy of 70% [NG]	High
Nontyphoidal *Salmonella*	A vaccine against nontyphoidal *Salmonella* infection given to 70% of infants, with 5-year efficacy of 80% [NTS]	Medium
Pseudomonas aeruginosa	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [PA_1]	Medium
	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [PA_2]	Low
Salmonella Paratyphi A	A vaccine against *S.* Paratyphi A infection given to 70% of infants in countries with a high typhoid burden, with 5-year efficacy of 70% [SPara]	Low
Salmonella Typhi	A vaccine against *S.* Typhi infection given to 70% of infants in countries with a high typhoid burden, with 15-year efficacy of 85% [ST]	High
Shigella	A vaccine against moderate to severe diarrhoea caused by *Shigella* infection given to 70% of infants, with 5-year efficacy of 60% [Shigella]	Medium
Staphylococcus aureus	A vaccine against *S. aureus* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 60% [SA_1]	Low
	A vaccine against *S. aureus* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 60% [SA_2]	Low
Streptococcus pneumoniae	A serotype-specific vaccine against *S. pneumoniae* infection given to **51% of infants** (2019 coverage), with 5-year efficacy of **25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype** [SP_1]	High
	A serotype-specific vaccine against *S. pneumoniae* infection given to **90% of infants**, with 5-year efficacy of **25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype** [SP_2]	High
	A serotype-specific vaccine against *S. pneumoniae* infection given to **90% of infants and elderly people**, with 5-year efficacy of **25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype** [SP_3]	High
	A non-serotype-specific vaccine against *S. pneumoniae* infection given to **90% of infants and elderly people**, with 5-year efficacy of **50% for lower respiratory tract infections and 70% for invasive pneumococcal disease** [SP_4]	Low
Parasite		
Plasmodium falciparum	A vaccine against clinical *P. falciparum* (malaria) infection given to 70% of infants, with 4-year efficacy of 40% [Malaria]	High
Viruses		
Influenza	A **seasonal maternal vaccine** against influenza infection given to 70% of pregnant women to protect neonates and infants, with 1-year efficacy of 70% [Influenza_1]	High
	A **universal vaccine** against type A influenza infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [Influenza_2]	Low
Norovirus	A vaccine against norovirus infection given to 70% of infants, with 5-year efficacy of 50% [Norovirus]	Medium
Rotavirus	An oral, live attenuated vaccine against rotavirus infection given to 90% of infants, with 2-year efficacy of 60% [Rotavirus]	High
Respiratory syncytial virus (RSV)	A vaccine against severe RSV infection given to 70% of **infants through maternal vaccination**, with 6-month efficacy of 70% [RSV_1]	High
	A vaccine against severe RSV infection given to 70% of **infants**, with 2-year efficacy of 70% [RSV_2]	High

Bold font is used to highlight the differences between vaccines targeting the same pathogen. AMR: antimicrobial resistance.

2.3 Potential impact of vaccines on AMR health burden

2.3.1 AMR burden data

The bacterial AMR burden estimates from the Global Research on Antimicrobial Resistance (GRAM) Project were used; these extensive estimates provided data for age-specific deaths and disability-adjusted life years (DALYs) associated with and attributable to AMR, by pathogen, infectious syndrome and region, for 2019 *(2)*. Statistical predictive modelling of data from systematic reviews, surveillance systems, hospital systems and other sources was used to generate these estimates of bacterial AMR burden for 88 pathogen–drug combinations for 204 countries in 2019. The AMR burden estimates for *Neisseria gonorrhoeae* include only morbidity, not mortality. Deaths attributable to AMR are those that could be averted if all drug-resistant infections were replaced by drug-sensitive infections. Data for the burden associated with AMR are presented; that is, deaths and DALYs that could be averted if all drug-resistant infections were replaced by no infections. Given that vaccines prevent both drug-resistant and drug-susceptible infections, it was decided that the AMR-associated burden is the appropriate metric for measuring the potential impact of vaccination on AMR burden.

2.3.2 Evaluated vaccines

This analysis focused on 16 pathogens – *Acinetobacter baumannii*, *Enterococcus faecium*, *Escherichia coli* (both enterotoxigenic *E. coli* [ETEC] and extraintestinal pathogenic *E. coli* [ExPEC]), Group A *Streptococcus* (GAS), Hib, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *N. gonorrhoeae*, nontyphoidal *Salmonella*, *Pseudomonas aeruginosa*, *Salmonella* Paratyphi A, *S.* Typhi, *Shigella* spp., *Staphylococcus aureus* and *S. pneumoniae*. The analysis included bacteria that are WHO priorities for AMR or that have a high AMR burden or a high mortality associated with AMR. For each pathogen, vaccine characteristics (the vaccine target population, efficacy, coverage, duration of protection and disease presentation prevented) were identified (Table 2.1 and the WHO website *(29)*). For the existing vaccines against Hib, *S. pneumoniae* and *S.* Typhi, the analysis considered expanded coverage of the vaccines to meet the strategic priority on coverage and equity in IA2030 *(16)*. For vaccines that are not yet available, hypothetical characteristics were identified based on PPCs, TPPs, characteristics of advanced vaccine candidates and consultations with expert working groups and pathogen experts (Table 2.1 and the WHO website *(29)*).

For pathogens with a highly diverse vaccine target population or highly uncertain feasibility of vaccine delivery, the estimated potential impact of the vaccines assumed that all individuals at risk would be vaccinated to protect against most of the syndromes. This was applicable to vaccines against *A. baumannii*, *E. faecium*, ExPEC, *K. pneumoniae* (all syndromes), *P. aeruginosa* and *S. aureus*. For *S. pneumoniae*, the high-potential scenario was explored; that is, administering a vaccine to elderly people with the highest disease burden.

2.3.3 Modelling process

A static proportional impact model was developed to estimate the vaccination impact in terms of reduction in age-specific AMR burden estimates for 2019 from the GRAM Project. A counterfactual[1] pre-vaccination scenario was estimated for diseases with existing vaccines and was adjusted for disease type specification before applying the vaccine impact. The reduction in pre-vaccination AMR burden after vaccination was calculated in direct proportion to efficacy, coverage, target population for protection and duration of protection of existing and potential future vaccines *(34)*.

For people of ages that lie within the duration of protection since the time of vaccination, the following equation was used:

AMR *burden* averted at age *i* = AMR *burden* at age *i* × pre-vaccination vaccine efficacy × vaccine coverage

[1] A counterfactual being something that has not happened or is not the case.

Vaccine-preventable deaths and DALYs attributable to and associated with AMR were estimated by region, infectious syndrome and pathogen, with 95% uncertainty intervals (UIs). The vaccine-preventable burden was estimated from the age of vaccination, under the assumption that vaccine-derived immunity would be sustained for the duration of protection of the corresponding vaccine. Vaccine waning dynamics were not considered because of limited evidence.

2.3.4 Estimating vaccine-preventable AMR burden of the target age group

The AMR burden data from the GRAM Project were disaggregated by age into the categories of early neonatal (first week after birth), late neonatal (2–4 weeks of age), postneonatal (5 weeks to <1 year), 1–4 years, 4–9 years … 90–94 years and 95 years and over. The reduction in AMR burden was estimated in direct proportion to efficacy, coverage, target population for protection and duration of protection of existing and potential future vaccines. It was considered that vaccinated individuals would gain vaccine-derived immunity 2 weeks after vaccination.

2.3.5 Estimating pre-vaccination burden for pathogens with existing vaccines

For the existing Hib vaccines and PCVs, the pre-vaccination (i.e. no vaccination) burden associated with and attributable to AMR in 2019 was estimated, using estimates of coverage and efficacy. The 2019 WHO/United Nations Children's Fund (UNICEF) Estimates of National Immunization Coverage (WUENIC) *(35)* and demography data from the United Nations World Population Prospects *(36)* were used to estimate vaccine coverage for Hib and PCV at the regional level. Vaccine efficacy estimates for the first dose, second dose and third dose scheduled at 6, 10 and 14 weeks for the Hib vaccines *(37, 38)* and PCVs *(39, 40)* were used. Applying the vaccine efficacies and regional coverage to the AMR burden data in 2019 made it possible to estimate the increase in AMR burden for the counterfactual scenario of no vaccination in direct proportion to efficacy, coverage, target population for protection and duration of protection.

The global and regional coverage of typhoid conjugate vaccine (TCV) and the post-vaccination impact were minimal in 2019 *(41)*; thus, TCV did not warrant additional estimation for the counterfactual scenario of no vaccination.

2.3.6 Disease type specification of the AMR burden

The GRAM Project estimates of AMR burden for *H. influenzae* were not stratified by serotype. Hib was responsible for about 95% of all infections from invasive *H. influenzae* among children aged under 5 years before the introduction of vaccines *(42)*. This 95% Hib proportion was applied to the total *H. influenzae* burden in the counterfactual scenario of no vaccination, to estimate the vaccine-preventable proportion of Hib-specific AMR burden of the total *H. influenzae* AMR burden in 2019.

The GRAM Project's AMR burden estimates do not differentiate between *E. coli* strains. Instead, the AMR burden estimates were stratified by symptoms. As ETEC and ExPEC are the two major *E. coli* strains that cause diarrhoea, the proportional contribution of ETEC to the AMR burden from *E. coli* causing diarrhoea was calculated, then the impact of the ETEC vaccine on reducing this burden was estimated.

2.3.7 Estimating the aggregated vaccine-preventable burden

To produce the aggregate estimates for the impact of vaccines by region and by infectious syndrome, the impact of all listed vaccines was estimated, provided the effects did not overlap (to avoid double counting). For situations where multiple vaccines target the same disease, infectious syndrome and age, the vaccines with greater efficacy were chosen for the estimates. However, for vaccines against *S. pneumoniae*, the analysis used the efficacy of the existing vaccine with increased coverage that met the strategic priority on coverage and equity in IA2030.

2.3.8 Uncertainty analysis

A Monte Carlo simulation of 400 runs (sufficient for results to converge) was conducted to propagate the uncertainty in the AMR burden, vaccine efficacy and coverage through the model simulations, to estimate the uncertainty in the projected outcomes of vaccination impact. Summary estimates are provided for vaccine-preventable deaths and DALYs

attributable to and associated with AMR by region, infectious syndrome and pathogen, with 95% UIs.

The estimates account for the uncertainties around AMR burden, efficacy and coverage. Based on data examination, the log-normal distribution was applied to the mean and the 2.5th and 97.5th percentiles of the AMR burden, to generate the randomly drawn values. For vaccine efficacy and coverage, the truncated normal distribution was used. For hypothetical vaccines, a variation of plus or minus 20% was applied to the vaccine efficacy and coverage. For existing vaccines, confidence intervals (CIs) of the vaccine efficacy from studies were used, and a variation of plus or minus 5% was applied to the vaccine coverage (i.e. coverage of existing vaccines increased to meet the strategic priority on coverage and equity in IA2030). When estimating the impact of the existing vaccines with current coverage (i.e. based on WUENIC estimates), only the uncertainty in efficacy was included because point estimates of actual coverage were used.

2.4 Potential impact of vaccines on antibiotic use

2.4.1 Summary

The potential impact of vaccines on antibiotic use was estimated for 23 pathogens and 43 vaccines. The impact on antibiotic use of a vaccine against *N. gonorrhoeae* was not evaluated because of limited data.

First, the total antibiotic use for each of 122 syndromes in the community and hospital settings was estimated. Second, the pathogen-attributable fraction for each of these syndromes was estimated (i.e. the proportion of each syndrome caused by a given pathogen). Finally, the proportional reduction in antibiotic use that could be achieved by vaccinating against each syndrome–pathogen combination was estimated.

2.4.2 Antibiotic use

The total antibiotic consumption in terms of defined daily dose (DDD) per 1000 people per year was extracted from the global study on antibiotic consumption and usage in humans from 2000 to 2018 *(43)*. This global study integrated data from multiple sources, including proprietary data provided by IQVIA *(44)*, published data from a 2018 WHO report on antibiotic use across 65 countries in 2015–2016 *(45)*, public data from the European Surveillance of Antimicrobial Consumption Network *(46)* and other studies *(43)*. Estimates of the proportion of antibiotics consumed in hospital versus retail settings were obtained for each year in 2000–2018 for all countries directly from the study authors *(43)*; these proportions had been estimated as part of the study but were not published.

2.4.3 Antibiotic use in communities

A systematic review and meta-analysis of indications for antibiotic prescriptions in primary care settings was conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines to determine antibiotic use in community settings. The systematic review included 82 studies with data on indications for antibiotic use in primary care settings (unpublished, available on request from the Product and Delivery Research [PDR] unit within the Immunization, Vaccines and Biologicals [IVB] Department at WHO). Data on "sick child" observations from service provision assessments for antibiotic use in children aged under 5 years were also included *(47)*. These observations were categorized into a hierarchy of indications for antibiotic use and were nested into several levels of detail; for example, wounds, burns and trauma were classified as injuries, which in turn fall under the broader category of skin, soft tissue, bone and joint-related indications.

Using the extracted and categorized data, a hierarchical Bayesian statistical model was fitted to the observations, using covariates for disease incidence from the Global Burden of Disease (GBD) study *(48)* as predictors for the incidence of the different antibiotic-treated syndromes. Using GBD data enabled incidence estimation of antibiotic use for countries not covered by the

review. Specifically, the Bayesian hierarchical model fit the incidence of each antibiotic-treated syndrome using fixed effects for each indication overall, by subregion and by country. Estimating effects by subregion and overall (i.e. globally) allowed estimates for the incidence of each antibiotic-treated syndrome to be pooled by subregion and globally, which in turn enabled antibiotic use estimates for countries excluded from the systematic review.

As data on antibiotic use for TB in primary care settings were limited, a separate model was developed to estimate antibiotic use for treating TB. Data from WHO's global TB database *(49)* and the GBD study *(48)* for 2000–2019 for all countries were used to derive age-specific TB incidence and were combined with WHO's consolidated guidelines on treatment regimens for TB *(50)*. Using these data, notified TB cases for each country and each year of the analysis were estimated as the sum of the reported number of new cases, relapse cases and cases with unknown previous TB treatment history, and the reported number of retreatments of previously treated patients (excluding relapse cases), as reported in WHO TB notifications data. Interpolation was done for the missing years for some countries, using the trends in TB incidence from the GBD study. For the age distribution of these cases, the reported age distributions for new and relapse cases in the WHO TB notifications dataset were used. Where age distributions were missing or coarse, GBD age-specific and country-specific incidence data were used to fill in the distributions. For resistance types, drug-susceptible infections were distinguished from multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB) infections, because guidelines for treatment of MDR-TB and RR-TB infections are similar, and the proportion of cases that were extensively drug-resistant (XDR) or pre-XDR was negligibly low. Each notified TB case was assumed to be treated according to WHO guidelines for the infection's susceptibility profile (drug-susceptible TB versus MDR/RR-TB) to calculate the volume of antibiotics used for TB treatment.

The etiology of selected community syndromes was compiled from existing systematic reviews and microbiological databases categorized by global region (unpublished, available on request from IVB/PDR). The syndromes were mapped to etiologies by feasibility; this mapping process was guided by the vaccines and their characteristics as evaluated in this report. For pneumonia, a published systematic review of incidence and causative pathogens for childhood pneumonia was used *(51)*. For gastrointestinal infections, evidence was synthesized from the Global Enteric Multicenter Study on the incidence and etiology of clinically attended, antibiotic-treated diarrhoea among children aged under 5 years in LMIC *(52)*. For otitis media, evidence was synthesized from a published systematic review of prevalence and AMR of bacteria in children with acute otitis media and ear discharge *(53)*. For pharyngotonsillitis, evidence was synthesized from increased identification of GAS in a prospective case–control study in primary health care settings in Kronoberg County, Sweden *(54)*. For skin and soft tissue infections, evidence was synthesized from the SENTRY Microbiology Visualization Platform of specimens recovered from skin and soft tissue infections in prevalence mode from children aged 0–4 years *(55)*. For UTIs, evidence was synthesized from a published systematic review and meta-analysis of etiological studies of community-acquired UTIs *(56)*. For malaria, evidence was synthesized from the *World malaria report 2023 (57)*, which included the proportion of malaria cases attributable to *Plasmodium vivax* for 2000–2020 by WHO region. For typhoid and paratyphoid fever, evidence was synthesized from the GBD study *(48)*, which included the relative incidence of typhoid and paratyphoid fevers *(48)*. All TB cases were attributed to *M. tuberculosis*.

2.4.4 Antibiotic use in hospitals

The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS) was used to calculate antibiotic use in hospital settings *(58)*. The Global-PPS reports the prevalence of antimicrobial use for more than 500 participating hospitals in 89 countries. A Bayesian hierarchical statistical model, similar to the model used to estimate antibiotic use in the community, was fitted to observations of the number of patients using antibiotics across 47 diagnostic codes used by the Global-PPS. To estimate etiologies for hospital conditions, data from the Global-PPS that provided the proportion under each diagnostic code for which a microbiological diagnosis was made, based on identification of one or more of 53 microbial pathogens, were used. This made it possible to directly estimate the etiology across the 47 syndromes, based on the pathogens that were isolated from patients with each diagnosis.

2.4.5 The impact of vaccines on antibiotic use

Vaccine profiles that defined the pathogen, syndromes, age group, coverage and efficacy for each vaccine were developed through WHO technical advisory group consultations (Table 2.1). Triangulation of data on antibiotic use in community and hospital settings and the estimates of vaccine-preventable AMR health burden were synthesized in a static model, to estimate the proportional reduction in antibiotic use achievable by vaccination against each syndrome–pathogen combination. Specifically, the reduction in antibiotic consumption for a given age group, syndrome, pathogen and population was calculated as VE × C × D, where VE is the vaccine efficacy for the given syndrome, C is the proportion of the age group vaccinated and D is the number of DDDs consumed for treatment of the specific syndrome or syndromes and pathogen in a given age group and setting.

2.5 Potential impact of vaccines on AMR economic burden

2.5.1 Summary

The economic burden per case of disease caused by infection associated with AMR was estimated. The methodology was developed based on previous scientific frameworks *(59)*. To quantify the potential vaccine-preventable economic burden, these estimates were combined with the estimates of AMR health burden (Sections 2.3 and 3.1) for each pathogen and region of interest. The analyses focused on hospital costs (due to cases) and labour productivity losses (due to excess deaths) associated with AMR; that is, the economic burden of an AMR infection compared with the economic burden of no infection.

The analysis was based on data and cost estimates from a variety of countries and settings, presented in different currencies and from different years. Therefore, all monetary values were inflated based on the relevant country's gross domestic product (GDP) and converted to a figure in 2019 US dollars.

This impact of vaccines on AMR economic burden is reported following the Consolidated Health Economic Evaluation Reporting (CHEERS) guidance for health economic evaluations *(60)*. The analysis focuses on key bacterial pathogens for which there is known literature on the health and economic burden associated with AMR and for which the impact on AMR health burden was evaluated (Sections 2.3 and 3.1) *(61)*. The evaluated pathogens, syndromes and antibiotic classes are listed in Table 2.2.

Table 2.2. Pathogens, syndromes and antibiotic classes evaluated

Pathogen	Syndromes	Resistance pattern or patterns
Acinetobacter baumannii	BSI, bacterial skin infections, cardiac infections, LRI, thorax infections and UTI	3G cephalosporins, carbapenems and fluoroquinolones
Enterococcus faecium	BSI, bone and joint infections, cardiac infections, IAI and UTI	Fluoroquinolones and glycopeptides
Escherichia coli (ETEC and ExPEC)	BSI, bacterial skin infections, bone and joint infections, CNS infections, cardiac infections, diarrhoea, IAI, LRI, thorax infections and UTI	3G cephalosporins, carbapenems and fluoroquinolones
Group A *Streptococcus*	BSI, bacterial skin infections, bone and joint infections, and cardiac infections	Macrolides
Haemophilus influenzae	CNS infections, LRI and thorax infections	3G cephalosporins
Klebsiella pneumoniae	BSI, bacterial skin infections, bone and joint infections, CNS infections, cardiac infections, IAI, LRI, thorax infections and UTI	3G cephalosporins, carbapenems and fluoroquinolones
Mycobacterium tuberculosis	Tuberculosis	Multidrug resistance
Pseudomonas aeruginosa	BSI, bacterial skin infections, bone and joint infections, cardiac infections, IAI, LRI, thorax infections and UTI	3G cephalosporins, carbapenems and fluoroquinolones
Salmonella (Paratyphi A, Typhi and nontyphoidal)	BSI, cardiac infections, typhoid, paratyphoid and iNTS	Fluoroquinolones or MDR in *Salmonella*
Shigella spp.	Diarrhoea	Fluoroquinolones
Staphylococcus aureus	BSI, bacterial skin infections, bone and joint infections, CNS infections, cardiac infections, IAI, LRI, thorax infections and UTI	Fluoroquinolones, glycopeptides, macrolides and penicillins
Streptococcus pneumoniae	LRI, thorax infections, BSI, CNS infections and cardiac infections	3G cephalosporins, carbapenems, fluoroquinolones, macrolides and penicillins

3G: third-generation; BSI: bloodstream infections; CNS: central nervous system; ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *Escherichia coli*; IAI: intra-abdominal infections; iNTS: invasive nontyphoidal *Salmonella*; LRI: lower respiratory tract infections; MDR: multidrug resistance; spp.: species; UTI: urinary tract infections.

2.5.2 Hospital unit costs

The hospital unit costs (informed by an overall hospital cost per case or length of hospital stay) associated with AMR for the selected bacteria, antibiotic classes and WHO regions were identified by a rapid review of systematic reviews. A total of 180 studies reporting 365 estimates of hospital costs or length of hospital stay were identified *(62)*. For the selected pathogens and six WHO regions, the reviews focused on penicillin and glycopeptide resistance in gram-positive bacteria, third-generation cephalosporin (3GC) and carbapenem resistance in gram-negative bacteria and MDR in TB (Table 2.2). To convert the estimates of hospital length of stay into hospital costs associated with AMR, each data point for hospital length of stay was multiplied by the estimated bed-day cost provided by WHO-CHOICE (CHOosing Interventions that are Cost-Effective), relative to the country where a study was conducted *(63)*.

The aim was to collect data on hospital costs or length of stay associated with AMR for each drug–pathogen combination for each country. If such data were not available, this was done using costing estimates for the same drug–pathogen combination from another country within the same WHO-CHOICE classification. If this information was not available, the analysis used estimates from the same WHO region or World Bank Income Group; failing this, global average values were used. Where estimates for drug–pathogen combinations were not available, the analysis used estimates of costs for a pathogen of the same antibiotic class resistance (gram-positive or gram-negative) and same syndrome, prioritizing cost estimates from the same WHO-CHOICE classification. All extracted

estimates were pooled using random-effects meta-analysis. Later, 1000 random samples of length of stay were drawn from the uncertainty distribution of the pooled estimate (assuming a normal distribution) and combined with 1000 random samples drawn from the distribution of hospital bed-day costs (assuming log-normal distributions) to estimate the mean and 95% UI. A numerical indicator of the strength of evidence behind each outcome was created by weighting the number of studies used in the meta-analysis by proximity to the country of interest *(64)*.

National estimates for hospital costs were averaged to WHO regions, weighted by 2019 population values *(65)*. All monetary values are reported in 2019 US dollars. To convert cost estimates of different currencies and years into 2019 US dollars, the World Bank data for purchasing power parity exchange rates and local currency unit exchange rates were used. The inflation and exchange rate conversion process converted cost estimates from study currency to national or local currency, inflated based on national GDP deflation data (or Eurozone equivalents if applicable), and subsequently converted them into US dollars. If data were missing, US dollar values and US GDP deflation estimates were used.

2.5.3 Labour productivity unit costs

Labour productivity costs were estimated using the human capital method *(66)*. Mean nominal monthly earnings of employees and employment-to-population ratios (from 1990 to 2019) were extracted from the International Labour Organization and aggregated by sex and age *(67)*. Monthly earnings, adjusted by employment ratios, were calculated for the working population and used as proxies of productivity costs per working day lost. It was assumed that the working population was aged 15–64 years. Mean annual growth rates were considered for both wage and employment ratio estimates, where 2019 values were not available.

2.5.4 Burden of drug-resistant infections and potential impact of vaccination

The included combinations of drug, pathogen, syndrome and country were those included in the health impact analysis of pre- and post-vaccination scenarios for each country in 2019 *(61)*. Point estimates of pre- and post-vaccination scenarios were used. These included the combinations of drug, pathogen, syndrome and country listed in Table 2.1, focusing on the AMR-associated burden (where no infection is the counterfactual).

Data on hospital costs or length of stay were limited for *Salmonella*, *Shigella* or AMR associated with gastrointestinal-related illnesses, GAS and Hib. Instead, a desk review was conducted to evaluate the length of stay in hospital for all patients with *Salmonella* infections associated with AMR. Results of an expert elicitation exercise examining the impacts on length of stay of AMR bacteria linked to gastrointestinal-related illness, GAS and Hib were used.

When combining health impact and economic outcomes, length of stay estimates were sampled from a truncated normal distribution and combined with WHO-CHOICE unit costs. To use all available data in estimating the associated burden of AMR, in cases where unit costs for associated AMR burden were not available, but attributable AMR burden estimates were available, adjustment factors were calculated by converting excess length of stay with a susceptible infection when compared with no infection. These adjustment factors were then used to adjust the attributable AMR burden to the associated AMR burden. To estimate the potential impact of vaccines on hospital costs, the analysis first estimated the proportion of cases treated in hospitals from region–syndrome-specific data in previous global AMR analyses and expert elicitation *(2)*. These estimates were then combined with the unit hospital costs associated with AMR at the country level.

Labour productivity losses were calculated by first combining deaths reported by WHO region and age group, and data reporting average length of life per WHO region (to estimate working life years lost), then with unit costs per person per year, calculated as above *(68, 69)*.

The time horizon was one year, with the impact of cases and deaths in 2019 being modelled (the lifetime horizon impact of those deaths is incorporated in labour productivity calculations). Bed-days and potential working life years lost (undiscounted and not considering employment rates) were also calculated, allowing for the quantification of unadjusted or maximum potential, direct capacity impacts. Medians and interquartile ranges of the hospital economic burden were estimated. Point estimates were calculated for labour productivity because only point estimates in both the unit costs and incidence were available at the time of analysis.

2.6 Limitations

The findings of this report are primarily based on modelling analyses rather than direct observations, which presents inherent limitations. A significant constraint is the reliance on estimates from the GRAM Project for determining the bacterial AMR burden. Despite being the most detailed source to date, the GRAM Project's data, especially from LMIC, are notably limited, affecting the robustness of these estimates. Specifically, the GRAM Project lacks data on TB associated with HIV, creating a significant gap in understanding the full scope of AMR. Similarly, DALYs reported by the GRAM Project often do not encapsulate the full morbidity associated with evaluated pathogens. Some examples include wasting and stunting caused by enteric pathogens, invasive nontyphoidal *Salmonella* associated with malaria, rheumatic heart disease after an infection with GAS, or infertility and ectopic pregnancy caused by an infection with *N. gonorrhoeae*. Hence, if morbidity outcomes were fully accounted for, the true impact of vaccines on DALYs associated with AMR could be markedly higher.

The approach to estimating the impact of vaccines on AMR is static, focusing solely on the direct effects and not accounting for indirect vaccine benefits, such as herd immunity. This methodology probably leads to an underestimation of the true impact of vaccines on AMR. The choice of modelling approach was dictated by a need to analyse and compare multiple vaccines, which needed a standardized approach and did not allow for incorporation of pathogen-specific characteristics and disease dynamics into the model.

The analyses of vaccine impact on AMR used 2019 WUENIC coverage (for existing vaccines) or assumed moderate to high coverage of vaccines (for new vaccines). This assumption probably overestimates vaccine impact on AMR given the increasing number of available vaccines, challenges that countries are facing with financing and delivering vaccines, and increasing vaccine hesitancy. The analyses only modelled the impact of routine vaccination on AMR. Additional analyses evaluating the impact of vaccination campaigns on AMR would probably increase the estimated impact of vaccines on AMR.

The report probably underestimates the impact of vaccines on AMR because it does not explore how the vaccine-averted reduction in antibiotic use impacts future AMR prevalence, nor does it consider the effects of vaccines on AMR for pathogens not directly targeted by vaccines (e.g. an influenza vaccine to protect against bacterial infections with *S. pneumoniae*). These effects were not considered because of the complexities involved in such analyses, requiring a different methodological approach that was beyond the scope of the report.

This report evaluates the impact of vaccines on averting antibiotic use. Except in the case of *M. tuberculosis*, the report did not evaluate the impact of vaccines on antimicrobial use (e.g. antiviral or antiparasitic medicines). Also, the report did not evaluate the effect of vaccine-averted secondary infections that result in empirical antibiotic treatment. Had these two issues been included, they would probably have increased the estimated vaccine impact on AMR.

Finally, the report does not address the impact of vaccines on drug-susceptible pathogens. This is because vaccine impact models have already been conducted for some drug-susceptible pathogens and vaccines. As such, the results presented here need to be considered in the context of the overall vaccine effect, including herd protection and vaccine impact on drug-susceptible pathogens.

3. Results of vaccine impact modelling on AMR by criterion

3.1 Potential vaccine impact on AMR health burden

Vaccines can reduce the number of infections caused by drug-susceptible and drug-resistant pathogens, disease and deaths; hence, they can reduce the overall pathogen burden in a population in which appropriate vaccine coverage is achieved. This reduction in pathogen burden and clinical infection will, in part, mitigate the impact of AMR on that population.

The GRAM Project estimated the deaths and DALYs attributable to and associated with AMR. The study estimated that 1.27 (95% UI: 0.91–1.7) million deaths and 47.9 (95% UI: 35–64) million DALYs were attributable to bacterial AMR, and that 4.95 (95% UI: 3.6–6.6) million deaths and 192 (95% UI: 146–248) million DALYs were associated with bacterial AMR in 2019 *(70)*. The term "burden attributable to AMR" refers to deaths and DALYs that could be averted if all drug-resistant infections were replaced by drug-susceptible infections, whereas "burden associated with AMR" refers to deaths and DALYs that could be averted if all drug-resistant infections were replaced by no infections.

As vaccines prevent diseases, this chapter reports on the potential impact of vaccines on deaths and DALYs associated with AMR rather than attributed to AMR. Using the GRAM Project data from 2019, it presents estimates of the vaccine-preventable bacterial AMR health burden (deaths and DALYs) for existing and future vaccines by pathogen and by infectious syndrome at the regional and global levels. Analyses to understand the potential impact of vaccines on AMR health burden from viruses, fungi or parasites were not conducted owing to a lack of data. Data accompanying this chapter can be viewed on the WHO website *(29)*. The findings have been peer-reviewed and published *(61)*.

3.1.1 Methodology

The vaccine-preventable bacterial AMR burden was estimated for a total of 34 different vaccines against 16 bacterial pathogens. For each vaccine, the associated short name is given in brackets [ ]; this short name is used consistently in graphs and tables throughout this document, and in the data on the WHO website *(29)*. The potential impact of existing and future vaccines at the regional and global levels, by pathogen and infectious syndrome, was estimated using a static proportional impact model (Fig. 3.1), in which the reduction in AMR burden after vaccination was calculated as being proportionate to the efficacy of the vaccine, the coverage level achieved in the target population and the duration of protection from existing and potential future vaccines *(61)*. Because vaccines reduce the burden from both drug-resistant and drug-susceptible pathogens, the AMR-associated burden was used in this report as the metric for measuring the impact of vaccination on AMR. The health burden caused by drug-susceptible pathogens and averted by vaccines is presented on the WHO website *(29)*.

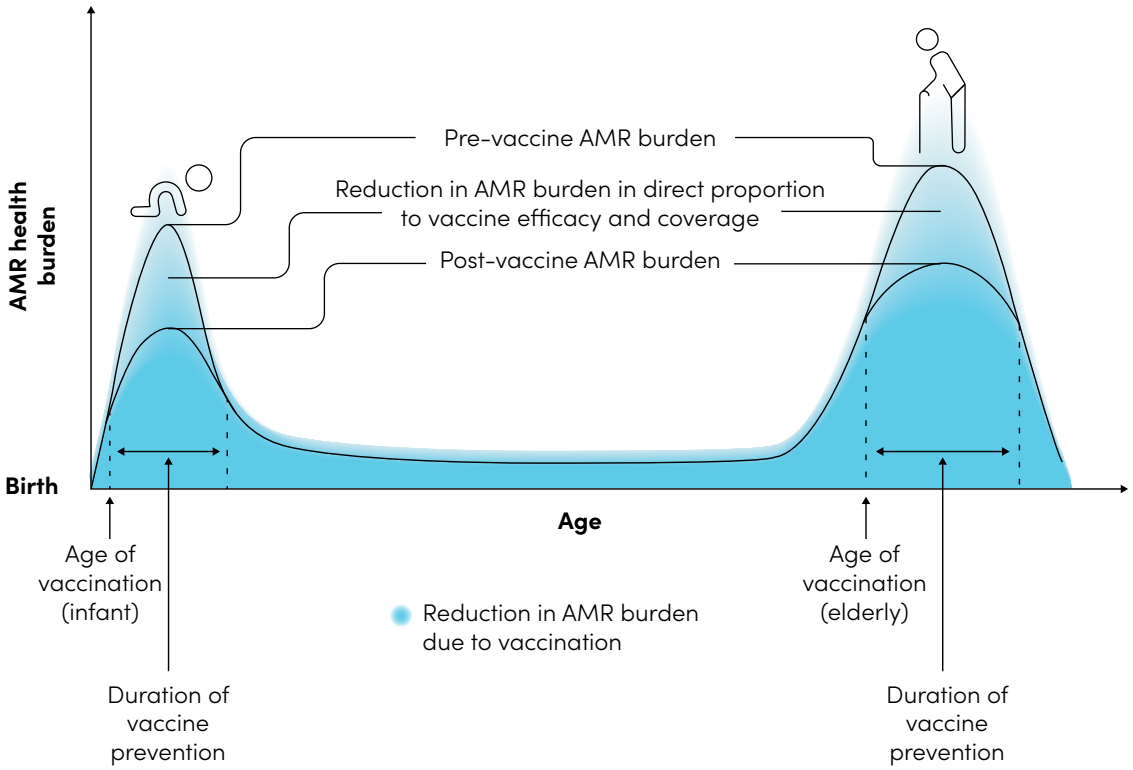
Table 2.1 in Chapter 2 presents the key characteristics for vaccines against 16 bacterial pathogens. These characteristics are vaccine efficacy, duration of protection for vaccine-derived immunity, vaccine coverage levels, target population or populations and the indication targeted by the vaccine. Vaccine characteristics were identified through published PPCs (where available), modelling studies that help inform the use and value of a vaccine, late-stage vaccine candidates currently in development, and analyses of clinical trials and post-licensure studies for those vaccines that are already licensed. Final consensus for the range of vaccine characteristics was reached through expert consultation.

As discussed in Chapter 2, the analysis was conducted for 16 pathogens to evaluate the effect of primary vaccination of specific age groups against specific syndromes; however, for seven of those pathogens, the vaccine impact was also evaluated for all age groups and against all infectious syndromes combined (Table 3.2 and Table 3.3). This high-potential scenario was evaluated for vaccines where delivery platforms or target groups are highly uncertain; for example, for pathogens that cause nosocomial infections.

3.1.2 Potential vaccine impact on AMR health burden

Based on the identified vaccine characteristics, vaccines against the 16 pathogens may prevent 510 000 (95% UI: 490 000–540 000) deaths and 28 (95% UI: 27–29) million DALYs associated with AMR (Fig. 3.2) (vaccines indicated with a superscript "b" in Tables 3.1–3.3). When the use of vaccines is expanded to all target populations at risk of infection, an additional 1.2 (1.18–1.23) million deaths and 37 (36–39) million DALYs associated with AMR could be averted. The non-serotype-specific vaccine against *S. pneumoniae* [SP_4], with increased efficacy against lower respiratory tract infections, would have the highest impact on both AMR-associated deaths and DALYs. Similarly, an infant vaccine against *M. tuberculosis* [TB_1] would have a significant impact on AMR-associated deaths and DALYs. The current *S. pneumoniae* vaccine given to children and elderly people, with 90% global coverage in both populations [SP_3], would have a significant incremental impact on averting DALYs, in addition to a measurable impact through averting AMR-associated deaths.

Fig. 3.1. A model to estimate vaccine impact on AMR health burden[a]



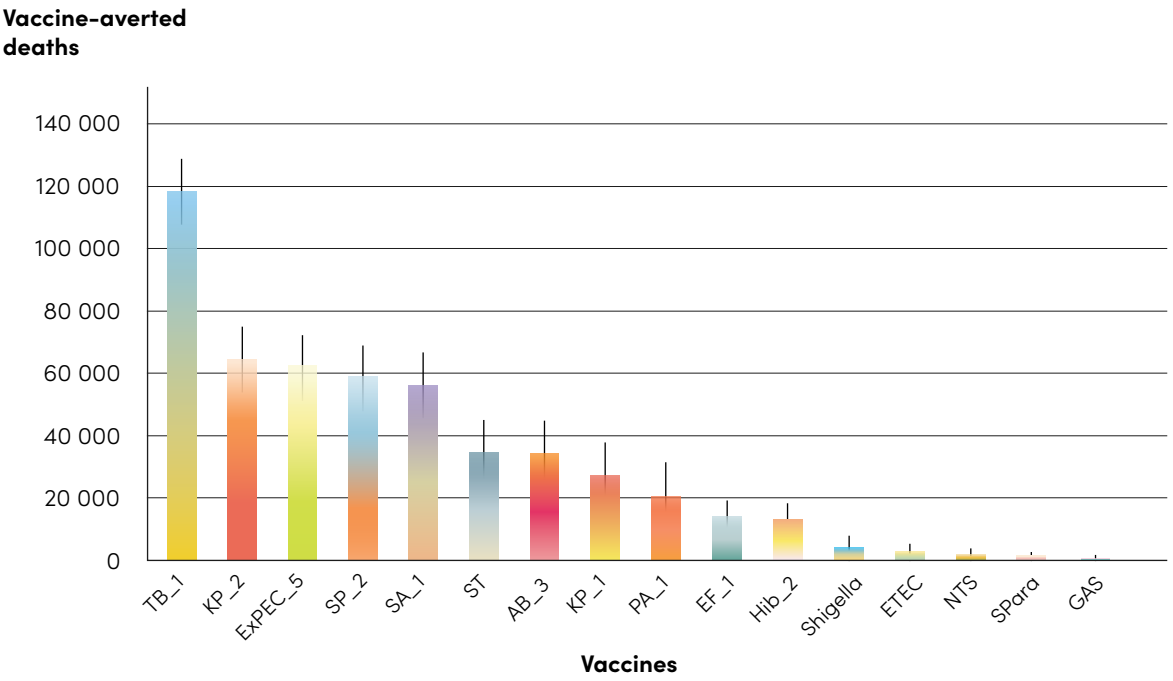
AMR: antimicrobial resistance.

[a] Static proportional impact model to estimate the reduction in AMR burden after vaccination in direct proportion to efficacy, coverage, target population for protection and duration of protection from existing and potential future vaccines. The AMR burden among infants may be higher or lower than the AMR burden among elderly people and depends on the pathogen. For example, the AMR burden for *Streptococcus pneumoniae* and *Haemophilus influenzae* is higher among infants than among elderly people, whereas the AMR burden for *Staphylococcus aureus* and *Acinetobacter baumannii* is lower among infants than among elderly people.

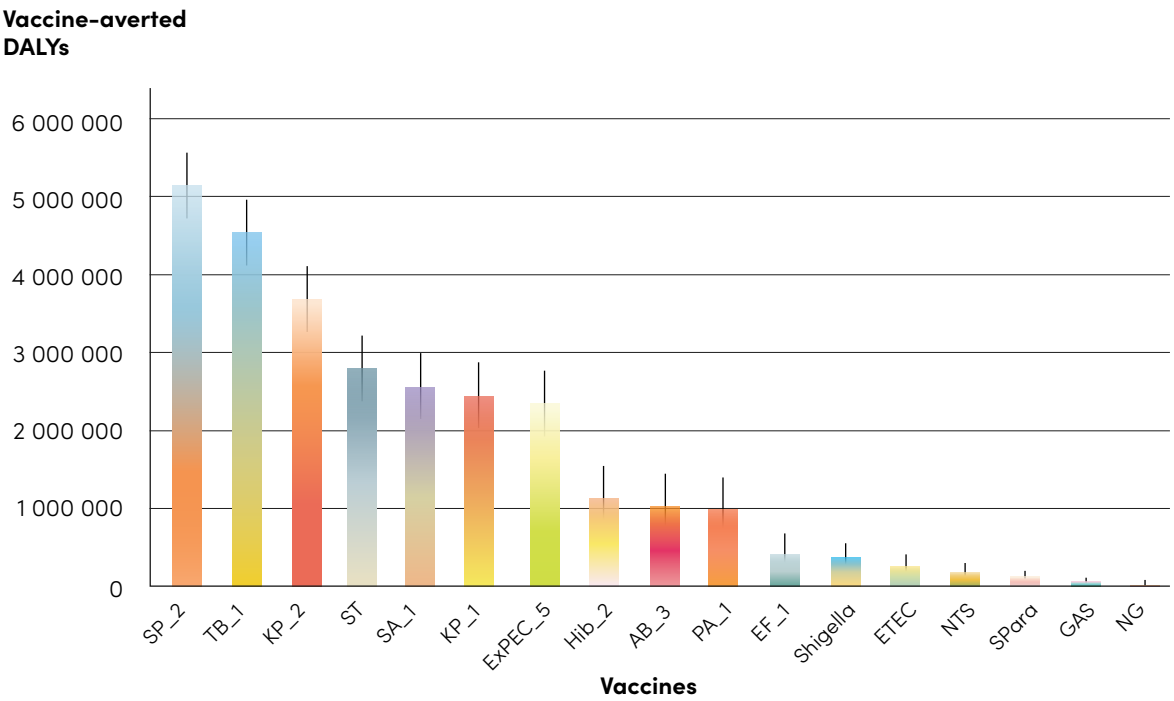
Source: reproduced with permission from Kim et al. 2023 *(61)*.

Fig. 3.2. Potential vaccine impact on AMR health burden by vaccine[a]

(a) Vaccine-preventable deaths associated with AMR, globally, in 2019



(b) Vaccine-preventable DALYs associated with AMR, globally, in 2019



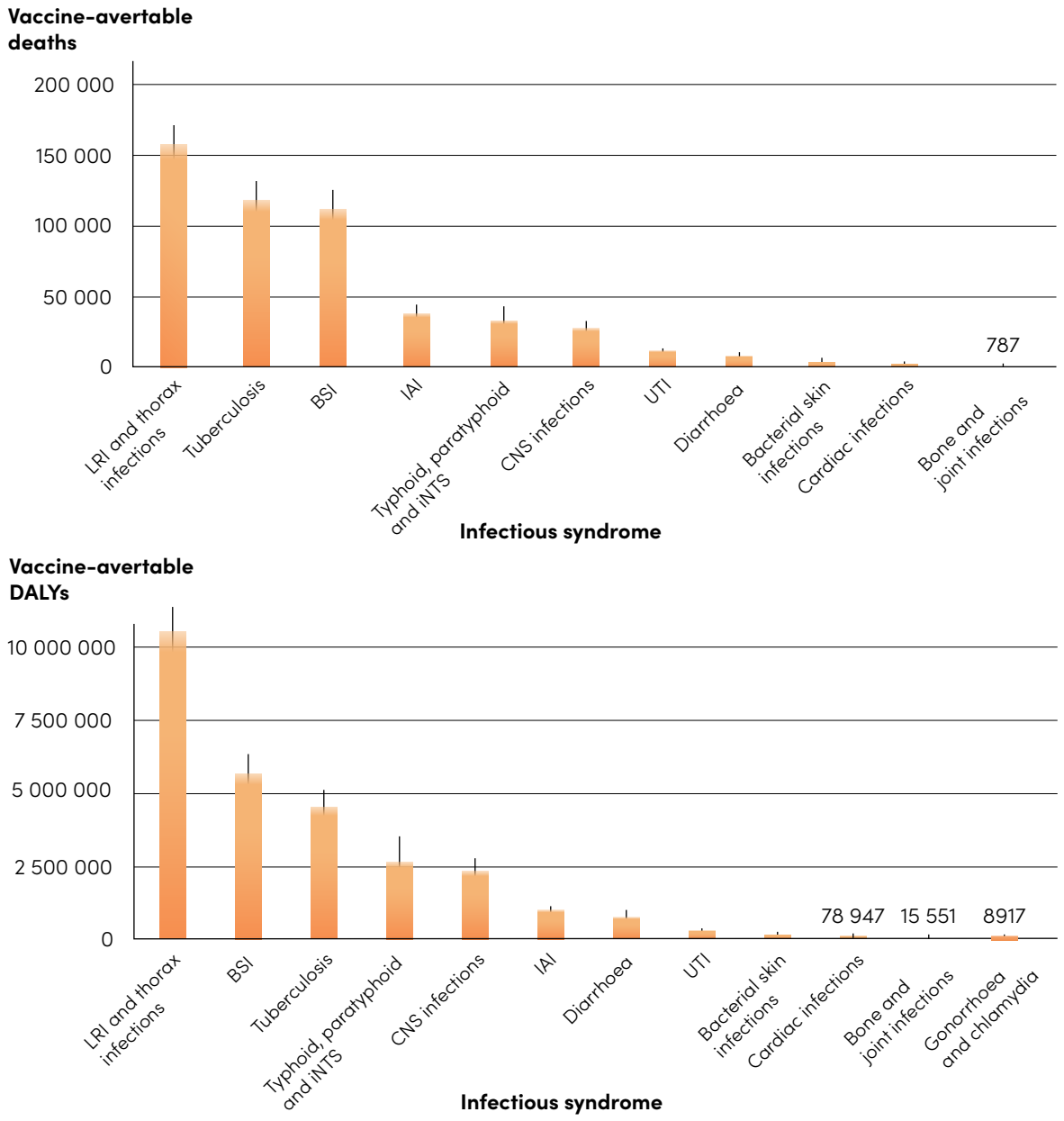
AB: *Acinetobacter baumannii*; AMR: antimicrobial resistance; DALY: disability-adjusted life year; EF: *Enterococcus faecium*; ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *Escherichia coli*; GAS: group A *Streptococcus*; Hib: *Haemophilus influenzae* type b; KP: *Klebsiella pneumoniae*; NG: *Neisseria gonorrhoeae*; NTS: nontyphoidal *Salmonella*; PA: *Pseudomonas aeruginosa*; SA: *Staphylococcus aureus*; SP: *Streptococcus pneumoniae*; SPara: *Salmonella* Paratyphi A; ST: *Salmonella* Typhi; TB: tuberculosis.

[a] The figure shows the global estimates (median and 95% uncertainty interval) of vaccine-preventable deaths and DALYs associated with bacterial AMR in 2019. See Tables 3.1–3.3 for vaccine characteristics.

3.1.3 Potential vaccine impact on AMR health burden by syndrome

Fig. 3.3 shows the vaccine-preventable deaths and DALYs associated with bacterial AMR for various infectious syndromes at the global level in 2019. Vaccine-preventable mortality associated with bacterial AMR was highest for lower respiratory tract and thorax infections, with 160 000 (95% UI: 140 000–170 000) deaths and 11 (9.6–11) million DALYs averted; this was followed by TB, with 118 000 (107 000–131 000) deaths and 4.6 (4.2–5.0) million DALYs, and bloodstream infections, with 110 000 (100 000–120 000) deaths and 5.6 (5.1–6.3) million DALYs averted in 2019. The pathogens *S. pneumoniae*, *S. aureus* and *K. pneumoniae* account for most of the estimated vaccine-preventable AMR burden associated with lower respiratory tract and thorax infections, whereas *K. pneumoniae*, *A. baumannii* and *E. coli* account for most of the vaccine-preventable AMR burden associated with bloodstream infections (Fig. 3.4).

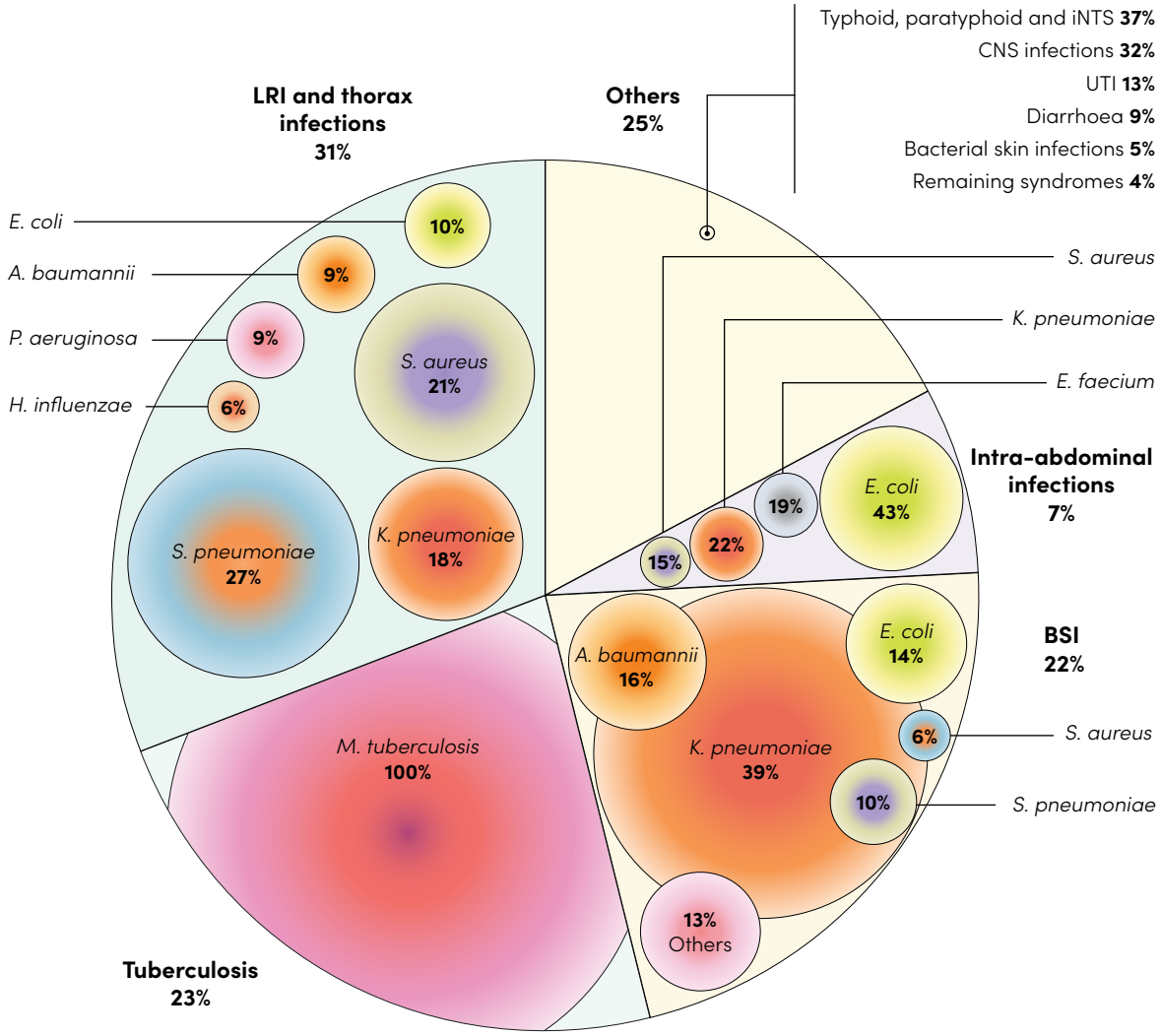
Fig. 3.3. Potential vaccine impact on AMR health burden by syndrome[a]



AMR: antimicrobial resistance; BSI: bloodstream infections; CNS: central nervous system; DALY: disability-adjusted life year; IAI: intra-abdominal infections; iNTS: invasive nontyphoidal *Salmonella*; LRI: lower respiratory tract infections; UTI: urinary tract infections.

[a] The figure shows the global estimates (median and 95% uncertainty interval) of vaccine-preventable deaths and DALYs associated with bacterial AMR in 2019.

Fig. 3.4. Estimated potential vaccine-preventable deaths associated with AMR by infectious syndrome and pathogen in 2019[a]

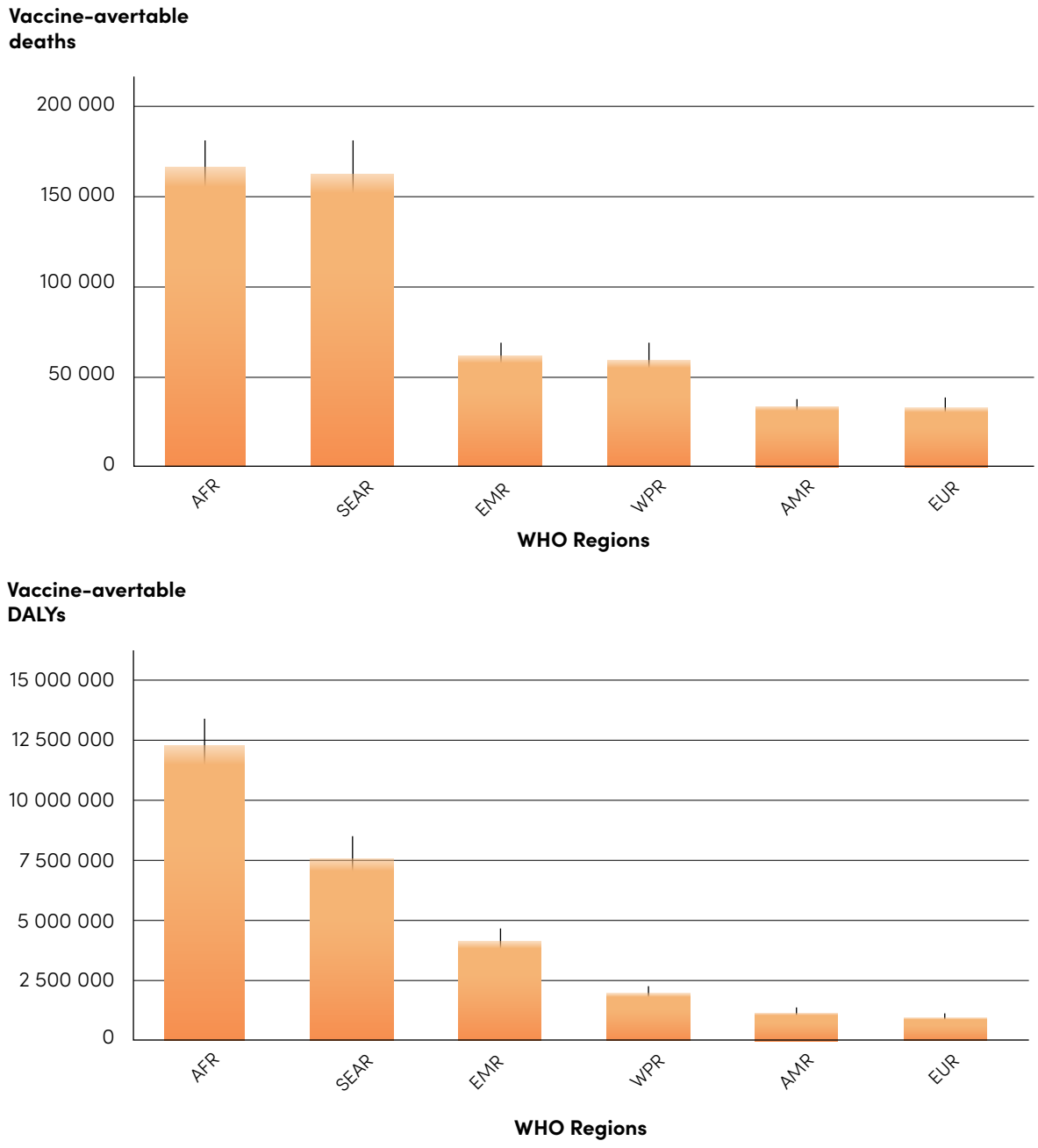


A. baumannii: Acinetobacter baumannii; AMR: antimicrobial resistance; BSI: bloodstream infection; CNS: central nervous system; *E. coli: Escherichia coli; E. faecium: Enterococcus faecium; H. influenzae: Haemophilus influenzae* type b; iNTS: invasive nontyphoidal *Salmonella; K. pneumoniae: Klebsiella pneumoniae;* LRI: lower respiratory tract infections; *M. tuberculosis: Mycobacterium tuberculosis; P. aeruginosa: Pseudomonas aeruginosa; S. aureus: Staphylococcus aureus; S. pneumoniae: Streptococcus pneumoniae;* UTI: urinary tract infections;

3.1.4 Potential vaccine impact on AMR health burden by region

The greatest impact of vaccines on reducing the burden of bacterial AMR in 2019 was seen in the WHO African Region, with an estimated 170 000 (95% UI: 150 000–180 000) deaths and 12 (11–13) million DALYs averted annually. In the WHO South-East Asia Region, vaccines were estimated to have prevented 160 000 (150 000–180 000) deaths and 7.5 (6.8–8.5) million DALYs annually. Together, these two regions could account for about two thirds of the global reduction in vaccine-preventable AMR burden in 2019 (Fig. 3.5).

Fig. 3.5. Potential vaccine impact on AMR health burden by WHO region in 2019[a]



AFR: WHO African Region; AMR: WHO Region of the Americas; DALY: disability-adjusted life year; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WHO: World Health Organization; WPR: WHO Western Pacific Region.

[a] The figure shows the estimates (median and 95% uncertainty interval) of vaccine-preventable deaths and DALYs associated with bacterial AMR in 2019.

3.1.5 Potential impact of existing vaccines on deaths and DALYs associated with AMR

Vaccination against *S. pneumoniae* [SP_1] in 2019 was estimated to have prevented about 44 500 (95% UI: 37 000–51 500) deaths and 3.8 (3.3–4.5) million DALYs associated with AMR (Table 3.1). By reaching the WHO-recommended coverage level of 90% globally [SP_2], an additional 14 500 deaths and 1.3 million DALYs associated with AMR could have been averted. Expanding the coverage to elderly populations [SP_3] would increase the vaccination impact by averting a further 12 500 deaths. Vaccination against Hib [Hib_1] in 2019 is estimated to have averted 11 500 (9690–13 000) deaths and 1.0 (0.9–1.2) million DALYs associated with AMR. If coverage were scaled up to 90% globally [Hib_2], a further 1 500 deaths and 0.12 million DALYs associated with AMR could have been averted. Wider introduction and scale-up of vaccination against *S.* Typhi [ST] could have averted 34 500 (26 000–44 000) deaths and 2.8 (2.2–3.6) million DALYs associated with AMR in 2019. This highlights the critical need to scale up existing vaccines to high and equitable vaccination coverage and to accelerate the introduction of TCV in high-burden countries.

Table 3.1. Potential impact of existing vaccines on deaths and DALYs associated with AMR[a]

Pathogen	Vaccine description and short name	Vaccine-averted deaths associated with AMR in 2019 (95% UI)	Vaccine-averted DALYs associated with AMR in 2019 (95% UI)
Haemophilus influenzae type b (Hib)	A vaccine against Hib infection given to **74% of infants** (2019 coverage), with 5-year efficacy of 93% [Hib_1]	11 500 (9690–13 000)	1.0 (0.9–1.2) million
	A vaccine against Hib infection given to **90% of infants**, with 5-year efficacy of 93% [Hib_2][b]	13 000 (11 000–15 000)	1.1 (1.0–1.3) million
Salmonella Typhi	A vaccine against *S.* Typhi infection given to 70% of infants in countries with a high typhoid burden, with 15-year efficacy of 85% [ST][b]	34 500 (26 000–44 000)	2.8 (2.2–3.6) million
Streptococcus pneumoniae	A serotype-specific vaccine against *S. pneumoniae* infection given to **51% of infants** (2019 coverage), with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_1]	44 500 (37 000–51 500)	3.8 (3.3–4.5) million
	A serotype-specific vaccine against *S. pneumoniae* infection given to **90% of infants**, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_2][b]	59 000 (50 000–69 000)	5.1 (4.5–6.0) million
	A serotype-specific vaccine against *S. pneumoniae* infection given to **90% of infants and elderly people**, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_3]	71 500 (62 500–81 500)	5.3 (4.7–6.1) million

AMR: antimicrobial resistance; DALY: disability-adjusted life year; UI: uncertainty interval.

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible AMR health burden.

3.1.6 Potential impact of new vaccines in late-stage clinical development on deaths and DALYs associated with AMR

Vaccines in late-stage clinical development with clear characteristics, or published PPCs or TPPs, such as those for ExPEC and *M. tuberculosis*, have the potential to prevent a significant proportion of the AMR burden (Table 3.2). A vaccine against *M. tuberculosis* that meets WHO's PPC criteria of 80% efficacy and is given to 70% of infants, with lifelong immunity or boosting [TB_1], would have averted 118 000 (95% UI: 107 000–131 000) deaths and 4.6 (4.2–5.0) million DALYs associated with AMR in 2019. Another vaccine against *M. tuberculosis* given to adolescents and older populations at 70% coverage and with 50% efficacy and lifelong immunity or boosting [TB_2] could have averted about 70 500 (64 000–78 000) deaths and 2.6 (2.3–2.8) million DALYs associated with AMR in 2019. Importantly, analyses from WHO show that if the length of protection is limited to 10 years, and no vaccine boosters are given, the TB vaccine targeting adolescents would have a significantly higher impact than a vaccine given to infants (71). As these vaccines progress through clinical development, AMR endpoints (e.g. reduction in antimicrobial prescribing or vaccine efficacy against drug-resistant pathogens) should, where feasible, be included in clinical trials, to collect and analyse data on the impact of vaccines on AMR. Such data could be useful for validating the modelling estimates, informing the full value of vaccines, undertaking cost–effectiveness analyses and making policy decisions; they could also influence decisions on whether to introduce vaccines to countries' immunization programmes.

Table 3.2. Potential impact of new vaccines in late-stage clinical development on deaths and DALYs associated with AMR[a]

Pathogen	Vaccine description and short name	Vaccine-averted deaths associated with AMR in 2019 (95% UI)	Vaccine-averted DALYs associated with AMR in 2019 (95% UI)
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	A vaccine against bloodstream ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_1]	15 500 (12 000–20 000)	349 000 (285 000–452 000)
	A vaccine against bloodstream ExPEC infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_2]	103 000 (93 500–115 000)	2.7 (2.5–2.9) million
Mycobacterium tuberculosis	A vaccine against pulmonary *M. tuberculosis* disease given to **70% of infants**, with 10-year efficacy of 80% and subsequent boosting to ensure lifelong protection [TB_1][b]	118 000 (107 000–131 000)	4.6 (4.2–5.0) million
	A vaccine against pulmonary *M. tuberculosis* disease given to **70% of children aged 10 years**, with 10-year efficacy of 50% and subsequent boosting to ensure lifelong protection [TB_2]	70 500 (64 000–78 000)	2.6 (2.3–2.8) million
Neisseria gonorrhoeae	A vaccine against *N. gonorrhoeae* infection given to 70% of adolescents, with 10-year efficacy of 70% [NG][b]	Not estimated	8917 (6929–11 500)
Salmonella Paratyphi A	A vaccine against *S.* Paratyphi A infection given to 70% of infants in countries with a high typhoid burden, with 5-year efficacy of 70% [SPara][b]	1463 (853–2793)	128 000 (74 500–224 000)

AMR: antimicrobial resistance; DALY: disability-adjusted life year; UI: uncertainty interval.

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible AMR health burden.

3.1.7 Potential impact of new vaccines in early clinical development or vaccines not in clinical development on deaths and DALYs associated with AMR

A vaccine against all disease presentations of *K. pneumoniae* infection given to infants and elderly populations at 70% coverage and with 70% efficacy [KP_2] could have averted about 64 500 (95% UI: 58 500–72 000) deaths and 3.7 (3.3–4.1) million DALYs associated with AMR in 2019 (Table 3.3). The high estimated vaccine-preventable burden associated with AMR for *K. pneumoniae*, *S. aureus* and *A. baumannii* highlights the urgent need for studies to enhance biological understanding of these pathogens, and to improve the feasibility of developing, delivering and effectively using vaccines against them.

Table 3.3. Potential impact of new vaccines in early clinical development or vaccines not in clinical development on deaths and DALYs associated with AMR[a]

Pathogen	Vaccine description and short name	Vaccine-averted deaths associated with AMR in 2019 (95% UI)	Vaccine-averted DALYs associated with AMR in 2019 (95% UI)
Acinetobacter baumannii	A vaccine against **bloodstream** *A. baumannii* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [AB_1]	18 000 (13 500–25 500)	505 000 (411 000–668 000)
	A vaccine against **bloodstream** *A. baumannii* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [AB_2]	116 000 (105 000–128 000)	3.5 (3.2–3.8) million
	A vaccine against *A. baumannii* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [AB_3][b]	34 500 (28 000–43 000)	1.0 (0.9–1.2) million
	A vaccine against *A. baumannii* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [AB_4]	217 000 (202 000–232 000)	6.0 (5.7–6.3) million
Enterococcus faecium	A vaccine against *E. faecium* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [EF_1][b]	14 000 (12 500–16 000)	414 000 (364 000–472 000)
	A vaccine against *E. faecium* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [EF_2]	101 000 (95 500–106 000)	2.7 (2.6–2.9) million
Enterotoxigenic *Escherichia coli* (ETEC)	A vaccine against moderate to severe diarrhoea caused by ETEC infection given to 70% of infants, with 5-year efficacy of 60% [ETEC][b]	2779 (2043–4136)	257 000 (181 000–367 000)
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	A vaccine against **urinary tract** ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_3]	6727 (5659–7934)	140 000 (124 000–159 000)
	A vaccine against **urinary tract** ExPEC infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_4]	49 500 (46 500–53 000)	1.1 (1.0–1.2) million
	A vaccine against ExPEC **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_5][b]	62 500 (56 500–68 500)	2.3 (2.1–2.6) million
	A vaccine against ExPEC **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_6]	389 000 (373 000–405 000)	12.6 (12.0–13.5) million
Group A *Streptococcus* (GAS)	A vaccine against GAS infection given to 70% of infants, with 5-year efficacy of 70% [GAS][b]	792 (643–998)	69 000 (56 000–88 000)

Pathogen	Vaccine description and short name	Vaccine-averted deaths associated with AMR in 2019 (95% UI)	Vaccine-averted DALYs associated with AMR in 2019 (95% UI)
Klebsiella pneumoniae	A vaccine against **bloodstream** *K. pneumoniae* infection given to 70% of **infants through maternal vaccination**, with 6-month efficacy of 70% [KP_1][b]	27 500 (22 000–35 000)	2.4 (2.0–3.1) million
	A vaccine against *K. pneumoniae* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [KP_2][b]	64 500 (58 500–72 000)	3.7 (3.3–4.1) million
	A vaccine against *K. pneumoniae* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [KP_3]	321 000 (309 000–336 000)	13.7 (12.8–14.7) million
Nontyphoidal *Salmonella*	A vaccine against nontyphoidal *Salmonella* infection given to 70% of infants, with 5-year efficacy of 80% [NTS][b]	1820 (1412–2624)	178 000 (134 000–253 000)
Pseudomonas aeruginosa	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [PA_1][b]	20 500 (18 000–23 500)	1.0 (0.9–1.1) million
	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [PA_2]	119 000 (113 000–126 000)	4.8 (4.5–5.3) million
Shigella	A vaccine against moderate to severe diarrhoea caused by *Shigella* infection given to 70% of infants, with 5-year efficacy of 60% [Shigella][b]	4133 (2765–6132)	369 000 (242 000–553 000)
Staphylococcus aureus	A vaccine against *S. aureus* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 60% [SA_1][b]	56 000 (51 000–62 500)	2.6 (2.3–2.9) million
	A vaccine against *S. aureus* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 60% [SA_2]	319 000 (307 000–331 000)	10.6 (10.1–11.2) million
Streptococcus pneumoniae	A non-serotype-specific vaccine against *S. pneumoniae* infection given to 90% of infants and elderly people, with 5-year efficacy of 50% for lower respiratory tract infections and 70% for invasive pneumococcal disease [SP_4][b]	119 000 (104 000–135 000)	9.0 (7.9–10.3) million

AMR: antimicrobial resistance; DALY: disability-adjusted life year; UI: uncertainty interval.

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible AMR health burden.

3.2 Potential vaccine impact on antibiotic use

This section evaluates the role of vaccines in reducing antibiotic use. Vaccines reduce the incidence of both drug-susceptible and drug-resistant bacterial infections, secondary infections and viral infections (for which antibiotics are often inappropriately prescribed). Through the bystander effect, antibiotic use leads to selective pressure for resistance on microorganisms that are not the target of treatment.

Evidence from a published systematic review and meta-analysis *(72)* has provided information about the impact of vaccines on reducing antibiotic use. The influenza vaccine, for example, has been shown to significantly reduce systemic antibiotic use among healthy adults, with a 28.1% reduction in the number of days of antibiotic treatment. Moderate-certainty evidence suggests that influenza vaccines probably reduce antibiotic use in children aged 6 months to 14 years. Additionally, pneumococcal vaccination in children aged 6 weeks to 6 years is likely to reduce antibiotic use and decrease the number of episodes of illness requiring antibiotics in children aged 12–35 months *(72)*.

A reduction in the use of antibiotics is often used as a proxy to gauge expected reductions in AMR prevalence in bacteria. This approach is used because of the complexity of directly measuring or modelling the impact of antibiotic reduction on AMR prevalence, which is affected by various confounding factors.

Detailed results are available on the WHO website *(29)*, as are pathogen-specific results, which are also presented in Chapter 4.

3.2.1 Methodology

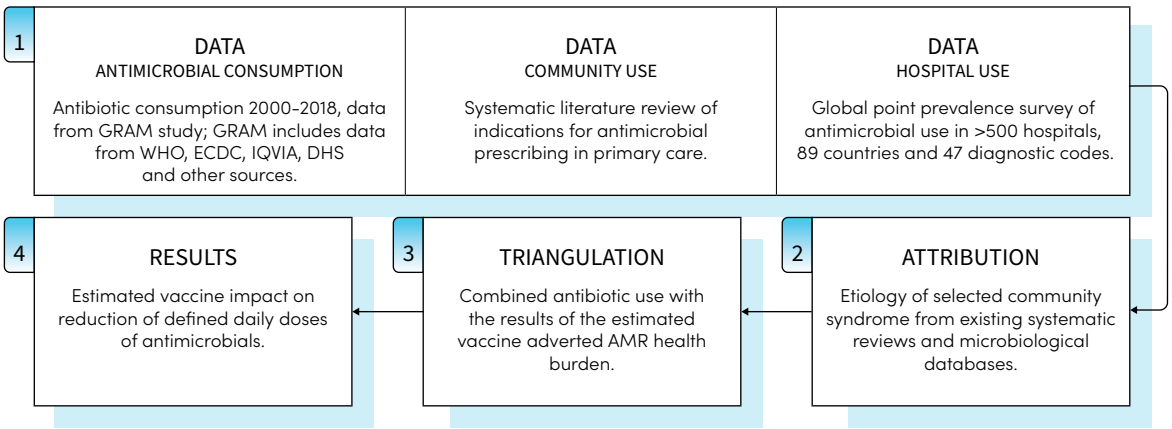
The potential impact on antibiotic use of 43 vaccines against 23 pathogens was evaluated. The assessment included vaccines against bacteria, a parasite (malaria) and viruses, considering that viruses often lead to inappropriate antibiotic treatment or secondary bacterial infections that require antibiotics. However, the effect on antibiotic use of a vaccine against *N. gonorrhoeae* was not evaluated owing to limited data. A rigorous methodology was employed, as shown in Fig. 3.6 and described in Chapter 2. Antibiotic consumption data from 2000 to 2018 were sourced from the GRAM Project, which integrates data from WHO, IQVIA and the European Surveillance of Antimicrobial Consumption Network.

For antibiotic use in the community, a systematic review was conducted following PRISMA guidelines to evaluate indications for antibiotic prescribing in primary care (unpublished, available on request from IVB/PDR). In hospital settings, antibiotic use was estimated using a global point prevalence survey, administered through an international network of hospitals, to assess antibiotic prescribing and resistance.

To understand the etiology of each syndrome and estimate the proportion of antibiotic use associated with each pathogen, additional literature searches were performed. This information was then triangulated with estimates of vaccine-averted health burden (see Section 3.1) to calculate vaccine-preventable antibiotic use for the 43 vaccines.

As explained in Chapter 2, the potential impact of vaccines on antibiotic use is estimated by multiplying antibiotic use by syndrome, the population-attributable fraction and the vaccine-preventable fraction. Antibiotic use is expressed in terms of DDDs for the year 2019, for both community and hospital-associated antibiotic use.

Fig. 3.6. Methodology to estimate vaccine-averted antibiotic use[a]



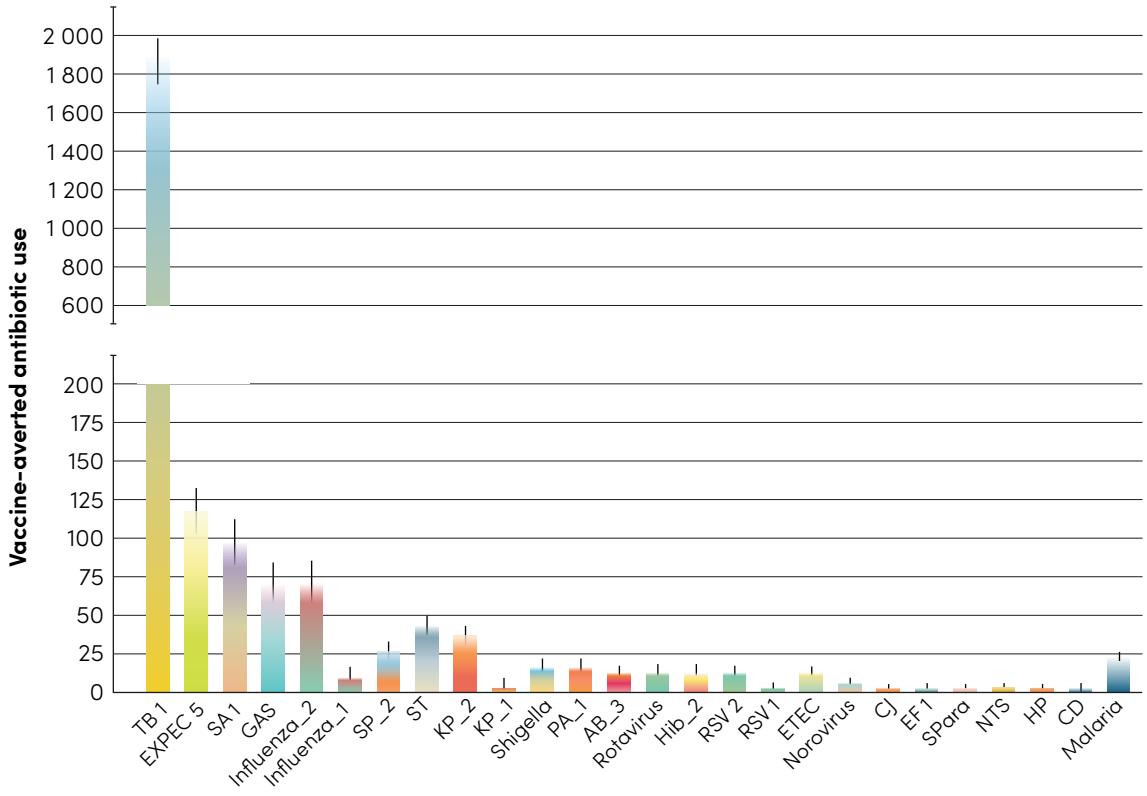
AMR: antimicrobial resistance; DHS: Demographic and Health Surveys; ECDC: European Centre for Disease Prevention and Control; GRAM: Global Research on Antimicrobial Resistance; WHO: World Health Organization.

[a] See Chapter 2 for a full description of the methodology and its limitations.

3.2.2 Potential vaccine impact on antibiotic use

Globally, human antibiotic use associated with the pathogens evaluated in this report is estimated at 11.3 billion DDDs per year (see the WHO website *(29)*). Most antibiotic use is in the WHO South-East Asia Region (3.7 billion DDDs), followed by the Western Pacific Region (1.8 billion DDDs). Pathogens associated with the highest volume of antibiotics used globally are *M. tuberculosis* (3.5 billion DDDs), ExPEC (3 billion DDDs) and *S. aureus* (1.8 billion DDDs) (see the WHO website *(29)*). If vaccines for all 23 pathogens were to be developed and used optimally (vaccines indicated with a superscript "b" in Tables 3.4–3.6), they could avert up to 2.5 billion DDDs per year (Fig. 3.7 and the WHO website *(29)*), which is nearly a quarter (22%) of the global estimated antibiotic use in humans associated with treating the evaluated pathogens. Importantly, this figure does not account for changes in prescribing patterns following vaccine introduction or herd immunity, both of which would further increase the impact of vaccines on AMR. The highest impact would be seen in the WHO South-East Asia Region, with 1.0 billion DDDs averted, followed by the African Region, with 505 million DDDs averted (see the WHO website *(29)*). A detailed breakdown of the results is presented below.

Fig. 3.7. Potential vaccine impact on antibiotic use by vaccine[a]



AB: *Acinetobacter baumannii*; CD: *Clostridioides difficile*; CJ: *Campylobacter jejuni*; DDD: defined daily dose; EF: *Enterococcus faecium*; ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *Escherichia coli*; GAS: group A *Streptococcus*; Hib: *Haemophilus influenzae* type b; HP: *Helicobacter pylori*; KP: *Klebsiella pneumoniae*; NTS: nontyphoidal *Salmonella*; PA: *Pseudomonas aeruginosa*; RSV: respiratory syncytial virus; SA: *Staphylococcus aureus*; SP: *Streptococcus pneumoniae*; SPara: *Salmonella* Paratyphi A; ST: *Salmonella* Typhi; TB: tuberculosis.

[a] The graph shows the estimates (median and 95% uncertainty interval) of vaccine-preventable antibiotic use (in DDDs) in 2019 for vaccines with a defined target population; see Tables 3.4–3.6 for vaccine characteristics.

3.2.3 Potential impact of existing vaccines on antibiotic use

The current use of pneumococcal vaccines [SP_1] is estimated to prevent about 23 (95% UI: 11–43) million DDDs annually (Table 3.4). Despite the availability of these vaccines, the AMR burden from *S. pneumoniae* remains high. Achieving IA2030 target vaccine coverage levels could be crucial in reducing antibiotic use and decreasing the prevalence of AMR. If use of pneumococcal vaccines is expanded to meet the IA2030 target of 90% coverage [SP_2], their impact could further increase, potentially averting an additional 4.6 million DDDs. Furthermore, the routine and extensive use of pneumococcal vaccines in the elderly population [SP_3] could prevent an additional 5.4 million DDDs.

The introduction and use of vaccines against *S.* Typhi [ST] in countries with a high burden of typhoid could prevent about 45 (11–88) million DDDs annually. This reduction is particularly important in countries such as India, Pakistan and Zimbabwe, where a growing prevalence of resistance has been seen in *S.* Typhi.

Finally, the introduction and use of recently approved malaria vaccines against *P. falciparum* [Malaria] could avert up to 25 (15–37) million DDDs of antibiotics annually, reflecting frequent misuse of antibiotics against malaria. This reduction could have a substantial impact on decreasing the prevalence of AMR in bacteria through the bystander effect *(73)*.

Table 3.4. Potential impact of existing vaccines on antibiotic use[a]

Pathogen	Vaccine description and short name	Vaccine-averted global antibiotic use in 2019, DDD (95% UI)
Haemophilus influenzae type b (Hib)	A vaccine against Hib infection given to **74% of infants** (2019 coverage), with 5-year efficacy of 93% [Hib_1]	14.0 (3.4–56.0) million
	A vaccine against Hib infection given to **90% of infants**, with 5-year efficacy of 93% [Hib_2][b]	15 (3.7–60.4) million
Influenza	A seasonal maternal vaccine against influenza infection given to 70% of pregnant women to protect neonates and infants, with 1-year efficacy of 70% [Influenza_1][b]	10 (5.1–18) million
Plasmodium falciparum	A vaccine against clinical *P. falciparum* (malaria) infection given to 70% of infants, with 4-year efficacy of 40% [Malaria][b]	25 (15–37) million
Rotavirus	An oral, live attenuated vaccine against rotavirus infection given to 90% of infants, with 2-year efficacy of 60% [Rotavirus][b]	15 (10–21) million
Respiratory syncytial virus (RSV)	A vaccine against severe RSV infection given to 70% of infants through maternal vaccination, with 6-month efficacy of 70% [RSV_1][b]	3.9 (0.9–8.7) million
Salmonella Typhi	A vaccine against *S.* Typhi infection given to 70% of infants in countries with a high typhoid burden, with 15-year efficacy of 85% [ST][b]	45 (11–88) million
Streptococcus pneumoniae	A serotype-specific vaccine against *S. pneumoniae* infection given to **51% of infants** (2019 coverage), with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_1]	23 (11–43) million
	A serotype-specific vaccine against *S. pneumoniae* infection given to **90% of infants**, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_2][b]	27.6 (13–53) million
	A serotype-specific vaccine against *S. pneumoniae* infection given to **90% of infants and elderly people**, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_3]	33 (15.7–64) million

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible antibiotic use.

3.2.4 Potential impact of new vaccines in late-stage clinical development on antibiotic use

The potential impact of vaccines in late-stage clinical development is noteworthy in terms of reducing antibiotic use (Table 3.5). Vaccines targeting TB [TB_1 and TB_2] are estimated to have the highest impact, potentially averting between 1.2 and 1.9 billion DDDs of antibiotics annually. This substantial effect can be attributed to the prolonged duration of antimicrobial treatment for TB, which typically ranges from 6 to 9 months. This duration is significantly longer than for other antimicrobial therapies. The antimicrobials used for TB treatment are unique, and their use appears to have limited impact on inducing resistance in other bacteria through the bystander effect.

Table 3.5. Potential impact of new vaccines in late-stage clinical development on antibiotic use[a]

Pathogen	Vaccine description and short name	Vaccine-averted global antibiotic use in 2019, DDD (95% UI)
Clostridioides difficile	A vaccine against *C. difficile* infection given to 70% of adults aged 45 years, with 5-year efficacy of 70% [CD][b]	33 000 (16 000–56 000)
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	A vaccine against bloodstream ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_1]	2.5 (1.8–3.3) million
	A vaccine against bloodstream ExPEC infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_2]	25 (20–32) million
Mycobacterium tuberculosis	A vaccine against pulmonary *M. tuberculosis* disease given to 70% of **infants**, with 10-year **efficacy of 80%** and subsequent boosting to ensure lifelong protection [TB_1][b]	1900 (1900–2000) million
	A vaccine against pulmonary *M. tuberculosis* disease given to 70% of **children aged 10 years**, with 10-year **efficacy of 50%** and subsequent boosting to ensure lifelong protection [TB_2]	1200 (1100–1200) million
Norovirus	A vaccine against norovirus infection given to 70% of infants, with 5-year efficacy of 50% [Norovirus][b]	6.6 (3.6–12) million
Salmonella Paratyphi A	A vaccine against *S.* Paratyphi A infection given to 70% of infants in countries with a high typhoid burden, with 5-year efficacy of 70% [SPara][b]	1.9 (0.4–3.8) million

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible antibiotic use.

3.2.5 Potential impact of new vaccines in early clinical development or vaccines not in clinical development on antibiotic use

A vaccine against urinary tract infections caused by ExPEC, used in infants and elderly people and currently in Phase 3 of clinical development [ExPEC_3], could avert up to 96 million DDDs of antibiotics annually, with an estimated range of 75–120 million (Table 3.6). A reduction in antibiotic use of this magnitude could significantly lower the current high AMR health burden.

A vaccine targeting GAS, if administered to infants [GAS], has the potential to avert up to 72 million DDDs annually. This is due to the frequent prescription of antibiotics for pharyngitis, up to 30% of which is caused by GAS *(74)*. Furthermore, a universal influenza vaccine for infants and elderly people [Influenza_2] could prevent up to 70 million DDDs annually. The need for this vaccine stems from the inappropriate prescription of antibiotics for treating influenza and the occurrence of secondary bacterial infections following primary influenza infection. The reduction in antibiotic use resulting from influenza vaccines could lead to a decrease in AMR prevalence in bacteria through the bystander effect.

Additionally, the broad use of vaccines designed to prevent multiple syndromes and administered to high-risk groups could lead to a significant reduction in antibiotic use. For example, such vaccines against ExPEC [ExPEC_6] could avert 1.5 billion DDDs, those against *K. pneumoniae* [KP_3] could avert 400 million DDDs, and those

against *S. aureus* [SA_2] could avert 740 million DDDs. However, the development and implementation of vaccines to protect against multiple syndromes in all high-risk individuals is highly challenging and not feasible at present.

Table 3.6. Potential impact of new vaccines in early clinical development or vaccines not in clinical development on antibiotic use[a]

Pathogen	Vaccine description and short name	Vaccine-averted global antibiotic use in 2019, DDD (95% UI)
Acinetobacter baumannii	A vaccine against **bloodstream** *A. baumannii* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [AB_1]	1.4 (1.0–2.1) million
	A vaccine against **bloodstream** *A. baumannii* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [AB_2]	15 (11–20) million
	A vaccine against *A. baumannii* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [AB_3][b]	16 (12–21) million
	A vaccine against *A. baumannii* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [AB_4]	170 (140–200) million
Campylobacter jejuni	A vaccine against *C. jejuni* infection given to 70% of infants, with 5-year efficacy of 70% [CJ][b]	4.8 (2.8–7.4) million
Enterococcus faecium	A vaccine against *E. faecium* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [EF_1][b]	4.2 (3.1–5.6) million
	A vaccine against *E. faecium* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [EF_2]	41 (32–55) million
Enterotoxigenic *Escherichia coli* (ETEC)	A vaccine against moderate to severe diarrhoea caused by ETEC infection given to 70% of infants, with 5-year efficacy of 60% [ETEC][b]	13 (9.2–19) million
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	A vaccine against **urinary tract** ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_3]	96 (75–120) million
	A vaccine against **urinary tract** ExPEC infection given to 70% **of all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_4]	1200 (1000–1500) million
	A vaccine against ExPEC **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_5][b]	120 (93–140) million
	A vaccine against ExPEC **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_6]	1500 (1300–1800) million
Group A *Streptococcus* (GAS)	A vaccine against GAS infection given to 70% of infants, with 5-year efficacy of 70% [GAS][b]	72 (54–92) million
Helicobacter pylori	A vaccine against *H. pylori* infection given to 70% of infants, with 5-year efficacy of 70% [HP][b]	1.1 (540 000–1.8) million
Influenza	A universal vaccine against type A influenza infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [Influenza_2][b]	70 (50–97) million
Klebsiella pneumoniae	A vaccine against **bloodstream** *K. pneumoniae* infection given to 70% of **infants through maternal vaccination**, with 6-month efficacy of 70% [KP_1][b]	100 000 (51 000–170 000)
	A vaccine against *K. pneumoniae* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [KP_2][b]	38 (29–48) million
	A vaccine against *K. pneumoniae* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [KP_3]	400 (360–440) million
Nontyphoidal *Salmonella*	A vaccine against nontyphoidal *Salmonella* infection given to 70% of infants, with 5-year efficacy of 80% [NTS][b]	1.3 (0.9–1.9) million

Pathogen	Vaccine description and short name	Vaccine-averted global antibiotic use in 2019, DDD (95% UI)
Pseudomonas aeruginosa	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [PA_1][b]	17 (13–22) million
	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [PA_2]	180 (160–200) million
Respiratory syncytial virus (RSV)	A vaccine against severe RSV infection given to 70% of infants, with 2-year efficacy of 70% [RSV_2][b]	14 (4.8–30) million
Shigella	A vaccine against moderate to severe diarrhoea caused by *Shigella* infection given to 70% of infants, with 5-year efficacy of 60% [Shigella]	19 (13–27) million
Staphylococcus aureus	A vaccine against *S. aureus* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 60% [SA_1][b]	97 (79–120) million
	A vaccine against *S. aureus* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 60% [SA_2]	740 (630–880) million
Streptococcus pneumoniae	A non-serotype-specific vaccine against *S. pneumoniae* infection given to 90% of infants and elderly people, with 5-year efficacy of 50% for lower respiratory tract infections and 70% for invasive pneumococcal disease [SP_4]	60 (28–120) million

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible antibiotic use.

3.3 Potential vaccine impact on AMR economic burden

In addition to death and disability, AMR has significant economic costs. The World Bank estimates that AMR could result in US$ 1 trillion of cumulative additional health care costs by 2050 and US$ 1 trillion to US$ 3.4 trillion of GDP losses per year by 2030 *(3)*. Increases in the use of health care as a result of reductions in antimicrobial efficacy against resistant pathogens may lead to increased costs in various ways; for example, patient-related out-of-pocket expenses, hospital-incurred insurance payer costs and broader societal productivity losses *(59)*. This section presents estimates of the global economic burden of antimicrobial-resistant infections and the potential of vaccines to reduce this economic burden. Specifically, it reports vaccine-preventable hospital costs of treating infections associated with AMR and vaccine-preventable productivity losses that result from early deaths due to infections associated with AMR.

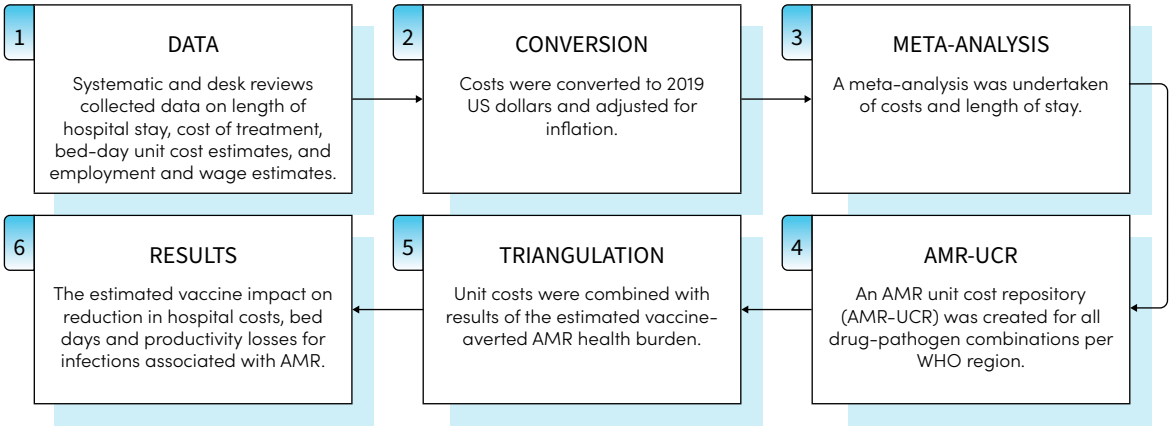
3.3.1 Methodology

A rigorous methodology was employed, as illustrated in Fig. 3.8 and detailed in Section 2.5 of Chapter 2. Desk reviews of literature were conducted to collate data on variables such as length of hospital stays, treatment costs, bed-day unit cost estimates, and employment and wage projections. All costs identified were standardized to 2019 US dollar values and adjusted for inflation. A meta-analysis of hospital costs and length of stay associated with resistant infections was performed. The results of the meta-analysis were then combined with WHO-CHOICE bed-day unit costs for each drug–pathogen combination to create the AMR Unit Cost Repository (AMR-UCR), which categorizes costs according to WHO regional classifications. The AMR-UCR was subsequently triangulated with data on estimated vaccine-averted AMR health burdens. The labour productivity costs were calculated by estimating the lost adjusted earnings (reported by the International Labour Organization) due to early death.

The potential impact of vaccines on the AMR-associated economic burden was assessed for 34 vaccines, with distinct characteristics, against 16 pathogens. This evaluation focused solely on bacterial vaccines. Assessment of the economic

impact of vaccines on resistance to antiviral, antiparasitic and other non-antibiotic treatments was not included, because of the paucity of data and low levels of resistance. The economic burden of drug-susceptible pathogens averted by vaccines is presented on the WHO website *(29)*. This section presents estimates of the potential of vaccines to reduce hospital costs and productivity losses associated with treatment-resistant infections. A detailed breakdown of results by WHO region is given in Chapter 4. Additional data are presented on the WHO website *(29)*, including metrics on vaccine-averted bed days. The methodology, discussed in detail in Chapter 2, is summarized in Fig. 3.8.

Fig. 3.8. Methodology to estimate vaccine-averted AMR economic burden



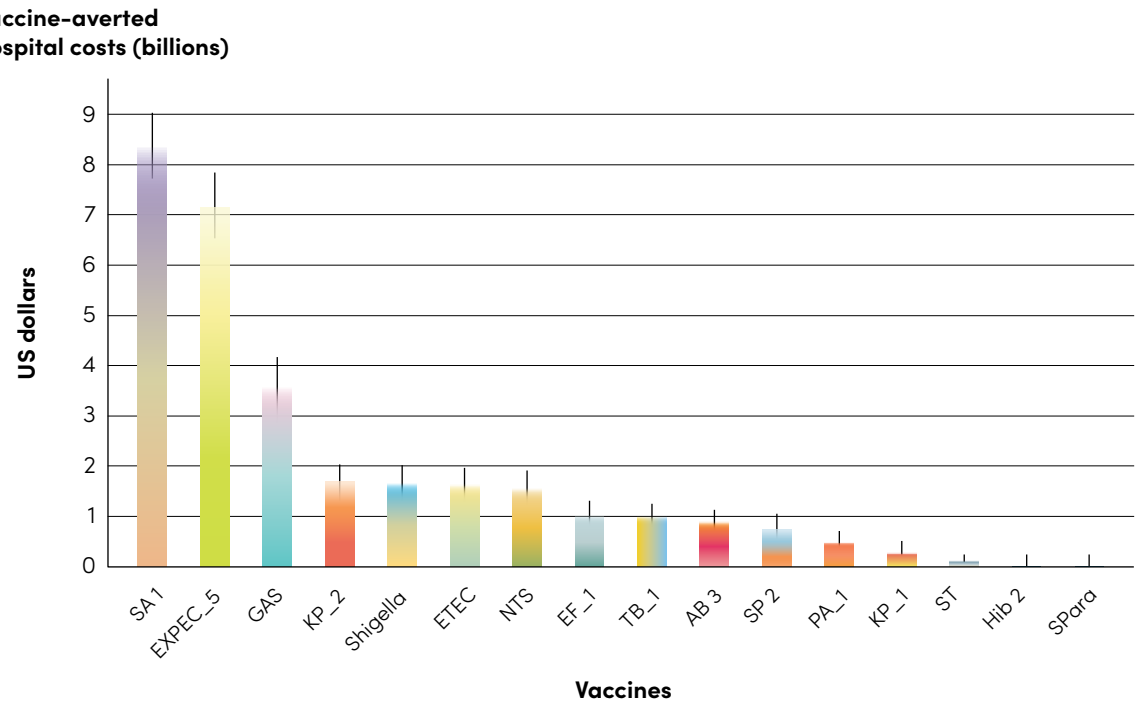
AMR: antimicrobial resistance; UCR: Unit Cost Repository; WHO: World Health Organization.

3.3.2 Potential vaccine impact on hospital costs and productivity losses associated with treatment-resistant pathogens

Globally, hospital costs associated with AMR were estimated to have a median annual value of US$ 730 billion (see the WHO website *(29)*). Most hospital costs were estimated to be incurred in the WHO Region of the Americas (US$ 217 billion), the European Region (US$ 188 billion) and the Western Pacific Region (US$ 176 billion). Pathogens responsible for the highest proportion of hospital costs were ExPEC (US$ 249 billion), *S. aureus* (US$ 138 billion) and GAS (US$ 108 billion). If vaccines for all 15 pathogens (vaccines indicated with a superscript "b" in Tables 3.7–3.9) were to be developed and optimally deployed, they would have the potential to avert up to US$ 30 billion in hospital costs annually associated with AMR (Fig. 3.9 and the WHO website *(29)*).

Global productivity losses associated with AMR were estimated to be US$ 191 billion annually (see the WHO website *(29)*). The largest productivity losses were estimated to be in the WHO South-East Asia Region (US$ 42 billion), the Region of the Americas (US$ 38 billion) and the Western Pacific Region (US$ 36 billion). The high productivity losses in these regions are due to wages being higher than in other regions, such as the WHO African Region. Globally, vaccines present an opportunity to mitigate up to US$ 19.6 billion of these losses annually (Fig. 3.9 and the WHO website *(29)*).

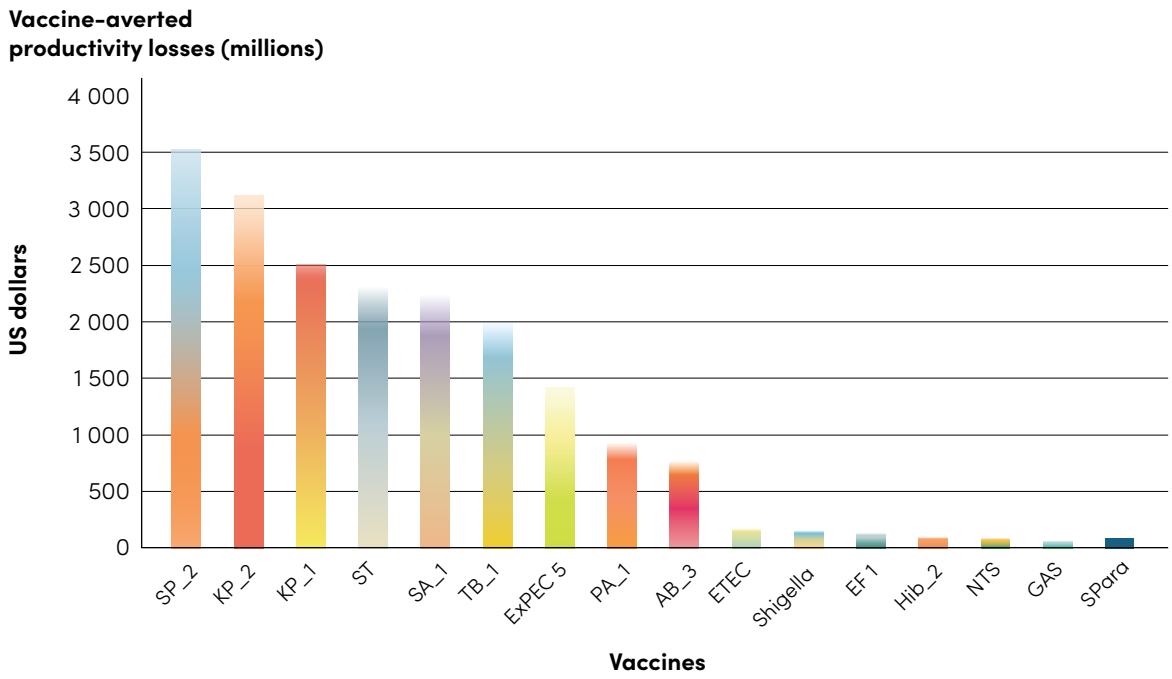
Fig. 3.9. Potential vaccine impact on hospital costs associated with AMR by vaccine[a]



AB: *Acinetobacter baumannii*; AMR: antimicrobial resistance; EF: *Enterococcus faecium*; ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *Escherichia coli*; GAS: group A *Streptococcus*; Hib: *Haemophilus influenzae* type b; KP: *Klebsiella pneumoniae*; NTS: nontyphoidal *Salmonella*; PA: *Pseudomonas aeruginosa*; SA: *Staphylococcus aureus*; SP: *Streptococcus pneumoniae*; SPara: *Salmonella* Paratyphi A; ST: *Salmonella* Typhi; TB: tuberculosis.

[a] The graph shows the estimates (median and 95% uncertainty interval) of vaccine-preventable hospital costs (in US dollars) associated with AMR in 2019 for vaccines with a defined target population; see Tables 3.7–3.9 for vaccine characteristics.

Fig. 3.10. Potential vaccine impact on productivity losses associated with AMR by vaccine[a]



AB: *Acinetobacter baumannii*; EF: *Enterococcus faecium*; ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *Escherichia coli*; GAS: group A *Streptococcus*; Hib: *Haemophilus influenzae* type b; KP: *Klebsiella pneumoniae*; NTS: nontyphoidal *Salmonella*; PA: *Pseudomonas aeruginosa*; SA: *Staphylococcus aureus*; SP: *Streptococcus pneumoniae*; SPara: *Salmonella* Paratyphi A; ST: *Salmonella* Typhi; TB: tuberculosis.

[a] The graph shows the estimates (median and 95% uncertainty interval) of vaccine-preventable productivity losses (in US dollars) associated with AMR in 2019 for vaccines with a defined target population; see Tables 3.7–3.9 for vaccine characteristics.

3.3.3 Potential impact of existing vaccines on hospital costs and productivity losses associated with treatment-resistant pathogens

The potential impact of vaccines on AMR economic burden was assessed for three pathogens with existing vaccines and six corresponding vaccine scenarios (Table 3.7). Currently licensed pneumococcal vaccines [SP_1], which comprise multiple conjugate vaccines that protect against different pneumococcal strains, are projected to avert US$ 0.6 billion in annual AMR-associated hospital costs and US$ 2.6 billion in productivity losses. By meeting WHO's 90% vaccine coverage target for pneumococcal vaccines [SP_2], an additional US$ 0.11 billion in hospital costs and US$ 0.9 billion in productivity losses associated with AMR could be averted.

Furthermore, if target coverage rates of 70% were achieved in countries with a high burden of typhoid, a broad introduction of the TCV against *S.* Typhi [ST] could potentially prevent up to US$ 117 million in hospital costs and US$ 2.3 billion in productivity losses associated with AMR every year.

Lastly, the use of a vaccine against Hib [Hib_1] is expected to prevent up to US$ 7.6 million in hospital costs and US$ 89.6 million in productivity losses associated with AMR annually. However, determining the precise impact of the Hib vaccine is challenging, because of the high coverage rate of the vaccine, the declining incidence of the disease and the lack of credible vaccine counterfactuals.

Table 3.7. Potential impact of existing vaccines on AMR economic burden[a]

Pathogen	Vaccine description and short name	Vaccine-averted global hospital costs associated with AMR in 2019, US dollars (95% UI)	Vaccine-averted global productivity losses associated with AMR in 2019, US dollars
Haemophilus influenzae type b (Hib)	A vaccine against Hib infection given to **73–94% of infants**, with 5-year efficacy of 93% [Hib_1]	7.6 (4.3–14.9) million	90 million
	A vaccine against Hib infection given to **90% of infants**, with 5-year efficacy of 93% [Hib_2][b]	7.9 (4.5–15.5) million	99 million
Salmonella Typhi	A vaccine against *S.* Typhi infection given to 70% of infants in countries with a high typhoid burden, with 15-year efficacy of 85% [ST][b]	117 (71.5–192) million	2301 million
Streptococcus pneumoniae	A serotype-specific vaccine against *S. pneumoniae* infection given to 51% of infants (2019 coverage), with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_1]"]	626 (433–911) million	2645 million
	A serotype-specific vaccine against bloodstream, central nervous system, cardiac and lower respiratory tract *S. pneumoniae* infections given to **90% of infants**, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for remaining syndromes [SP_2][b]	737 (522–1056) million	3524 million
	A serotype-specific vaccine against *S. pneumoniae* infection given to 90% of infants and elderly people, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_3]	1132 (795–1621) million	3524 million

AMR: antimicrobial resistance; UI: uncertainty interval.

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible AMR economic burden.

3.3.4 Potential impact of new vaccines in late-stage clinical development on hospital costs and productivity losses associated with treatment-resistant pathogens

An analysis of the vaccine-preventable AMR economic burden was conducted for three pathogens with new vaccines in late-stage clinical development and their five associated vaccine scenarios, as shown in Table 3.8. A vaccine targeting pulmonary TB that is administered to 70% of infants, with 80% efficacy and durability of 10 years, and is subsequently followed up with periodic boosters [TB_1] has the potential to prevent up to US$ 1.0 billion in AMR-related hospital costs and US$ 2.0 billion in productivity losses each year. Such a vaccine is currently undergoing Phase 3 clinical trials.

Additionally, a vaccine against bloodstream ExPEC infections, if provided to 70% of infants and elderly people [ExPEC_1], could prevent hospital costs due to AMR equating to about US$ 136 million and productivity losses of almost US$ 144 million on an annual basis. This is based on the vaccine having 70% efficacy and a duration of protection of 5 years; however, the efficacy and duration of protection for the vaccine, which is currently in a Phase 3 clinical trial, remain unknown.

Table 3.8. Potential impact of vaccines in late-stage clinical development on AMR economic burden[a]

Pathogen	Vaccine description and short name	Vaccine-averted global hospital costs associated with AMR in 2019, US dollars (95% UI)	Vaccine-averted global productivity losses associated with AMR in 2019, US dollars
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	A vaccine against bloodstream ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_1]	136 (103–177) million	144 million
	A vaccine against bloodstream ExPEC infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_2]	2091 (1633–2670) million	2649 million
Mycobacterium tuberculosis	A vaccine against pulmonary *M. tuberculosis* disease given to 70% of **infants**, with 10-year efficacy of 80% and subsequent boosting to ensure lifelong protection [TB_1][b]	1012 (545–1781) million	1999 million
	A vaccine against pulmonary *M. tuberculosis* disease given to 70% of **children aged 10 years**, with 10-year efficacy of 50% and subsequent boosting to ensure lifelong protection [TB_2]	617 (330–1089) million	1165 million
Salmonella Paratyphi A	A vaccine against *S.* Paratyphi A infection given to 70% of infants in countries with a high typhoid burden, with 5-year efficacy of 70% [SPara][b]	7 (3.7–13.1) million	87 million

AMR: antimicrobial resistance; UI: uncertainty interval.

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible AMR economic burden.

3.3.5 Potential impact of new vaccines in early clinical development or vaccines not in clinical development on hospital costs and productivity losses associated with treatment-resistant pathogens

An assessment of the impact of new vaccines on the economic burden associated with AMR was conducted for 11 pathogens that have either new vaccines in early clinical development or no vaccine candidates, with the 22 specific vaccine scenarios shown in Table 3.9. In theoretical models where vaccines are administered in a timely manner to targeted at-risk populations and are designed to prevent all types of pathogen-specific disease presentations, the reduction in economic burden of AMR is significant. Such a vaccine against ExPEC [ExPEC_6] could prevent up to US$ 94.6 billion in AMR-related hospital costs and about US$ 13.3 billion in productivity losses annually. A vaccine against *S. aureus*, in the most optimistic scenario [SA_2], may prevent up to US$ 57.8 billion in hospital costs and US$ 15.3 billion in productivity losses associated with AMR each year. However, the likelihood of developing vaccines with these broad preventive capabilities, and having efficient delivery and acceptance of them, is low.

In a more conservative approach, vaccinating only children aged under 5 years and elderly people with a vaccine against *S. aureus* infections [SA_1] could lead to annual savings of up to US$ 8.3 billion in AMR-associated hospital costs and about US$ 2.2 billion in productivity losses.

For a vaccine targeting urinary tract ExPEC infections [ExPEC_3], hospital costs could be reduced by up to US$ 6.2 billion and productivity losses by about US$ 54.6 million each year, primarily owing to the prevalence of this disease among elderly people.

Furthermore, a vaccine targeting bloodstream *K. pneumoniae* infections and administered to 70% of infants via maternal vaccination [KP_1] could save up to US$ 279.0 million in AMR-related hospital costs and US$ 2.5 billion in productivity losses annually. This significant reduction is mainly attributed to the vaccine's potential impact on reducing neonatal mortality.

Although there is already a vaccine against *S. pneumoniae*, a newly developed vaccine with a higher efficacy rate of 50% for lower respiratory tract infections [SP_4] could prevent up to US$ 2.1 billion in hospital costs and about US$ 6.0 billion in productivity losses associated with AMR annually.

Table 3.9. Potential impact of new vaccines in early clinical development (or vaccines not in clinical development) on AMR economic

Pathogen	Vaccine description and short name	Vaccine-averted global hospital costs associated with AMR in 2019, US dollars (95% UI)	Vaccine-averted global productivity losses associated with AMR in 2019, US dollars
Acinetobacter baumannii	A vaccine against **bloodstream** *A. baumannii* infection given to **70% of infants and elderly people**, with 5-year efficacy of 70% [AB_1]	109 (80–152) million	430 million
	A vaccine against **bloodstream** *A. baumannii* infection given to 70% **of all people at risk of infection**, with 5-year efficacy of 70% [AB_2]	2858 (2132–3827) million	7333 million
	A vaccine against *A. baumannii* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [AB_3][b]	900 (699–1173) million	771 million
	A vaccine against *A. baumannii* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [AB_4]	11 158 (8679–14 628) million	11 144 million
Enterococcus faecium	A vaccine against *E. faecium* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [EF_1]	1019 (537–1991) million	140 million
	A vaccine against *E. faecium* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [EF_2]	10 255 (5919–18 551) million	3678 million
Enterotoxigenic *Escherichia coli* (ETEC)	A vaccine against moderate to severe diarrhoea caused by ETEC infection given to 70% of infants, with 5-year efficacy of 60% [ETEC][b]	1620 (166–2531) million	176 million
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	A vaccine against **urinary tract** ExPEC infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_3]	6178 (3780–9727) million	55 million
	A vaccine against **urinary tract** ExPEC infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_4]	84 276 (55 068–124 285) million	1210 million
	A vaccine against ExPEC **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [ExPEC_5][b]	7164 (4628–10 772) million	1415 million
	A vaccine against ExPEC **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [ExPEC_6]	94 600 (63 733–133 829) million	13 270 million
Group A *Streptococcus* (GAS)	A vaccine against GAS infection given to 70% of infants, with 5-year efficacy of 70% [GAS][b]	3566 (1424–8423) million	66 million
Klebsiella pneumoniae	A vaccine against **bloodstream** *K. pneumoniae* infection given to 70% of **infants through maternal vaccination**, with 6-month efficacy of 70% [KP_1][b]	279 (224–357) million	2508 million
	A vaccine against *K. pneumoniae* **infection** given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [KP_2][b]	1700 (1244–2322) million	3122 million
	A vaccine against *K. pneumoniae* **infection** given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [KP_3]	19 879 (14 885–26 178) million	16 056 million

Pathogen	Vaccine description and short name	Vaccine-averted global hospital costs associated with AMR in 2019, US dollars (95% UI)	Vaccine-averted global productivity losses associated with AMR in 2019, US dollars
Nontyphoidal *Salmonella*	A vaccine against nontyphoidal *Salmonella* infection given to 70% of infants, with 5-year efficacy of 80% [NTS][b]	1556 (930–2636) million	94 million
Pseudomonas aeruginosa	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 70% [PA_1][b]	488 (337–725) million	929 million
	A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 70% [PA_2]	4756 (3306–751) million	5953 million
Shigella	A vaccine against moderate to severe diarrhoea caused by *Shigella* infection given to 70% of infants, with 5-year efficacy of 60% [Shigella][b]	1649 (911–2872) million	158 million
Staphylococcus aureus	A vaccine against *S. aureus* infection given to 70% of **infants and elderly people**, with 5-year efficacy of 60% [SA_1][b]	8337 (6407–11 085) million	2235 million
	A vaccine against *S. aureus* infection given to 70% of **all people at risk of infection**, with 5-year efficacy of 60% [SA_2]	57 819 (43 930–78 302) million	15 313 million
Streptococcus pneumoniae	A non-serotype-specific vaccine against *S. pneumoniae* infection given to 90% of infants and elderly people, with 5-year efficacy of 50% for lower respiratory tract infections and 70% for invasive pneumococcal disease [SP_4]	2062 (1438–2970) million	6041 million

[a] Differences between vaccine characteristics for the same pathogen are highlighted in bold.

[b] Indicates vaccines that were included in the calculation of the total vaccine-avertible AMR economic burden.

Chapter 4 at a Glance

4. Results of vaccine impact on AMR by pathogen

This chapter presents the impacts on AMR of 44 vaccines against the 24 pathogens reported in Chapter 3, but here organized by pathogen and vaccines. Each vaccine has the associated short name in brackets [ ]. Each pathogen is presented in terms of its epidemiology, treatment and prevention strategies, AMR challenges and available vaccines. For each pathogen, the impact of at least one vaccine on AMR is assessed. For most bacterial pathogens, the vaccine impact is estimated in terms of the AMR health burden (including deaths and DALYs) and the economic impact, encompassing hospital costs and productivity losses. Additionally, the vaccine impact on antibiotic use is evaluated. For viruses or pathogens not associated with mortality, or where data are limited, the focus is on the vaccine's impact on antibiotic use. Also included are summaries of studies assessing the impact of vaccines on reducing AMR, conducted by WHO collaborators or other researchers. Recommendations for vaccine research, development or use are provided for each pathogen.

Data on the WHO website *(29)* includes additional information on the role of vaccines in reducing hospital bed occupancy due to prolonged stays associated with AMR infections.

4.1 *Acinetobacter baumannii*

Pathogen and its epidemiology

A. baumannii is a gram-negative bacterium that causes a wide range of opportunistic infections, particularly in hospital settings. The clinical manifestations include pneumonia, meningitis and bloodstream infection, as well as soft tissue, urinary tract and wound infections *(75, 77)*. Globally in 2019, there were an estimated 452 000 deaths associated with *A. baumannii*, about 94% of which were associated with antibiotic resistance *(2)*. It is estimated that most deaths from this pathogen occur in neonates and elderly people, in the WHO South-East Asia Region, North Africa and the Middle East *(70)*; however, data from high-burden regions are limited.

A. baumannii primarily affects society's most vulnerable populations, including infants, elderly people and individuals who are immunocompromised or chronically ill. Its adverse effects are amplified by socioeconomic challenges; for example, rates of infection coupled with antibiotic resistance are notably higher among low-income families *(77)*. *A. baumannii* is primarily transferred in hospitals via contaminated equipment or health care workers. The bacteria can survive on various surfaces in hospitals and have even been detected in pets, slaughter animals and soil. Health care facilities with inadequate resources or poor infection control practices are at heightened risk of outbreaks. Facilities with a higher level of care, equipped with devices such as ventilators, medical implants and central venous catheters, can also exacerbate *A. baumannii* infections through increased biofilm formation *(76)*. The broader ramifications include financial strain, prolonged hospitalization, isolation and significant psychological distress, such as anxiety, fear and loneliness *(77)*.

Treatment and prevention

Treatment of *A. baumannii* infections relies on antibiotics, the administration of which is determined by local antibiotic susceptibility assessments. There is an urgent need for enhanced antimicrobial stewardship, encompassing improved diagnostics, better education for health care workers and optimized prescribing practices.

Prevention measures recommended by WHO include education, hand hygiene, environmental cleaning, screening, contact tracing and isolation *(78)*. Alternative treatments encompass passive immunization using monoclonal antibodies, phage therapy and antimicrobial peptides; however, these treatments are not in routine clinical use.

Antimicrobial resistance

WHO has classified the AMR threat posed by carbapenem-resistant *A. baumannii* as critical *(10)*. The bacterium can rapidly develop resistance mechanisms, resulting in strains that are non-susceptible to all available antibiotics. The CDC lists carbapenem-resistant *A. baumannii* as an urgent AMR threat *(27)*, which often manifests as extensively drug resistant. MDR and XDR strains have been reported globally. In 2022, according to reports to the Global Antimicrobial Resistance and Use Surveillance System (GLASS), the median proportion of carbapenem and aminoglycoside resistance in *Acinetobacter* spp. was over 56% *(79)*. The incidence of such strains has escalated in the past decade, highlighting the critical urgency of the threat.

Vaccines

There is no available vaccine for *A. baumannii*, and there are no vaccines in clinical development *(33)*. In this report, the potential impact on AMR of four vaccines with varying characteristics was assessed (Table 4.1). The first vaccine was chosen for its targeted approach against bloodstream infections, which predominantly affect vulnerable groups such as infants and elderly people [AB_1]. The impact of extended use of such a vaccine [AB_2] was also evaluated. The third vaccine is a broader, hypothetical vaccine designed to evaluate the impact against multiple disease presentations [AB_3] in infants and elderly people. The potential impact of extended use of such a vaccine in all age groups [AB_4] was also evaluated. The vaccine characteristics were identified through consultation with pathogen and vaccine experts.

Acinetobacter baumannii (AB_1)

Table 4.1. A vaccine against bloodstream *A. baumannii* infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [AB_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Acinetobacter baumannii	**Infants and elderly**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name:				Feasibility of vaccine development and implementation
AB_1				LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	16 000 (14 000–19 000)	1169 (771–1685)	949 000 (789 000–1.2 million)	70 500 (48 500–106 000)
EUR	14 000 (11 500–17 000)	867 (440–1829)	312 000 (267 000–369 000)	21 000 (11 500–39 500)
EMR	16 500 (14 000–19 000)	1229 (766–1981)	648 000 (566 000–757 000)	45 500 (30 500–66 000)
SEAR	66 500 (56 500–79 000)	4764 (2751–9166)	2.2 (1.9–2.6) million	128 000 (83 000–217 000)
AMR	23 500 (20 000–27 500)	1600 (957–2921)	603 000 (532 000–678 000)	47 000 (31 000–70 000)
WPR	99 500 (83 500–121 000)	7901 (4462–14 500)	2.4 (2–2.8) million	181 000 (114 000–313 000)
GLOBAL	**236 000** (217 000–261 000)	**18 000** (13 500–25 500)	**7** (6.5–7.6) **million**	**505 000** (411 000–668 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	5.6 (2.6–9.8) million	280 000 (110 000–520 000)
EUR	1 (0.5–2.0) million	50 000 (23 000–98 000)
EMR	4.6 (3.3–6.5) million	210 000 (140 000–320 000)
SEAR	12 (8.8–16) million	520 000 (350 000–850 000)
AMR	1 (0.4–1.6) million	50 000 (22 000–83 000)
WPR	6 (4.5–7.9) million	280 000 (200 000–430 000)
GLOBAL	**30** (22–41) million	**1.4 million** (950 000–2.1 million)

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	205 (118–337) million	2.4 (1.4–3.9) million	526 million	33 million
EUR	709 (517–974) million	14.3 (10.7–18.9) million	1324 million	30 million
EMR	881 (442–1821) million	10.7 (5.3–22.2) million	1087 million	50 million
SEAR	386 (220–644) million	5.8 (3.3–9.3) million	2587 million	65 million
AMR	2244 (1271–3772) million	46.3 (24.3–84.4) million	3096 million	121 million
WPR	1408 (708–2586) million	30.1 (16.8–52.2) million	6345 million	132 million
GLOBAL	**5832** (4350–7811) **million**	**109** (79.8–152) **million**	**14 966 million**	**430 million**

Acinetobacter baumannii (AB_2)

A vaccine against bloodstream *A. baumannii* infection given to 70% of all people at risk of infection, with 5-year efficacy of 70% [AB_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Acinetobacter baumannii	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **AB_2**				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	16 000 (14 000–19 000)	7841 (6593–9465)	949 000 (789 000–1.2 million)	465 000 (377 000–616 000)
EUR	14 000 (11 500–17 000)	6761 (5479–8772)	312 000 (267 000–369 000)	152 000 (128 000–182 000)
EMR	16 500 (14 000–19 000)	8093 (6899–9680)	648 000 (566 000–757 000)	319 000 (267 000–384 000)
SEAR	66 500 (56 500–79 000)	32 500 (26 500–40 000)	2.2 (1.9–2.6) million	1.1 million (885 000–1.3 million)
AMR	23 500 (20 000–27 500)	11 500 (9577–14 000)	603 000 (532 000–678 000)	297 000 (257 000–341 000)
WPR	99 500 (83 500–121 000)	49 000 (40 500–59 500)	2.4 (2–2.8) million	1.2 (1.0–1.4) million
GLOBAL	**236 000** (217 000–261 000)	**116 000** (105 000–128 000)	**7** (6.5–7.6) **million**	**3.5** (3.2–3.8) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	5.6 (2.6–9.8) million	2.8 (1.3–4.8) million
EUR	1 (0.5–2.0) million	500 000 (230 000–990 000)
EMR	4.6 (3.3–6.5) million	2.2 (1.6–3.2) million
SEAR	12 (8.8–16) million	5.7 (4.3–7.6) million
AMR	1 (0.4–1.6) million	510 000 (200 000–810 000)
WPR	6 (4.5–7.9) million	2.9 (2.2–3.8) million
GLOBAL	**30** (22–41) **million**	**15** (11–20) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	205 (118–337) million	100 (57.6–165) million	526 million	258 million
EUR	709 (517–974) million	347 (254–477) million	1324 million	649 million
EMR	881 (442–1821) million	431 (217–892) million	1087 million	533 million
SEAR	386 (220–644) million	189 (108–316) million	2587 million	1268 million
AMR	2244 (1271 –3772) million	1099 (623–1848) million	3096 million	1517 million
WPR	1408 (708–2586) million	690 (347–1267) million	6345 million	3109 million
GLOBAL	**5832** (4350 –7811) **million**	**2858** (2132 –3827) **million**	**14 966 million**	**7333 million**

Acinetobacter baumannii (AB_3)

A vaccine against *A. baumannii* infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [AB_3]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Acinetobacter baumannii	**Infants and elderly**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name:				Feasibility of vaccine development and implementation
AB_3				LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	50 000 (45 500–56 000)	4585 (3353–6125)	2.2 (1.9–2.5) million	248 000 (193 000–323 000)
EUR	29 000 (26 000–33 500)	1702 (1091–2790)	606 000 (548 000–675 000)	38 500 (27 000–58 000)
EMR	34 500 (30 500–38 000)	2728 (2093–3977)	1.2 (1.1–1.3) million	104 000 (78 500–136 000)
SEAR	149 000 (132 000–170 000)	11 500 (8055–17 000)	4.1 (3.7–4.6) million	305 000 (229 000–432 000)
AMR	47 500 (43 000–53 500)	3109 (2065–4705)	1.1 (1–1.2) million	84 000 (60 500–111 000)
WPR	130 000 (114 000–153 000)	10 000 (6230–16 500)	3 (2.7–3.5) million	227 000 (156 000–361 000)
GLOBAL	**442 000** (416 000–471 000)	**34 500** (28 000–43 000)	**12.3** (11.6–12.9) **million**	**1.0** (0.9–1.2) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	35 (16–63) million	1.8 (0.9–3.3) million
EUR	29 (17–43) million	1.4 (0.8–2.1) million
EMR	31 (24–43) million	1.4 (0.9–1.9) million
SEAR	150 (130–170) million	6.8 (5–9) million
AMR	16 (9.9–23) million	780 000 (460 000–1.1 million)
WPR	81 (68–96) million	3.9 (2.9–5.1) million
GLOBAL	**340** (290–410) **million**	**16** (12–21) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	586 (367–940) million	26.4 (16.8–40.9) million	1102 million	105 million
EUR	5108 (3665–6758) million	198 (140–264) million	2338 million	51 million
EMR	292 (1231–3580) million	66 (39.4–110) million	1893 million	112 million
SEAR	1525 (770–2951) million	54.2 (25.7–105) million	4313 million	150 million
AMR	8357 (4691–14 313) million	330 (181–574) million	5325 million	187 million
WPR	5104 (3063–8174) million	225 (135–359) million	7773 million	165 million
GLOBAL	**22 772** (17 712–29 852) **million**	**900** (699–1173) **million**	**22 500 million**	**771 million**

Acinetobacter baumannii (AB_4)

A vaccine against *A. baumannii* infection given to 70% of all people at risk of infection, with 5-year efficacy of 70% [AB_4]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Acinetobacter baumannii	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name:				Feasibility of vaccine development and implementation
AB_4				LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	50 000 (45 500–56 000)	24 500 (22 000–28 000)	2.2 (1.9–2.5) million	1.1 million (927 000–1.3 million)
EUR	29 000 (26 000–33 500)	14 000 (12 500–17 000)	606 000 (548 000–675 000)	297 000 (266 000–334 000)
EMR	34 500 (30 500–38 000)	17 000 (15 000–19 000)	1.2 (1.1–1.3) million	587 000 (524 000–659 000)
SEAR	149 000 (132 000–170 000)	73 000 (63 500–85 000)	4.1 (3.7–4.6) million	2 (1.8–2.3) million
AMR	47 500 (43 000–53 500)	23 500 (20 500–27 000)	1.1 (1–1.2) million	549 000 (499 000–607 000)
WPR	130 000 (114 000–153 000)	64 000 (55 000–75 000)	3 (2.7–3.5) million	1.5 (1.3–1.7) million
GLOBAL	**442 000** (416 000–471 000)	**217 000** (202 000–232 000)	**12.3** (11.6–12.9) **million**	**6.0** (5.7–6.3) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	35 (16–63) million	17 (8–31) million
EUR	29 (17–43) million	14 (8.4–21) million
EMR	31 (24–43) million	15 (12–21) million
SEAR	150 (130–170) million	74 (64–85) million
AMR	16 (9.9–23) million	8.1 (4.8–11) million
WPR	81 (68–96) million	40 (33–47) million
GLOBAL	**340** (290–410) **million**	**170** (140–200) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	586 (367–940)	287 (180–461)	1102 million	540 million
EUR	5108 (3665–6758) million	2503 (1796–3311) million	2338 million	1145 million
EMR	292 (1231–3580) million	1025 (603–1754) million	1893 million	928 million
SEAR	1525 (770–2951) million	747 (377–1446) million	4313 million	2114 million
AMR	8357 (4691–14 313) million	4095 (2299–7013) million	5325 million	2609 million
WPR	5104 (3063–8174) million	2501 (1501–4005) million	7773 million	3809 million
GLOBAL	**22 772** (17 712–29 852) **million**	**11 158** (8679–14 628) **million**	**22 500 million**	**11 000 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.2 *Campylobacter jejuni*

Pathogen and its epidemiology

C. jejuni is a foodborne gram-negative bacterium responsible for most cases of bacterial gastroenteritis globally. Infections can range from asymptomatic to severe, characterized by diarrhoea (frequently bloody), abdominal pain, fever, headache, nausea or vomiting *(80)*. *Campylobacter* infections have also been associated with postacute sequelae such as enteric enteropathy, stunted growth, functional bowel disorders and autoimmune disorders *(81)*. It is estimated that, in 2019, *C. jejuni* caused 139 000 deaths, with the highest incidence rates reported in the WHO African Region, South-East Asia Region and Eastern Mediterranean Region, in children aged under 5 years and in adults aged over 55 years *(48)*. The greatest burden of *C. jejuni* infection falls on communities with inadequate access to clean water and sanitation. Those in close contact with live animals or manure are also at heightened risk. Specific populations (e.g. children, people with HIV and pregnant women) face more severe complications, from neonatal sepsis to pregnancy loss *(81)*. The ramifications are not only physical; they also perpetuate socioeconomic inequalities, limiting opportunities for those affected. The economic fallout of *Campylobacter* infections is significant, pushing already vulnerable families further into poverty. Costs associated with medical fees and reduced work productivity exacerbate financial strains *(82)*.

Treatment and prevention

Usually, *C. jejuni* infections do not require treatment beyond rehydration and electrolyte replacement. Antimicrobial treatment is recommended in invasive cases (i.e. when bacteria invade the intestinal mucosa cells and damage the tissues) or to eliminate the carrier state (the condition of people who harbour *Campylobacter* in their bodies and keep shedding the bacteria while remaining asymptomatic) *(80)*. Prevention is based on control measures at all stages of the food chain, from agricultural production on a farm to processing, manufacturing and preparation of foods, both commercially and domestically. Public health measures, including community education about safe food preparation and sanitation, can help to mitigate the spread *(80)*. Vaccines being investigated for chickens show promise, but there are currently no vaccines available for use in humans or animals *(83)*.

Antimicrobial resistance

The AMR threat posed by fluoroquinolone-resistant *Campylobacter* was classified by WHO as high in 2017 *(9)*, but not in 2024 *(10)*, and by the CDC as serious *(27)*. With the rise of MDR, XDR and even pan-drug resistant (PDR) *Campylobacter* strains, the need for effective interventions has never been greater *(84)*. The WHO priority pathogen list indicates a high potential for animal-to-human transmission, underscoring the importance of using a One Health approach to address this global health challenge.

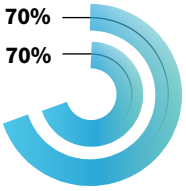
Vaccines

There is no licensed vaccine for *C. jejuni*, nor is there one in clinical development *(33)*. This report evaluates the impact on AMR of a vaccine against *C. jejuni* infection given to 70% of infants, with 5-year efficacy of 70%, as recommended by pathogen experts (Table 4.2). The vaccine characteristics were identified through consultation with pathogen experts. Given the paucity of the data, only the impact of the vaccine on antibiotic use was estimated.

Campylobacter jejuni

Table 4.2. A vaccine against *C. jejuni* infection given to 70% of infants, with 5-year efficacy of 70% [CJ]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Campylobacter jejuni	**Infants**	**5 years**	Efficacy: **70%** Coverage: **70%**	HIGH
				Feasibility of vaccine development and implementation: MEDIUM



Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	2.9 (1.5–4.9) million	1.4 million (730 000–2.4 million)
EUR	450 000 (190 000–770 000)	220 000 (95 000–380 000)
EMR	3.2 (1.7–4.9) million	1.6 million (810 000–2.4 million)
SEAR	1.6 million (940 000–2.6 million)	790 000 (460 000–1.3 million)
AMR	760 000 (350 000–1.6 million)	370 000 (170 000–760 000)
WPR	810 000 (440 000–1.4 million)	400 000 (210 000–680 000)
GLOBAL	**9.8** (5.8–15) **million**	**4.8** (2.8–7.4) **million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.3 *Clostridioides difficile*

Pathogen and its epidemiology

C. difficile is a gram-positive, spore-forming bacterium that causes severe colitis and diarrhoea. It is a primary cause of nosocomial disease, particularly among hospitalized and elderly people treated with antimicrobial therapies for other infections. The disruption of normal gut microbiota that occurs with antimicrobial therapy often leads to an infection with *C. difficile*. In 2019, the pathogen was associated with about 32 000 deaths, with the highest incidence rates reported in the WHO Region of the Americas and European Region, in adults aged over 55 years and children aged under 5 years *(48)*. Patients might be at risk through factors such as long hospital stays, previous chemotherapy sessions, HIV infection and the use of proton pump inhibitors *(85)*. A lack of testing means that the incidence of disease in LMIC may be grossly underestimated *(86)*. Overcrowding and poor hygiene standards in many LMIC, combined with the inappropriate use of antibiotics – mainly the "watch" element of the WHO AWaRe (Access, Watch, Reserve) classification *(87)* – might also contribute to the incidence of *C. difficile* infection *(88)*.

Treatment and prevention

Managing *C. difficile* infection often requires the cessation of any antibiotics the patient is taking once symptoms manifest. People with infections that recur despite antibiotic treatment might be candidates for faecal or microbiota transplants *(89)*. There is ongoing research into other treatments, including passive immunization with monoclonal antibodies *(90)*, bacteriophages *(91)* and microbiome-based therapies *(92)*. Preventive measures against the spread of *C. difficile* involve rigorous hand hygiene and use of gloves and gowns by health care staff; thorough environmental cleaning; and provision of isolation rooms for infected patients *(90)*.

Antimicrobial resistance

The widespread use of third-generation cephalosporins in the late 20th century led to a spike in diseases associated with *C. difficile*. In the early 21st century, the emergence of a "hypervirulent" fluoroquinolone-resistant strain resulted in a significant increase in cases and fatalities *(93)*. The CDC classifies this pathogen as an urgent AMR threat *(27)*. Although many isolates remain susceptible to common treatments, resistance to other antimicrobials can vary greatly, depending on the region. Recent data suggest that resistance trends for *C. difficile* are stabilizing, although concerns remain *(93, 94)*.

Vaccines

There is no licensed vaccine for *C. difficile*, but there are three candidate vaccines in clinical development *(33)*. This report evaluated the impact on AMR of a vaccine against *C. difficile* infection given to 70% of adults aged 45 years, with 5-year efficacy of 70% (Table 4.3). The vaccine characteristics were identified through analysis of a late-stage candidate vaccine (which recently failed) and with input from pathogen experts. Given the limited data, only the impact of the vaccine on antibiotic use was estimated. The impact of monoclonal antibodies and microbiota-based treatments on AMR was not considered in this report.

Clostridioides difficile

Table 4.3. A vaccine against *C. difficile* infection given to 70% of 45 adults aged 45 years, with 5-year efficacy of 70% [CD]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Clostridioides difficile	**Adults**	**5 years**	Efficacy: **70%** Coverage: **70%**	*Not assessed*
				Feasibility of vaccine development and implementation: LOW

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	3800 (120–12 000)	1900 (60–5900)
EUR	8700 (3300–20 000)	4300 (1600–9900)
EMR	7600 (3000–16 000)	3700 (1500–8000)
SEAR	27 000 (8500–53 000)	13 000 (4200–26 000)
AMR	8600 (1700–20 000)	4200 (820–10 000)
WPR	12 000 (4000–23 000)	5800 (2000–11 000)
GLOBAL	**67 000** (34 000–120 000)	**33 000** (16 000–56 000)

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.4 *Enterococcus faecium*

Pathogen and its epidemiology

E. faecium is a gram-positive bacterium that is predominantly associated with hospital-acquired infections globally. Although it typically resides harmlessly in the gut of humans and animals, in vulnerable individuals this bacterium can lead to clinical presentations, ranging from urinary tract infections and bloodstream infections to complications linked to medical devices and implants (e.g. catheters and artificial heart valves). It was estimated that, in 2019, *E. faecium* caused about 219 000 deaths, of which about 91% were associated with AMR; the highest mortality rates were in central and eastern sub-Saharan Africa *(2)*. *E. faecium* primarily affects some of the most medically at-risk populations, including immunocompromised individuals, patients in intensive care, elderly people and those with comorbidities or medical devices or implants. Although this bacterium is a global concern, its impact is particularly profound in underresourced settings; for example, in impoverished rural communities, the inability to adequately sterilize medical equipment heightens the infection risk. The repercussions of *E. faecium* infection extend beyond its immediate physical symptoms. Medical complications, extended hospital stays and the ensuing financial and psychological strain significantly affect people who are already marginalized *(95, 96)*.

Treatment and prevention

E. faecium should be treated with antibiotics, the selection of which should be informed by guidelines, such as the AWaRe classification of antibiotics for evaluation and monitoring of use, and local resistance patterns *(87)*. To prevent and control resistance, antimicrobial stewardship is pivotal. This can be achieved by educating health care workers, refining prescribing practices and raising public awareness through comprehensive media campaigns. As most *E. faecium* infections are acquired in hospitals, strategies to curb its spread emphasize improved hygiene, patient screening and isolation, and prevention of biofilm formation on medical devices *(97)*. Exploratory alternative treatments include passive immunization and antisense therapies *(98)*. *E. faecium's* prevalence in humans, domestic animals and wildlife, coupled with the potential for resistance genes to spread through horizontal gene transfer, underlines the importance of improved hygiene throughout the animal production process *(99)*.

Antimicrobial resistance

The threat posed by vancomycin-resistant strains of *E. faecium* was categorized by WHO as high *(10)* and by the CDC as serious *(27)*. Historically, *Enterococcus faecalis* was the predominant infectious agent; however, *E. faecium* has now surpassed *E. faecalis*, probably owing to its accelerated resistance development. In particular, its resistance to key antibiotics, such as penicillin, aminoglycosides and vancomycin, is increasing, making MDR and XDR strains of *E. faecium* especially concerning. Such strains have been documented in various WHO regions. The overall surge in vancomycin-resistant *E. faecium* infections, particularly in the WHO Region of the Americas, and the moderate potential for AMR outbreaks underscore the gravity of this health threat *(9, 100)*.

Vaccines

There is no licensed vaccine against *E. faecium* and none in clinical development *(33)*. This report evaluated the impact on AMR of a hypothetical vaccine against *E. faecium* infection with 5-year efficacy of 70%, as advised by pathogen experts. The use of such a vaccine was evaluated in infants and elderly people [EF_1] and in all populations at risk of infection [EF_2] (Table 4.4).

Enterococcus faecium (EF_1)

Table 4.4. A vaccine against *E. faecium* infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [EF_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Enterococcus faecium	**Infants and elderly**	**5 years**	Efficacy: **70%** Coverage: **70%**	HIGH
Vaccine name:				Feasibility of vaccine development and implementation
EF_1				LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	20 500 (18 000–22 500)	1605 (1182–2265)	866 000 (766 000–982 000)	75 500 (58 500–101 000)
EUR	42 000 (38 500–46 000)	2494 (1828–3468)	906 000 (833 000–984 000)	62 000 (45 500–83 500)
EMR	15 000 (14 000–17 000)	1078 (815–1568)	524 000 (470 000–598 000)	39 000 (29 500–51 000)
SEAR	45 000 (40 000–50 000)	3156 (2241–4486)	1.3 (1.2–1.5) million	88 500 (64 000–121 000)
AMR	34 500 (31 500–37 500)	2208 (1704–2944)	823 000 (754 000–893 000)	61 000 (48 000–77 000)
WPR	48 000 (43 500–53 500)	3272 (2309–4443)	1.1 (1–1.3) million	85 000 (63 500–115 000)
GLOBAL	**205 000** (196 000–214 000)	**14 000** (12 500–16 000)	**5.6** (5.3–5.9) **million**	**414 000** (364 000–472 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	2.7 (0.5–7.7) million	150 000 (22 000–480 000)
EUR	16 (11–25) million	780 000 (510 000–1.2 million)
EMR	6.9 (3.7–12) million	340 000 (180 000–580 000)
SEAR	25 (16–34) million	1.2 million (760 000–1.7 million)
AMR	17 (12–22) million	850 000 (590 000–1.2 million)
WPR	17 (11–24) million	850 000 (520 000–1.2 million)
GLOBAL	**85** (65–110) **million**	**4.2** (3.1–5.6) **million**

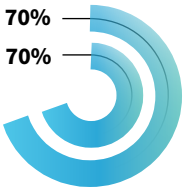
AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	152 (84.4–267) million	4.1 (2.2–7.5) million	340 million	20 million
EUR	483 (2229–7058) million	166 (95.6–272) million	1894 million	15 million
EMR	997 (475–1930) million	26 (12.1–52.6) million	442 million	15 million
SEAR	390 (157–830) million	11.8 (4.9–24.8) million	815 million	13 million
AMR	11 985 (3763–27 451) million	665 (198–1565) million	2557 million	55 million
WPR	3322 (1431–6535) million	146 (62.7–287) million	1458 million	23 million
GLOBAL	**20 928** (1279–37 859) **million**	**1019** (537–1991) **million**	**7506 million**	**140 million**

Enterococcus faecium (EF_2)

A vaccine against *E. faecium* infection given to 70% of all people at risk of infection, with 5-year efficacy of 70% [EF_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Enterococcus faecium	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	HIGH
Vaccine name:				Feasibility of vaccine development and implementation
EF_2				LOW



AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	20 500 (18 000–22 500)	9944 (8723–11 000)	866 000 (766 000–982 000)	421 000 (363 000–487 000)
EUR	42 000 (38 500–46 000)	20 500 (18 500–23 000)	906 000 (833 000–984 000)	443 000 (401 000–488 000)
EMR	15 000 (14 000–17 000)	7497 (6708–8443)	524 000 (470 000–598 000)	257 000 (225 000–298 000)
SEAR	45 000 (40 000–50 000)	22 000 (19 500–25 500)	1.3 (1.2–1.5) million	643 000 (574 000–725 000)
AMR	34 500 (31 500–37 500)	17 000 (15 500–18 500)	823 000 (754 000–893 000)	403 000 (363 000–444 000)
WPR	48 000 (43 500–53 500)	23 500 (21 000–27 000)	1.1 (1–1.3) million	553 000 (498 000–619 000)
GLOBAL	**205 000** (196 000–214 000)	**101 000** (95 500–106 000)	**5.6** (5.3–5.9) **million**	**2.7** (2.6–2.9) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	2.7 (0.5–7.7) million	1.3 (0.2–3.8) million
EUR	16 (11–25) million	8 (5.4–12) million
EMR	6.9 (3.7–12) million	3.4 (1.8–5.7) million
SEAR	25 (16–34) million	12 (7.8–17) million
AMR	17 (12–22) million	8.4 (5.7–11) million
WPR	17 (11–24) million	8.1 (5.2–12) million
GLOBAL	**85** (65–110) **million**	**41** (32–55) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	152 (84.4–267) million	74.4 (41.3–131) million	340 million	167 million
EUR	483 (2229–7058) million	21 (192–3459) million	1894 million	928 million
EMR	997 (475–1930) million	489 (233–946) million	442 million	217 million
SEAR	390 (157–830) million	191 (77.1–407) million	815 million	399 million
AMR	11 985 (3763–27 451) million	5873 (1844–13 451) million	2557 million	1253 million
WPR	3322 (1431–6535) million	1628 (701–3202) million	1458 million	714 million
GLOBAL	**20 928** (1279–37 859) **million**	**10 255** (5919–18 551) **million**	**7506 million**	**3678 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.5 Enterotoxigenic *Escherichia coli*

Pathogen and its epidemiology

ETEC belongs to the gram-negative group of *Enterobacteriaceae* and is a leading global causative agent for diarrhoeal disease, especially among children in low-resource settings and among travellers and military personnel from high-income countries *(101)*. ETEC mortality estimates in children aged under 5 years range between 19 000 deaths (Institute for Health Metrics and Evaluation [IHME] estimates) and 42 000 deaths (Maternal and Child Epidemiology Estimation estimates) *(48, 102)*. Most reported deaths are associated with resistance to antibiotics, such as fluroquinolones and vancomycin *(2)*. Among people aged over 5 years, the IHME estimates 32 000 annual deaths *(48, 101)*. ETEC predominantly affects LMIC in regions such as South-East Asia, the Middle East, Africa and Central and South America. These are areas where there is often a lack of clean water and sanitation facilities. Young children are particularly at risk of severe disease, with ETEC infections potentially leading to long-term consequences, such as reduced immune function, malnutrition, stunted growth, hindered cognitive development and other health and developmental issues *(101)*.

Treatment and prevention

WHO guidelines on the treatment of diarrhoea should be followed when treating ETEC diarrhoeal infections *(103)*. The misuse of antibiotics to treat ETEC infections has underscored the need for enhanced antimicrobial stewardship, including advanced diagnostics, comprehensive education for health care professionals to optimize prescribing habits and heightened public awareness. ETEC is transmitted via the faecal–oral route, often by faecal contamination of food and water. Preventive measures to curb ETEC transmission, including improved food and water hygiene, stringent hand hygiene, better sanitation practices and measures to restore natural microbiomes (e.g. probiotics), are essential *(101)*.

Antimicrobial resistance

The AMR threat posed by ETEC is notably high. Resistance to drugs, including critical second-line agents, is increasing in *E. coli* strains, including ETEC. WHO has classified third-generation cephalosporin-resistant *E. coli* as a critical priority *(10)*. The CDC classifies third-generation cephalosporin-resistant and carbapenem-resistant *Enterobacteriaceae*, including ETEC, as severe and immediate AMR threats *(27)*. In Asia, a systematic review has estimated the overall prevalence of MDR *E. coli* and extended-spectrum beta-lactamase-producing, diarrhoea-causing *E. coli* strains to be 66.3% and 48.6% (95% CI: 35.1–62.1), respectively *(104)*. In a study of travellers returning to the United Kingdom of Great Britain and Northern Ireland and reporting symptoms of gastrointestinal disease, 65.6% of ETEC isolates were resistant to at least one antimicrobial agent *(105)*; however, in a study of Finnish travellers, reported ETEC resistance rates were much lower *(106)*.

Vaccines

There is no vaccine against ETEC, but there are six vaccines in clinical development *(33)*. In this report, the impact on AMR was evaluated for a vaccine against moderate to severe diarrhoea caused by ETEC infection given to 70% of infants, with 5-year efficacy of 60% (Table 4.5). The vaccine characteristics were based on previously published WHO PPC for ETEC vaccines *(107)*.

Enterotoxigenic Escherichia coli (ETEC)

Table 4.5. A vaccine against moderate to severe diarrhoea caused by ETEC infection given to 70% of infants, with 5-year efficacy of 60% [ETEC]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Enterotoxigenic *Escherichia coli* (ETEC)	**Infants**	**5 years**	Efficacy: **60%** Coverage: **70%**	CRITICAL
				Feasibility of vaccine development and implementation: MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	7167 (5250–10 500)	1688 (1007–2975)	585 000 (408 000–866 000)	155 000 (96 500–262 000)
EUR	239 (193–310)	7 (4–13)	14 500 (12 000–17 500)	1183 (688–1953)
EMR	2516 (1881–3434)	420 (231–706)	170 000 (118 000–252 000)	39 000 (22 500–66 500)
SEAR	13 500 (10 500–19 000)	608 (340–992)	449 000 (355 000–573 000)	54 500 (33 500–92 000)
AMR	163 (129–204)	14 (8–23)	8728 (6937–11 000)	1710 (1076–2626)
WPR	142 (111–181)	12 (7–21)	7703 (5777–10 000)	1377 (798–2367)
GLOBAL	**24 500** (20 000–30 500)	**2779** (2043–4136)	**1.3** (1.0–1.5) **million**	**257 000** (181 000–367 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	9.3 (5.2–16) million	3.9 (2.2–6.7) million
EUR	1.4 (0.6–2.7) million	600 000 (270 000–1.1 million)
EMR	10 (5.7–16) million	4.3 (2.4–6.7) million
SEAR	5.2 (3.5–7.9) million	2.2 (1.5–3.3) million
AMR	2.4 (1.1–4.3) million	1 (0.5–1.8) million
WPR	2.6 (1.5–4) million	1.1 (0.6–1.7) million
GLOBAL	**31** (22–44) **million**	**13.0** (9.2–19) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	1680 (849–3323) million	101 (50.8–199) million	526 million	63 million
EUR	18 548 (8283–37 942) million	475 (210–1010) million	22 million	2 million
EMR	15 824 (6310–37 571) million	510 (230–1130) million	382 million	44 million
SEAR	9191 (3579–21 031) million	208 (88.7–452) million	770 million	61 million
AMR	8126 (2826–21 109) million	273 (102–670) million	36 million	4 million
WPR	2755 (1331–5365) million	52.6 (23.9–106) million	21 million	2 million
GLOBAL	**56 124** (35 971–87 726) **million**	**1620** (166–2531) **million**	**1757 million**	**176 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.6 Extraintestinal pathogenic *Escherichia coli*

Pathogen and its epidemiology

ExPEC, or *E. coli* causing extraintestinal infections, is the most common gram-negative bacterial pathogen in humans that can move out of the gastrointestinal tract and infect otherwise sterile parts of the body, leading to invasive *E. coli* disease (IED). IED is defined as an acute illness consistent with systemic bacterial infection, which is microbiologically confirmed either by the isolation and identification of *E. coli* from blood or other sterile body sites, or by the isolation and identification of *E. coli* from urine in patients with urosepsis. ExPEC also causes extraintestinal mucosal diseases, such as UTIs, wound infections, pulmonary infections and other similar intra-abdominal infections *(108)*. It was estimated that, in 2019, the pathogen caused 210 000 deaths from bloodstream infections and 101 000 deaths from UTIs, all associated with AMR *(2)*.

ExPEC infections show a significant bias towards specific demographic groups. Women aged 16–35 years are particularly susceptible to UTIs caused by ExPEC, whereas neonates and elderly people are more prone to bacteraemia or sepsis and meningitis *(108, 109)*. Socioeconomic disparities further exacerbate vulnerability to ExPEC diseases; for example, those living in poverty are at a heightened risk because of insufficient access to hygiene, nutrition, sanitation and timely medical care. The economic ramifications of ExPEC infections are profound, especially in resource-limited settings, where the costs associated with the disease can push families into extreme poverty *(110)*. Moreover, untreated *E. coli* UTIs have been linked to fertility issues and miscarriages, profoundly affecting family dynamics *(111)*. Cultural nuances further compound the problem, as seen in the United Republic of Tanzania, where women with UTIs face stigmatization *(112)*. In countries such as Benin, losing a child to meningitis or sepsis can result in the family being shunned by their community owing to the belief that they have incurred some sort of divine punishment *(113)*.

Treatment and prevention

The primary treatment for ExPEC infections is antibiotics, the regimen for which is determined by local resistance patterns. To combat AMR, there is a pressing need for antimicrobial stewardship, including enhanced diagnostic procedures, education for health care workers, improved prescription practices and public awareness campaigns *(78, 114)*. To curb the spread of infection, community-level preventive measures, such as effective hygiene practices, safe food preparation and better sanitation and nutrition, are crucial. For patients in medical facilities, rigorous infection control and prompt medical intervention are vital to prevent progression to sepsis *(114)*. Alternative treatments, including monoclonal antibodies, phage therapies and narrow-spectrum antibiotics, are being explored. Probiotics are also being examined as a preventive measure for UTIs *(115)*.

Antimicrobial resistance

WHO has classified the AMR threat from ExPEC as critical *(10)*. There is growing anxiety about ExPEC strains becoming resistant to all major antibiotic classes, especially with the rise of MDR strains. One notable MDR strain, *E. coli* O25 ST131, now constitutes more than 10% of all ExPEC infections *(116)*. The incidence of other carbapenem-resistant strains of *E.coli* (e.g. ST167 and ST410) has risen in the past decade *(117)*. The 2022 GLASS report highlights that 42% of *E. coli* bloodstream infections are resistant to third-generation cephalosporins, representing a 15% increase compared with 2020; however, the resistance was lower in countries or regions with high testing coverage *(79)*.

Reports indicate that 20–45% of ExPEC strains in the WHO Region of the Americas and European Region show resistance to first-line antibiotics *(118)*. The CDC categorizes third-generation cephalosporin-resistant and carbapenem-

resistant *Enterobacteriaceae*, including ExPEC, as significant AMR threats *(27)*. Alarmingly, there is growing resistance to carbapenem, a last-resort antibiotic. Colistin is one of the few remaining alternatives; however, resistance to colistin is also on the rise globally. The presence of PDR strains in *E. coli* only heightens the urgency of the situation *(108, 109, 119)*.

Vaccines

There is no effective vaccine available against ExPEC, but there are four vaccines in clinical development *(33)*. In this report, given the heterogeneity of syndromes caused by *E. coli*, the impact on AMR was estimated for six vaccines with distinct characteristics (Table 4.6). Vaccine impact on AMR was evaluated for vaccines targeting bloodstream infections [ExPEC_1 and 2], UTIs [ExPEC_3 and 4] and multiple disease presentations [ExPEC_5 and 6]. Vaccines were identified through consultation with pathogen experts and information on vaccine candidates in development.

Extraintestinal pathogenic *Escherichia coli* (ExPEC_1)

Table 4.6. A vaccine against bloodstream ExPEC infection given to 70% of infants and elderly people, with 5-year efficacy of 70%

Target pathogen: **Extraintestinal pathogenic *Escherichia coli* (ExPEC)**	Targeting: **Infants and elderly**	Duration: **5 years**	Usage scenario: Efficacy: **70%** Coverage: **70%**	WHO AMR priority: CRITICAL
Vaccine name: **ExPEC_1**				Feasibility of vaccine development and implementation: MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	23 500 (20 500–27 000)	1791 (1233–2785)	1.2 million (979 000–1.4 million)	84 500 (57 500–123 000)
EUR	71 000 (59 500–89 500)	4613 (2514–8737)	1.3 (1.1–1.6) million	76 500 (45 500–145 000)
EMR	14 500 (12 500–16 500)	1006 (631–1633)	563 000 (475 000–685 000)	34 000 (24 000–50 500)
SEAR	34 500 (29 500–42 000)	2645 (1418–4695)	947 000 (809 000–1.1 million)	52 000 (32 500–86 000)
AMR	28 000 (24 000–34 000)	1944 (1141–3640)	632 000 (556 000–730 000)	42 500 (28 000–66 000)
WPR	38 000 (31 500–46 000)	2737 (1479–4971)	796 000 (683 000–919 000)	50 000 (29 500–84 000)
GLOBAL	**210 000** (194 000–233 000)	**15 500** (12 000–20 000)	**5.5** (5.1–5.8) **million**	**349 000** (285 000–452 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	6.5 (2.8–11) million	330 000 (130 000–570 000)
EUR	7.5 (5.7–9.7) million	400 000 (290 000–550 000)
EMR	7.1 (5.5–9.7) million	320 000 (210 000–470 000)
SEAR	15 (12–21) million	690 000 (420 000–1 million)
AMR	7 (4.7–9.7) million	360 000 (230 000–520 000)
WPR	8.4 (6.4–11) million	400 000 (260 000–590 000)
GLOBAL	**52** (41–65) **million**	**2.5** (1.8–3.3) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	76.2 (51.9–114) million	1.4 million (958 000–2.2 million)	412 million	26 million
EUR	2343 (1693–3240) million	78.3 (55.4–109) million	1710 million	19 million
EMR	192 (125–306) million	3.2 (2–5.5) million	589 million	26 million
SEAR	101 (58.5–170) million	2.1 (1.2–3.5) million	715 million	17 million
AMR	122 (540–1812) million	30.5 (15.2–56.3) million	1011 million	35 million
WPR	533 (320–858)	20.5 (12–34.1) million	969 million	20 million
GLOBAL	**4266** (3333–5449) **million**	**136** (103–177) **million**	**5407 million**	**144 million**

Extraintestinal pathogenic *Escherichia coli* (ExPEC_2)

A vaccine against bloodstream ExPEC infection given to 70% of all people at risk of infection, with 5-year efficacy of 70%

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **ExPEC_2**				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	23 500 (20 500–27 000)	11 500 (9793–13 500)	1.2 (1.0–1.4) million	569 000 (459 000–687 000)
EUR	71 000 (59 500–89 500)	35 000 (28 500–44 500)	1.3 (1.1–1.6) million	650 000 (531 000–807 000)
EMR	14 500 (12 500–16 500)	7056 (5970–8186)	563 000 (475 000–685 000)	277 000 (230 000–351 000)
SEAR	34 500 (29 500–42 000)	17 000 (14 000–21 000)	947 000 (809 000–1.1 million)	465 000 (393 000–558 000)
AMR	28 000 (24 000–34 000)	13 500 (11 500–17 000)	632 000 (556 000–730 000)	309 000 (268 000–365 000)
WPR	38 000 (31 500–46 000)	18 500 (15 000–23 000)	796 000 (683 000–919 000)	389 000 (329 000–459 000)
GLOBAL	**210 000** (194 000–233 000)	**103 000** (93 500–115 000)	**5.5** (5.1–5.8) **million**	**2.7** (2.5–2.9) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	6.5 (2.8–11) million	3.2 (1.4–5.3) million
EUR	7.5 (5.7–9.7) million	3.7 (2.8–4.8) million
EMR	7.1 (5.5–9.7) million	3.5 (2.7–4.7) million
SEAR	15 (12–21) million	7.5 (5.7–10) million
AMR	7 (4.7–9.7) million	3.4 (2.3–4.7) million
WPR	8.4 (6.4–11) million	4.1 (3.1–5.6) million
GLOBAL	**52** (41–65) **million**	**25** (20–32) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	76.2 (51.9–114) million	37.3 (25.4–55.9) million	412 million	202 million
EUR	2343 (1693–3240) million	1148 (830–1588) million	1710 million	838 million
EMR	192 (125–306) million	93.9 (61.4–150) million	589 million	289 million
SEAR	101 (58.5–170) million	49.4 (28.7–83.3) million	715 million	350 million
AMR	122 (540–1812) million	501 (264–888) million	1011 million	495 million
WPR	533 (320–858)	261 (157–420) million	969 million	475 million
GLOBAL	**4266** (3333–5449) **million**	**291** (1633–2670) **million**	**5407 million**	**2649 million**

Extraintestinal pathogenic *Escherichia coli* (ExPEC_3)

A vaccine against urinary tract ExPEC infection given to 70% of infants and elderly people, with 5-year efficacy of 70%

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	**Infants and elderly**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **ExPEC_3**				Feasibility of vaccine development and implementation: MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**4488** (4085–5043)	**340** (244–474)	**152 000** (140 000–166 000)	**14 500** (11 000–19 500)
EUR	**21 500** (19 500–23 000)	**1229** (807–1716)	**352 000** (332 000–378 000)	**19 500** (14 000–27 000)
EMR	**5281** (4713–5873)	**382** (268–549)	**170 000** (157 000–184 000)	**13 000** (9706–17 000)
SEAR	**30 000** (27 500–32 000)	**2076** (1428–2976)	**792 000** (740 000–843 000)	**44 500** (34 000–59 000)
AMR	**23 500** (22 000–24 500)	**1564** (1060–2076)	**407 000** (386 000–429 000)	**29 000** (21 000–38 000)
WPR	**17 000** (14 500–19 500)	**1075** (647–1858)	**328 000** (287 000–377 000)	**18 500** (11 000–29 500)
GLOBAL	**101 000** (97 500–106 000)	**6727** (5659–7934)	**2.2** (2.1–2.3) **million**	**140 000** (124 000–159 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**200** (130–300) **million**	**7.1** (4.5–11) **million**
EUR	**700** (500–950) **million**	**28** (19–43) **million**
EMR	**350** (220–510) **million**	**12** (7.5–18) **million**
SEAR	**550** (410–720) **million**	**14** (11–19) **million**
AMR	**480** (320–630) **million**	**23** (14–32) **million**
WPR	**270** (210–350) **million**	**11** (8.5–15) **million**
GLOBAL	**2500** (2100–3100) **million**	**96** (75–120) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**1569** (844–2735) **million**	**42.4** (21.9–76.7) **million**	**58 million**	**4 million**
EUR	**34 761** (17 958–60 869) **million**	**924** (505–1573) **million**	**481 million**	**3 million**
EMR	**12 665** (5944–24 181) **million**	**329** (156–631) **million**	**210 million**	**11 million**
SEAR	**11 409** (4570–24 625) **million**	**166** (65.8–361) **million**	**790 million**	**18 million**
AMR	**69 282** (25 597–142 586) **million**	**3105** (199–6452) **million**	**504 million**	**13 million**
WPR	**42 305** (19 492–78 589) **million**	**1612** (686–3374) **million**	**427 million**	**5 million**
GLOBAL	**171 991** (112 384–253 643) **million**	**6178** (3780–9727) **million**	**2470 million**	**55 million**

Extraintestinal pathogenic *Escherichia coli* (ExPEC_4)

A vaccine against urinary tract ExPEC infection given to 70% of all people at risk of infection, with 5-year efficacy of 70%

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **ExPEC_4**				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**4488** (4085–5043)	**2219** (1964–2519)	**152 000** (140 000–166 000)	**74 500** (67 000–83 500)
EUR	**21 500** (19 500–23 000)	**10 500** (9319–12 000)	**352 000** (332 000–378 000)	**172 000** (155 000–190 000)
EMR	**5281** (4713–5873)	**2587** (2254–2978)	**170 000** (157 000–184 000)	**83 500** (75 000–92 000)
SEAR	**30 000** (27 500–32 000)	**14 500** (13 000–16 000)	**792 000** (740 000–843 000)	**387 000** (353 000–427 000)
AMR	**23 500** (22 000–24 500)	**11 500** (10 000–13 000)	**407 000** (386 000–429 000)	**200 000** (182 000–219 000)
WPR	**17 000** (14 500–19 500)	**8260** (6864–9828)	**328 000** (287 000–377 000)	**161 000** (138 000–186 000)
GLOBAL	**101 000** (97 500–106 000)	**49 500** (46 500–53 000)	**2.2** (2.1–2.3) **million**	**1.1** (1.0–1.2) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**200** (130–300) **million**	**97** (64–140) **million**
EUR	**700** (500–950) **million**	**340** (250–470) **million**
EMR	**350** (220–510) **million**	**170** (110–250) **million**
SEAR	**550** (410–720) **million**	**270** (200–350) **million**
AMR	**480** (320–630) **million**	**230** (160–310) **million**
WPR	**270** (210–350) **million**	**130** (100–170) **million**
GLOBAL	**2500** (2100–3100) **million**	**1200** (1000–1500) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**1569** (844–2735) **million**	**769** (414–1340) **million**	**58 million**	**28 million**
EUR	**34 761** (17 958–60 869) **million**	**1733** (8799–29 826) **million**	**481 million**	**236 million**
EMR	**12 665** (5944–24 181) **million**	**6206** (2913–11 849) **million**	**210 million**	**103 million**
SEAR	**11 409** (4570–24 625) **million**	**5590** (2239–12 066) **million**	**790 million**	**387 million**
AMR	**69 282** (25 597–142 586) **million**	**33 948** (12 542–69 867) **million**	**504 million**	**247 million**
WPR	**42 305** (19 492–78 589) **million**	**20 730** (9551–38 509) **million**	**427 million**	**209 million**
GLOBAL	**171 991** (112 384–253 643) **million**	**84 276** (5568–124 285) **million**	**2470 million**	**1210 million**

Extraintestinal pathogenic *Escherichia coli* (ExPEC_5)

A vaccine against ExPEC infection given to 70% of infants and elderly people, with 5-year efficacy of 70%

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	**Infants and elderly**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **ExPEC_5**				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	134 000 (122 000–146 000)	15 500 (13 000–19 000)	7.6 (6.8–8.7) million	1.1 million (862 000–1.3 million)
EUR	158 000 (144 000–176 000)	9601 (7461–14 000)	3.1 (2.8–3.3) million	170 000 (134 000–243 000)
EMR	64 500 (60 000–69 500)	5580 (4627–6637)	3 (2.7–3.4) million	289 000 (244 000–347 000)
SEAR	193 000 (180 000–206 000)	14 000 (11 500–17 000)	6.6 (6.1–7.3) million	430 000 (374 000–499 000)
AMR	111 000 (105 000–119 000)	7622 (6193–9404)	2.5 (2.4–2.7) million	175 000 (148 000–208 000)
WPR	132 000 (121 000–144 000)	9495 (7260–12 500)	3 (2.8–3.3) million	207 000 (173 000–257 000)
GLOBAL	**793 000** (768 000–819 000)	**62 500** (56 500–68 500)	**25.8** (24.7–27.2) **million**	**2.3** (2.1–2.6) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	230 (160–320) million	8.8 (5.8–13) million
EUR	760 (570–1000) million	32 (22–46) million
EMR	390 (260–550) million	14 (8.9–20) million
SEAR	720 (580–890) million	22 (17–27) million
AMR	540 (370–690) million	26 (17–35) million
WPR	380 (310–460) million	17 (14–21) million
GLOBAL	**3000** (2600–3600) **million**	**120** (93–140) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	3648 (2176–5867) million	72.5 (46–115) million	3451 million	400 million
EUR	61 908 (37 989–97 784) million	1257 (795–1972) million	5035 million	83 million
EMR	29 939 (15 232–58 418) million	403 (207–740) million	3717 million	282 million
SEAR	2259 (9890–46 016) million	236 (103–481) million	7413 million	295 million
AMR	81 727 (33 485–161 620) million	3309 (1254–6748) million	4617 million	187 million
WPR	49 904 (2526–89 419) million	1887 (880–3703) million	4606 million	168 million
GLOBAL	**249 184** (173 423–343 156) **million**	**7164** (4628–10 772) **million**	**29 000 million**	**1415 million**

Extraintestinal pathogenic *Escherichia coli* (ExPEC_6)

A vaccine against ExPEC infection given to 70% of all people at risk of infection with 5-year efficacy of 70%

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Extraintestinal pathogenic *Escherichia coli* (ExPEC)	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **ExPEC_6**				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**134 000** (122 000–146 442)	**65 500** (59 500–73 000)	**7.6** (6.8–8.7) **million**	**3.7** (3.3–4.4) **million**
EUR	**158 000** (144 000–176 000)	**77 500** (70 000–86 500)	**3.1** (2.8–3.3) **million**	**1.5** (1.4–1.7) **million**
EMR	**64 500** (60 000–69 500)	**31 500** (29 000–34 500)	**3** (2.7–3.4) **million**	**1.5** (1.3–1.7) **million**
SEAR	**193 000** (180 000–206 000)	**94 000** (87 000–103 000)	**6.6** (6.1–7.3) **million**	**3.2** (2.9–3.7) **million**
AMR	**111 000** (105 000–119 000)	**54 500** (50 500–59 000)	**2.5** (2.4–2.7) **million**	**1.2** (1.1–1.3) **million**
WPR	**132 000** (121 000–144 000)	**64 500** (59 000–71 500)	**3** (2.8–3.3) **million**	**1.5** (1.4–1.6) **million**
GLOBAL	**793 000** (768 000–819 000)	**389 000** (373 000–405 000)	**25.8** (24.7–27.2) **million**	**12.6** (12.0–13.5) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**230** (160–320) **million**	**110** (79–160) **million**
EUR	**760** (570–1000) **million**	**370** (280–500) **million**
EMR	**390** (260–550) **million**	**190** (130–270) **million**
SEAR	**720** (580–890) **million**	**350** (280–440) **million**
AMR	**540** (370–690) **million**	**260** (180–340) **million**
WPR	**380** (310–460) **million**	**190** (150–230) **million**
GLOBAL	**3000** (2600–3600) **million**	**1500** (1300–1800) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**3648** (2176–5867) **million**	**964** (570–1557) **million**	**3451 million**	**1433 million**
EUR	**61 908** (37 989–97 784) **million**	**21 246** (12 295–34 813) **million**	**5035 million**	**2457 million**
EMR	**29 939** (15 232–58 418) **million**	**6916** (3409–12 888) **million**	**3717 million**	**1634 million**
SEAR	**2259** (9890–46 016) **million**	**6305** (2609–13 125) **million**	**7413 million**	**3255 million**
AMR	**81 727** (33 485–161 620) **million**	**3665** (13 956–72 696) **million**	**4617 million**	**2245 million**
WPR	**49 904** (2526–89 419) **million**	**23 103** (11 307–4234) **million**	**4606 million**	**2246 million**
GLOBAL	**249 184** (173 423–343 156) **million**	**94 600** (63 733–133 829) **million**	**28 839 million**	**13 270 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.7 Group A *Streptococcus*

Pathogen and its epidemiology

Streptococcus pyogenes, commonly referred to as Group A *Streptococcus* (GAS), is a gram-positive bacterium responsible for a broad spectrum of health issues, ranging from mild infections (e.g. pharyngitis and impetigo) to more severe invasive infections (e.g. necrotizing fasciitis, streptococcal toxic shock syndrome and scarlet fever) and the development of immune-mediated life-threatening conditions (e.g. acute rheumatic fever and rheumatic heart disease) *(120)*. Estimates suggest that rheumatic heart disease claims more than 280 000 lives each year – mainly in LMIC *(121)*. Data from the GBD study suggest that GAS accounted for an estimated 198 000 deaths in 2019, up to 20% of which were associated with resistance *(2)*. More recently, the emergence of the $M1_{UK}$ serotype has been associated with surges in invasive cases in Argentina, Europe and Japan *(83)*. GAS infections predominantly affect children, older adults, immunosuppressed individuals and marginalized groups, including homeless and indigenous populations, especially in LMIC (e.g in sub-Saharan Africa, South Asia and the Pacific Islands). People in these settings often experience overcrowding, inadequate nutrition and substandard living conditions, fostering endemic disease *(122-124)*. The economic repercussions are significant, with GAS infections causing substantial loss of income, educational attainment and quality of life *(125)*. Rheumatic heart disease, for instance, imposes a disability burden comparable to a quarter of that from all cancer types and increases in maternal mortality *(126)*.

Treatment and prevention

Managing GAS infections requires a multifaceted approach, including the use of antibiotics, which varies according to the severity of disease. People with invasive infections could require intensive care and surgical interventions. Preventive strategies involve improving hand hygiene, cleaning environments and enhancing living standards to prevent transmission. Public health education and improved prescribing practices are pivotal in controlling the spread of GAS and its resistance to antibiotics *(120, 127)*.

Antimicrobial resistance

Most GAS strains are susceptible to the preferred treatments of penicillin or amoxicillin. However, there are concerns about macrolide-resistant strains, which WHO has identified as medium priority *(10)*, and erythromycin-resistant strains, which the CDC has identified as a growing concern after a noticeable increase in resistance rates *(27)*. Although penicillin resistance in GAS is rarely detected, there has been a decrease in susceptibility to penicillin, probably because of the influence of resistant microbiota. Monitoring and managing resistance trends are challenging owing to a lack of comprehensive global data *(128)*.

Vaccines

There is no approved vaccine against GAS, but there are four vaccine candidates in early clinical development *(129)*. This report evaluated the impact on AMR of a vaccine against GAS infection given to 70% of infants, with 5-year efficacy of 70% (Table 4.7). The vaccine characteristics were identified in the WHO PPC for GAS vaccines *(130)* and through consultation with pathogen experts.

Other analyses of vaccine impact on AMR

In addition to the analyses conducted by WHO, research by Miller and colleagues *(131)* assessed the potential effects of a vaccine targeting GAS. They found that a GAS vaccine that reduces GAS infection rates by 80%, achieves 80% vaccination coverage and offers protection for a decade might prevent 2.8 million antibiotic prescriptions for treating sore throats in children aged 5–14 years. This could rise to 7.5 million prevented prescriptions if a successful vaccine programme also reduced prescribing as a precautionary measure.

Group A *Streptococcus* (GAS)

Table 4.7. A vaccine against GAS infection given to 70% of infants, with 5-year efficacy of 70% [GAS]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Group A *Streptococcus* (GAS)	**Infants**	**5 years**	Efficacy: **70%** Coverage: **70%**	*Not assessed*
				Feasibility of vaccine development and implementation: MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	4611 (3983–5357)	354 (235–520)	242 000 (206 000–289 000)	30 500 (20 500–45 500)
EUR	1983 (1636–2449)	13 (8–19)	39 500 (35 500–45 000)	1367 (1006–1860)
EMR	1087 (934–1318)	60 (40–94)	48 500 (40 500–61 500)	4874 (2946–7567)
SEAR	4415 (3664–5582)	62 (42–92)	126 000 (107 000–149 000)	5715 (4024–7895)
AMR	3738 (3179–4508)	63 (44–94)	98 000 (86 000–112 000)	6053 (4050–8744)
WPR	25 500 (20 500–34 500)	224 (154–346)	646 000 (542 000–778 000)	20 500 (13 500–30 000)
GLOBAL	**42 000** (36 000–50 500)	**792** (643–998)	**1.2** (1.1–1.4) **million**	**69 000** (56 000–88 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	25 (14–41) million	12 (6.9–20) million
EUR	22 (14–32) million	11 (6.8–16) million
EMR	33 (23–47) million	16 (11–23) million
SEAR	35 (24–53) million	17 (12–26) million
AMR	20 (13–29) million	10 (6.2–14) million
WPR	12 (8.1–18) million	6 (4.0–8.8) million
GLOBAL	**150** (110–190) **million**	**72** (54–92) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	857 (432–1614) million	73.4 (36.1–144) million	74 million	10 million
EUR	25 850 (12 318–49 304) million	483 (244–892) million	86 million	3 million
EMR	2560 (1065–5479) million	115 (50.8–242) million	35 million	4 million
SEAR	1771 (326–6178) million	64 (12.8–220) million	59 million	3 million
AMR	23 690 (3852–80 651) million	561 (121–1771) million	196 million	14 million
WPR	52 901 (8764–156 180) million	2269 (371–6896) million	766 million	33 million
GLOBAL	**107 629** (48 533–231 704) **million**	**3566** (1424–8423) **million**	**1216 million**	**66 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.8 *Haemophilus influenzae* type b

Pathogen and its epidemiology

H. influenzae is a gram-negative bacterium that predominantly resides as a harmless commensal in the nasopharynx of many healthy children and adults. However, it has the potential to cause both mild infections and severe invasive diseases, such as meningitis and pneumonia. In the past decade, about 90% of these invasive infections were attributed to the *H. influenzae* serotype b, commonly referred to as Hib *(132)*. However, recently, non-typeable *H. influenzae* has been the dominant pathogen causing invasive disease *(133, 134)*. There are conjugate vaccines for Hib, and these are routinely administered to infants as a preventive measure *(132)*; nevertheless, there were an estimated 76 000 deaths from Hib in 2019, of which 87% occurred in children aged under 5 years *(135)*. Other vulnerable populations include elderly people, those residing in overcrowded or low-income settings, and immunocompromised individuals. LMIC in Asia and central Africa report the highest mortality rates from Hib *(132)*; these high rates are often caused by insufficient coverage of Hib vaccines. Factors such as distrust of foreign-manufactured vaccines and physical inaccessibility (e.g. for nomadic pastoralists in Africa) contribute to reduced vaccine uptake *(136, 137)*. Beyond the immediate health implications, Hib disease imposes substantial economic and social burdens, particularly in underresourced communities with lower vaccine coverage. The illness can result in missed educational and work opportunities, push families into poverty and even lead to lifelong complications, such as blindness or learning difficulties in affected children *(137-139)*.

Treatment and prevention

Invasive Hib infections such as meningitis and pneumonia are generally treated with antibiotics *(132)*. A crucial aspect of managing Hib is antimicrobial stewardship, which emphasizes public education about vaccination, audit and feedback for health care personnel and improved prescribing practices *(114)*. Hib bacteria are transmitted from person to person through respiratory droplets, with the infection pathway being through either the bloodstream or neighbouring tissues. The primary preventive measure against Hib is vaccination. There are no known animal–human or environmental transmission routes *(132)*.

Antimicrobial resistance

In 2017 and 2024, WHO categorized ampicillin-resistant *H. influenzae* (all serotypes) as a medium AMR priority *(9, 10)*. Although resistance to ampicillin has been observed, vaccination initiatives have significantly reduced infection rates, including infection from resistant strains. Rates of ampicillin-resistant Hib infection have remained consistent globally over the past decade, indicating a low potential for AMR outbreaks *(9)*. MDR and XDR strains have been identified in most WHO regions, but PDR strains remain unreported, meaning that treatments such as cefotaxime still remain effective against Hib *(140)*.

Vaccines

Hib conjugate vaccines – comprising the capsule component polyribosylribitol phosphate joined to a carrier protein – are licensed and recommended by WHO for inclusion in all infant immunization programmes, with global coverage of the third dose estimated to be 73% in 2022 *(141)*. Additionally, there are four vaccines in clinical development *(33)*. This report evaluated the impact on AMR of the existing Hib vaccine [Hib_1] and its expanded use [Hib_2] to meet the WHO-recommended vaccine coverage of 90% (Table 4.8).

Haemophilus influenzae type b (Hib_1)

Table 4.8. A vaccine against Hib infection given to 74% of infants (2019 coverage), with 5-year efficacy of 93% [Hib_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
***Haemophilus influenzae* type b (Hib)**	**Infants**	**5 years**	Efficacy: **93%** Coverage: **74%**	MEDIUM
Vaccine name: **Hib_1**				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	19 000 (17 000–22 000)	6485 (5059–8281)	1.5 (1.3–1.8) million	571 000 (441 000–735 000)
EUR	1604 (1497–1718)	150 (114–195)	42 000 (38 000–46 500)	11 500 (8360–15 000)
EMR	4950 (4308–5769)	2020 (1600–2588)	397 000 (338 000–461 000)	179 000 (138 000–228 000)
SEAR	4202 (3755–4609)	1083 (847–1359)	259 000 (228 000–291 000)	95 500 (76 000–122 000)
AMR	2823 (2645–3063)	337 (260–435)	101 000 (90 500–111 000)	28 500 (21 000–35 500)
WPR	8982 (8307–9709)	1093 (843–1333)	318 000 (292 000–345 000)	95 000 (76 000–120 000)
GLOBAL	**42 000** (39 500–45 500)	**11 500** (9690–13 000)	**2.6** (2.4–2.9) **million**	**979 000** (850 000–1.2 million)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	6.3 (1.7–26.4) million	3.2 million (790 000–13 million)
EUR	4.6 million (960 000–17.1 million)	3.4 million (710 000–13 million)
EMR	4 million (830 000–14.7 million)	2.5 million (510 000–9.3 million)
SEAR	3.2 million (730 000–12.8 million)	2.3 million (510 000–9.2 million)
AMR	2.4 million (407 000–8.9 million)	1.6 million (270 000–5.9 million)
WPR	1.8 million (405 000–6.7 million)	1.1 million (250 000–4.3 million)
GLOBAL	**22.2** (5.5–87) **million**	**14** (3.4–56) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	2.7 (1.2–5.4) million	500 000 (227 000–1.1 million)	105 million	33 million
EUR	25.3 (12.8–46.5) million	1.6 million (863 000–2.8 million)	24 million	6 million
EMR	9.5 (3.8–20.9) million	1.4 million (513 000–3.3 million)	61 million	19 million
SEAR	7.8 (1.3–26.3) million	582 000 (105 000–1.9 million)	43 million	11 million
AMR	40.4 (7.2–157) million	2.8 million (605 000–10.4 million)	32 million	8 million
WPR	9.4 (2.8–22.9) million	676 000 (228 000–1.5 million)	46 million	13 million
GLOBAL	**95** (49.1–214) **million**	**7.6** (4.3–14.9) **million**	**312 million**	**90 million**

Haemophilus influenzae type b (Hib_2)

A vaccine against Hib infection given to 90% of infants, with 5-year efficacy of 93% [Hib_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
***Haemophilus influenzae* type b (Hib)**	**Infants**	**5 years**	Efficacy: **93%** Coverage: **90%**	MEDIUM
Vaccine name: **Hib_2**				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	19 000 (17 000–22 000)	8005 (6275–10 000)	1.5 (1.3–1.8) million	699 000 (544 000–911 000)
EUR	1604 (1497–1718)	144 (110–189)	42 000 (38 000–46 500)	11 000 (7919–14 500)
EMR	4950 (4308–5769)	2148 (1690–2722)	397 000 (338 000–461 000)	189 000 (144 000–243 000)
SEAR	4202 (3755–4609)	1079 (840–1355)	259 000 (228 000–291 000)	94 000 (75 000–123 000)
AMR	2823 (2645–3063)	357 (275–467)	101 000 (90 500–111 000)	30 000 (22 000–37 500)
WPR	8982 (8307–9709)	1143 (877–1414)	318 000 (292 000–345 000)	99 500 (80 000–126 000)
GLOBAL	**42 000** (39 500–45 500)	**13 000** (11 000–15 000)	**2.6** (2.4–2.9) **million**	**1.1 million** (961 000–1.3 million)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	6.3 (1.7–26.4) million	3.9 million (970 000–16.1 million)
EUR	4.6 million (960 000–17.1 million)	3.4 million (710 000–13 million)
EMR	4 million (830 000–14.7 million)	2.7 million (544 000–10 million)
SEAR	3.2 million (730 000–12.8 million)	2.3 million (510 000–9.2 million)
AMR	2.4 million (407 000–8.9 million)	1.7 million (282 000–6.1 million)
WPR	1.8 million (405 000–6.7 million)	1.2 million (266 000–4.6 million)
GLOBAL	**22.2** (5.5–87) **million**	**15** (3.7–60.4) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	2.7 (1.2–5.4) million	615 000 (279 000–1.3 million)	105 million	40 million
EUR	25.3 (12.8–46.5) million	1.6 million (830 000–2.7 million)	24 million	6 million
EMR	9.5 (3.8–20.9) million	1.5 million (548 000–3.5 million)	61 million	21 million
SEAR	7.8 (1.3–26.3) million	580 000 (105 000–1.9 million)	43 million	11 million
AMR	40.4 (7.2–157) million	3 million (632 000–10.9 million)	32 million	9 million
WPR	9.4 (2.8–22.9) million	720 000 (242 000–1.6 million)	46 million	13 million
GLOBAL	**95** (49.1–214) **million**	**7.9** (4.5–15.6) **million**	**312 million**	**99 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.9 *Helicobacter pylori*

Pathogen and its epidemiology

H. pylori is a gram-negative bacterium that is known to be the most common chronic bacterial infection globally; it is thought to colonize the stomachs of more than half the human population. Although often asymptomatic, this microorganism is a significant etiological factor for chronic gastritis, peptic ulcer disease and gastric cancer – conditions serious enough for *H. pylori* to be classified as a group 1 carcinogen *(142)*. *H. pylori* accounts for most cases of gastric ulcer and cancer, marking its prominence in gastroenterological diseases. The estimated global prevalence of *H. pylori* infection decreased from 58.2% (95% CI: 50.7–65.8) in 1980–1990 to 43.1% (40.3–45.9) in 2011–2022 *(143)*.

H. pylori infection shows a stark disparity in incidence and impact among different populations, disproportionately affecting people in LMIC, especially in Asia. Infection risk is increased by socioeconomic factors such as poor sanitation, high-density living and inadequate health care access *(144)*. The economic implications are profound, with medical costs and income loss due to illness exacerbating poverty *(145)*. Furthermore, cultural practices, including alternative healing traditions and gendered health-seeking behaviour, influence disease prevalence and outcomes *(146)*; for example, African Americans in the US have a higher infection rate, and gendered differences in health literacy and treatment-seeking are noted across various cultures *(147, 148)*.

Treatment and prevention

Management of *H. pylori* infection employs combination antibiotic therapies, such as a triple-therapy regimen of proton pump inhibitors and antibiotics (e.g. clarithromycin and amoxicillin). However, treatment success is not guaranteed, necessitating post-therapy testing and alternative treatment if the initial treatment fails *(149)*.

Innovative and improved diagnostics and improved antimicrobial stewardship are part of the effort to counter AMR in *H. pylori*, alongside adjunctive strategies such as bismuth supplementation and probiotics *(150)*. Preventive measures against *H. pylori* transmission primarily target human-to-human routes, such as saliva and contaminated food or water. Access to clean water, enhanced sanitation and hygiene education are critical in preventing infection, especially within households and during early childhood *(151)*.

Antimicrobial resistance

AMR in *H. pylori* is an escalating threat, with clarithromycin resistance becoming more common. In 2017, WHO classified the threat of AMR from clarithromycin-resistant *H. pylori* as high *(9)*, but not in 2024 *(10)*. In a systematic review and meta-analysis, primary and secondary resistance rates to clarithromycin, metronidazole and levofloxacin were at least 15% in all WHO regions, except for primary clarithromycin resistance in the WHO Region of the Americas (10%; 95% CI, 4–16) and the South-East Asia Region (10%; 95% CI, 5–16) and primary levofloxacin resistance in the European Region (11%; 95% CI, 9–13) *(152)*. The surge in clarithromycin-resistant strains over the past decade underscores the urgent need for vigilant surveillance and innovative management strategies against this persistent pathogen.

Vaccines

There is no licensed vaccine for *H. pylori*, and there are no vaccines in active clinical development *(33)*. This report evaluated the impact on AMR of a vaccine against *H. pylori* infection given to 70% of infants, with 5-year efficacy of 70% (Table 4.9), as suggested by pathogen experts. Due to limited data, only the vaccine's potential impact on antibiotic use was evaluated.

Helicobacter pylori

Table 4.9. A vaccine against *H. pylori* infection given to 70% of infants, with 5-year efficacy of 70% [HP]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Helicobacter pylori	**Infants**	**5 years**	Efficacy: **70%** Coverage: **70%**	HIGH
				Feasibility of vaccine development and implementation: MEDIUM

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**910 000** (330 000–1.6 **million**)	**440 000** (160 000–760 000)
EUR	**48 000** (19 000–82 000)	**23 000** (9300–40 000)
EMR	**410 000** (190 000–680 000)	**200 000** (95 000–330 000)
SEAR	**690 000** (290 000–1.2 **million**)	**340 000** (140 000–570 000)
AMR	**58 000** (20 000–110 000)	**28 000** (9800–53 000)
WPR	**160 000** (66 000–280 000)	**78 000** (32 000–140 000)
GLOBAL	**2.3** (1.1–3.6) **million**	**1.1 million** (540 000–1.8 **million**)

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.10 *Klebsiella pneumoniae*

Pathogen and its epidemiology

K. pneumoniae is a gram-negative bacterium that belongs to the *Enterobacteriaceae* family. It can be acquired in the community or in hospitals, with major presentations ranging from bloodstream infections and UTIs to meningitis, pneumonia and surgical site infections. It was estimated that, in 2019, about 790 000 deaths were caused by drug-susceptible and drug-resistant *K. pneumoniae*, of which about 656 000 were associated with AMR *(2)*.

K. pneumoniae poses a significant threat to certain populations, including neonates, elderly people, immunocompromised individuals and hospitalized patients with underlying health conditions. This pathogen is the leading cause of sepsis in neonates in LMIC and is responsible for most of the half million neonatal deaths from sepsis that occur each year in sub-Saharan Africa and parts of Asia *(153)*. In a multicentre study across seven sub-Saharan African and South Asian countries between 2015 and 2017, *K. pneumoniae* was reported as the leading cause of neonatal sepsis *(154, 155)*. IPC is paramount in limiting the spread of *K. pneumoniae*, given that most cases in neonates and adults are hospital-associated infections *(153)*. Regions with inadequate access to clean water and proper sanitation and hygiene, especially in LMIC, experience heightened risks. Hospital hygiene is paramount, and lapses can result in outbreaks. Cultural practices (e.g. certain postbirth rituals in Uganda) can also elevate the risk of infection *(156)*. Beyond the health implications, infections with *K. pneumoniae* have profound economic and social consequences, particularly in impoverished areas, from prolonged hospital stays, loss of income and long-term psychological distress *(153, 157)*.

Treatment and prevention

A high proportion of *K. pneumoniae* infections are MDR, including resistance to carbapenem, as shown by studies of child deaths in LMIC *(155)*. Treating *K. pneumoniae* is complex but should be based on regional resistance profiles, presentation and severity of infection and the target population *(78)*. In health care environments, transmission often occurs via contaminated equipment or inadequate hand hygiene by health care personnel. Improvement of hospital IPC includes strategies to strengthen rigorous cleaning procedures, non-contact disinfection, hand hygiene and equipment use policies *(114)*. Stewardship initiatives to improve the use of appropriate antibiotics – encompassing health care staff education and awareness campaigns – have also been employed to variable effect. In addition to being found in the gut, *K. pneumoniae* is found in environmental sources; thus, enhancing access to clean water, sanitation and improved food hygiene can aid in curbing infections *(153, 158)*. Passive immunization using monoclonal antibodies is an area of active research but is inherently challenging, given the multiple serotypes of *Klebsiella* that cause invasive infection *(159)*.

Antimicrobial resistance

WHO has categorized the AMR threat posed by the third-generation cephalosporin-resistant *K. pneumoniae* as critical *(10)*. This bacterium has amassed an unparalleled number of AMR-associated genes, acting as a nexus for AMR gene accumulation and dissemination to other bacteria. A new hypervirulent *K. pneumoniae* pathotype with enhanced potential to cause disease has emerged *(160)*. This pathotype was previously reported primarily in South-East Asia but is now spreading to other geographical regions. The resistance to third-generation cephalosporins and carbapenems is particularly concerning. The CDC classifies certain resistant strains of *K. pneumoniae* as an urgent AMR threat *(27)*. Reports of MDR, XDR and PDR strains of *K. pneumoniae* are widespread, underscoring the urgency of managing this pathogen *(9, 153, 161)*.

Vaccines

There is no licensed vaccine against *K. pneumoniae*, but there is one vaccine in clinical development *(33)*. This report evaluated the potential impact of vaccines on AMR for a maternal

vaccine against bloodstream infection [KP_1] and a vaccine against a broad range of syndromes given to different population groups [KP_2 and 3] (Table 4.10), as suggested by pathogen experts.

Other analyses of vaccine impact on AMR

In addition to analyses coordinated by WHO, a study assessed the potential impact on neonatal sepsis infections and mortality of a maternal vaccine against *K. pneumoniae* with 70% efficacy, administered at coverage levels similar to those of the maternal tetanus vaccine *(162)*. That study used data from three global studies of neonatal sepsis and mortality, which included surveillance of 2330 neonatal deaths from sepsis between 2016 and 2020 in 18 countries, mainly LMIC, across all WHO regions. Its findings suggest that, globally, maternal vaccination could prevent 80 500 neonatal deaths (credible interval [CrI]: 18 000–189 000) and 399 000 cases of neonatal sepsis (CrI: 335 000–485 000) each year, accounting for more than 3.40% (CrI: 0.75–8.01) of all neonatal deaths. The most substantial relative benefits were seen in African nations (Mali, Niger and Sierra Leone) and in South-East Asia (specifically Bangladesh), where vaccination could avert more than 6% of all neonatal deaths.

Klebsiella pneumoniae (KP_1)

Table 4.10. A vaccine against bloodstream *K. pneumoniae* infection given to 70% of infants through maternal vaccination, with 6-month efficacy of 70% [KP_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Klebsiella pneumoniae	**Infants**	**6 month**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **KP_1**				Feasibility of vaccine development and implementation: MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	57 500 (49 000–67 500)	14 000 (9889–20 500)	3.8 (3.1–4.6) million	1.3 million (892 000–1.8 million)
EUR	26 500 (22 000–32 000)	345 (251–495)	601 000 (522 000–697 000)	31 000 (22 000–42 500)
EMR	26 000 (22 000–31 000)	4981 (3497–7598)	1.5 (1.2–1.9) million	451 000 (300 000–690 000)
SEAR	57 500 (49 000–67 500)	5529 (3831–8201)	2.1 (1.8–2.7) million	489 000 (324 000–790 000)
AMR	22 500 (19 500–25 500)	1249 (915–1654)	697 000 (616 000–797 000)	109 000 (85 000–148 000)
WPR	31 000 (25 500–36 500)	726 (554–1001)	798 000 (697 000–912 000)	66 500 (50 000–89 000)
GLOBAL	**221 000** (204 000–240 000)	**27 500** (22 000–35 000)	**9.5** (8.6–10.5) **million**	**2.4** (2.0–3.1) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	76 000 (30 000–140 000)	37 000 (15 000–69 000)
EUR	3200 (1500–5700)	1600 (760–2800)
EMR	44 000 (22 000–70 000)	22 000 (11 000–35 000)
SEAR	58 000 (31 000–91 000)	29 000 (15 000–45 000)
AMR	11 000 (5900–18 000)	5500 (2900–9000)
WPR	18 000 (9500–29 000)	8700 (4700–14 000)
GLOBAL	**210 000** (110 000–340 000)	**100 000** (51 000–170 000)

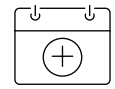
AMR economic burden

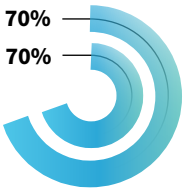
WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	170 (124–235) million	34.3 (25.6–46.7) million	1863 million	607 million
EUR	1110 (736–1700) million	77.3 (46.4–128.8) million	1802 million	133 million
EMR	259 (168–421) million	48.3 (30.4–79.1) million	1814 million	577 million
SEAR	178 (96–321) million	28.5 (15.8–50.6) million	2189 million	600 million
AMR	568 (362–871) million	49 (33–73.3) million	2137 million	413 million
WPR	230 (128–392) million	41.6 (19.8–77.3) million	1450 million	177 million
GLOBAL	**2516** (216–3231) **million**	**279** (224–357) **million**	**11 255 million**	**2508 million**

Klebsiella pneumoniae (KP_2)

A vaccine against *K. pneumoniae* infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [KP_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Klebsiella pneumoniae	**Infants and elderly**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **KP_2**				Feasibility of vaccine development and implementation: LOW





AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	187 000 (175 000–205 000)	26 500 (22 000–31 000)	11.9 (10.8–13.1) million	2 (1.7–2.5) million
EUR	71 000 (66 000–77 000)	4217 (3271–5933)	1.6 (1.5–1.7) million	116 000 (94 500–146 000)
EMR	71 000 (65 500–77 500)	7656 (6455–9206)	3.9 (3.5–4.4) million	509 000 (416 000–638 000)
SEAR	179 000 (167 000–192 000)	15 000 (12 500–18 500)	6.8 (6.2–7.6) million	638 000 (531 000–782 000)
AMR	67 500 (64 000–72 000)	4850 (3967–6135)	1.8 (1.7–1.9) million	179 000 (151 000–217 000)
WPR	79 000 (72 000–86 500)	6097 (4777–8246)	2 (1.9–2.2) million	200 000 (166 000–244 000)
GLOBAL	**656 000** (636 000–679 000)	**64 500** (58 500–72 000)	**28** (26.6–29.5) **million**	**3.7** (3.3–4.1) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	56 (36–78) million	2.8 (1.6–4.1) million
EUR	74 (57–100) million	3.7 (2.7–5) million
EMR	63 (52–77) million	2.8 (2.1–3.8) million
SEAR	360 (320–400) million	16 (12–21) million
AMR	72 (59–87) million	3.5 (2.8–4.6) million
WPR	190 (170–220) million	9.4 (6.9–12) million
GLOBAL	**820** (730–900) **million**	**38** (29–48) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	781 (531–1156) million	38.5 (26.9–54.8) million	6088 million	1036 million
EUR	1588 (9787–23 295) million	619 (401–939) million	5003 million	194 million
EMR	3363 (1901–5942) million	118 (69.4–200) million	4939 million	589 million
SEAR	3801 (1662–7680) million	121 (52.9–247) million	7616 million	580 million
AMR	12 134 (6019–22 508) million	592 (279–1137) million	5334 million	434 million
WPR	5402 (2973–9278) million	213 (124–347) million	3787 million	290 million
GLOBAL	**40 569** (30 378–53 424) **million**	**1700** (1244–2322) **million**	**32 767 million**	**3122 million**

Klebsiella pneumoniae (KP_3)

A vaccine against *K. pneumoniae* infection given to 70% of all people at risk of infection, with 5-year efficacy of 70% [KP_3]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Klebsiella pneumoniae	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **KP_3**				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**187 000** (175 000–205 000)	**92 000** (84 000–102 000)	**11.9** (10.8–13.1) **million**	**5.8** (5–6.6) **million**
EUR	**71 000** (66 000–77 000)	**35 000** (32 000–38 500)	**1.6** (1.5–1.7) **million**	**771 000** (719 000–831 000)
EMR	**71 000** (65 500–77 500)	**34 500** (31 500–38 500)	**3.9** (3.5–4.4) **million**	**1.9** (1.7–2.2) **million**
SEAR	**179 000** (167 000–192 000)	**88 000** (80 500–95 500)	**6.8** (6.2–7.6) **million**	**3.4** (3–3.8) **million**
AMR	**67 500** (64 000–72 000)	**33 000** (31 000–35 500)	**1.8** (1.7–1.9) **million**	**880 000** (812 000–950 000)
WPR	**79 000** (72 000–86 500)	**38 500** (35 000–42 500)	**2.0** (1.9–2.2) **million**	**990 000** (912 000–1.1 **million**)
GLOBAL	**656 000** (636 000–679 000)	**321 000** (309 000–336 000)	**28** (26.6–29.5) **million**	**13.7** (12.8–14.7) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**56** (36–78) **million**	**27** (18–38) **million**
EUR	**74** (57–100) **million**	**36** (28–49) **million**
EMR	**63** (52–77) **million**	**31** (26–38) **million**
SEAR	**360** (320–400) **million**	**180** (160–200) **million**
AMR	**72** (59–87) **million**	**35** (29–43) **million**
WPR	**190** (170–220) **million**	**95** (83–110) **million**
GLOBAL	**820** (730–900) **million**	**400** (360–440) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**781** (531–1156 million) **million**	**383** (260–566) **million**	**6088 million**	**2983 million**
EUR	**1588** (9787–23 295) **million**	**7393** (4795–11 415) **million**	**5003 million**	**2451 million**
EMR	**3363** (1901–5942) **million**	**1648** (931–2912) **million**	**4939 million**	**2420 million**
SEAR	**3801** (1662–7680) **million**	**1862** (815–3763) **million**	**7616 million**	**3732 million**
AMR	**12 134** (6019–22 508) **million**	**5946** (2950–11 029) **million**	**5334 million**	**2614 million**
WPR	**5402** (2973–9278) **million**	**2647** (1457–4546) **million**	**3787 million**	**1855 million**
GLOBAL	**40 569** (30 378–53 424) **million**	**19 879** (14 885–26 178) **million**	**32 767 million**	**16 056 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.11 *Mycobacterium tuberculosis*

Pathogen and its epidemiology

M. tuberculosis is an intracellular bacterial pathogen that causes the disease TB. Although the primary site for this infection is the lungs, it has the potential to affect other body parts. An estimated one quarter of the world's population has been infected with *M. tuberculosis*, with 5–10% of those infected developing active disease during the course of their lives, usually within the first 5 years after infection *(163-165)*. It is estimated that the pathogen resulted in 1.3 million deaths in 2022, of which MDR TB or rifampicin resistant TB (RR-TB) caused an estimated 160 000 deaths *(166, 167)*.

TB predominantly affects people in underprivileged and marginalized sectors of society. Two thirds of the global TB cases in 2022 were in eight countries: India (27%), Indonesia (10%), China (7.1%), the Philippines (7.0%), Pakistan (5.7%), Nigeria (4.5%), Bangladesh (3.6%) and the Democratic Republic of the Congo (3.0%) *(167)*. Vulnerable populations include infants, children, adolescents, pregnant women and elderly people, especially if coupled with malnutrition. TB is also the leading cause of death among people living with HIV *(166, 167)*.

Socioeconomic challenges increase the infection risk, with TB transmission being rampant in poorly ventilated, crowded and impoverished settings. TB's economic repercussions are grave, as people with TB are often unable to work, leading to substantial loss of income *(168)*. The societal consequences are equally pressing – people with TB face stigma, isolation and mental health problems *(168)*.

Treatment and prevention

This bacterial pathogen primarily spreads through droplets released into the air, such as during a cough. Strategies to curb its dissemination include preventive measures, such as respiratory hygiene infection control measures *(169)*, early diagnosis, rapid treatment initiation *(163)* and compliance with antibiotic stewardship programmes. WHO recommends that treatment for drug-susceptible TB should include combination treatment with rifampicin, isoniazid, pyrazinamide and ethambutol *(50)*. Managing drug-resistant TB involves following treatment regimens tailored to the specific resistance profile *(50)*. Overall, a multisectoral approach is required to curb the MDR-TB crisis, including early diagnosis, adherence to treatment, affordable and accessible health care, socioeconomic support, and education and awareness raising to eliminate stigma and discrimination associated with TB *(166, 167)*.

Antimicrobial resistance

Drug-resistant forms of TB cause significant morbidity and mortality and impose a substantial burden on health care and community systems, especially in LMIC. Rifampicin is usually a highly effective drug in the treatment of TB, but it was estimated that 410 000 people developed RR-TB in 2022. Although considerable attention has been directed towards TB showing resistance to rifampicin, an estimated 1.3 million people developed TB resistant to isoniazid (a first-line drug for TB treatment) in that same year. Accurately estimating the prevalence of various resistance profiles remains challenging because of underdiagnosis, exemplified by the limited use (47% in 2022) of WHO-recommended rapid molecular diagnostics as the initial TB test. Additionally, problems persist regarding accessibility, affordability and availability of tests for drug susceptibility, particularly for recently recommended new or repurposed drugs *(166, 167)*.

Recently, WHO endorsed the use of new all-oral 6-month regimens that shorten treatment duration and improve health outcomes, to treat people with RR-TB, MDR-TB and pre-XDR-TB *(50)*. To expand access to these regimens, it is essential to fill evidence gaps on their efficacy, safety and tolerability across regions, countries and subpopulations for whom data are limited or missing. Overall, treatment for MDR-TB is costlier and carries more potential side-effects, emphasizing the urgent need for continued R&D for better tests and treatment regimens, and comprehensive approaches to limiting the emergence and impact of drug resistance across the continuum of care *(166, 167)*.

Vaccines

Licensed vaccines based on bacille Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, are effective at preventing severe disease caused by *M. tuberculosis* in young children when administered at birth or soon after. These vaccines are widely used, but their efficacy varies depending on geography and strain, ranging from zero to 80% in preventing pulmonary TB disease, with efficacy appearing to fall in areas closer to the equator and effectiveness decreasing in adolescence *(170)*. There are multiple vaccines in development for prevention of *M. tuberculosis*, targeting people of different ages, and stages of infection or disease; however, most of these vaccines are intended to prevent disease in adults and adolescents *(167)*. Based on the published WHO PPCs *(171)*, the potential impact of two types of new TB vaccines on AMR was evaluated: a vaccine given to infants to prevent TB disease [TB_1] and a vaccine given to adolescents to prevent progression infection to active TB disease [TB_2] (Table 4.11).

Other analyses of vaccine impact on AMR

In addition to WHO's analyses, the potential impact of a postexposure TB vaccine on the global burden of RR-TB and MDR-TB has been evaluated *(172)*. Focusing on 30 countries that accounted for 90% of global RR-TB cases in 2018, researchers estimated that a vaccine with 50% efficacy could avert 10% of RR-TB cases and 7.3% of deaths from 2020 to 2035. This impact would be most pronounced in China, India, Indonesia, Pakistan and the Russian Federation. Furthermore, when combined with improvements in diagnosis and treatment, the vaccine's effect could increase to a 14% reduction in cases and a 31% decrease in deaths, highlighting its potential in substantially mitigating the global challenge of RR-TB and MDR-TB.

Mycobacterium tuberculosis (TB_1)

Table 4.11. A vaccine against pulmonary *M. tuberculosis* disease given to 70% of infants, with 10-year efficacy of 80% and subsequent boosting to ensure lifelong protection [TB_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Mycobacterium tuberculosis	**Infants**	**10 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **TB_1**				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	43 000 (39 000–48 000)	24 000 (21 500–27 500)	1.9 (1.7–2.1) million	1.1 million (934 000–1.2 million)
EUR	12 000 (11 000–13 000)	6661 (5909–7462)	504 000 (466 000–545 000)	282 000 (250 000–317 000)
EMR	19 500 (17 000–22 500)	10 500 (9191–13 000)	899 000 (776 000–1 million)	501 000 (419 000–588 000)
SEAR	116 000 (98 000–134 000)	64 500 (54 500–76 500)	4.1 (3.5–4.9) million	2.3 (2–2.7) million
AMR	2508 (2224–2829)	1399 (1201–1614)	88 000 (78 000–99 500)	49 000 (42 500–57 000)
WPR	18 500 (16 500–21 000)	10 500 (8947–12 000)	632 000 (570 000–700 000)	353 000 (309 000–401 000)
GLOBAL	**211 000** (193 000–231 000)	**118 000** (107 000–131 000)	**8.1** (7.5–8.9) **million**	**4.6** (4.1–5.0) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	690 (670–700) million	380 (380–390) million
EUR	150 (150–160) million	85 (83–87) million
EMR	260 (250–270) million	150 (140–150) million
SEAR	1600 (1500–1600) million	870 (830–910) million
AMR	120 (120–120) million	69 (68–70) million
WPR	700 (680–720) million	390 (380–400) million
GLOBAL	**3500** (3400–3500) **million**	**1900** (1900–2000) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	32.2 (17.2–60.3) million	18.1 (9.6–33.8) million	451 million	253 million
EUR	1399 (690–2648) million	784 (387–1483) million	824 million	461 million
EMR	49.7 (23.5–89.6) million	27.8 (13.2–50.2) million	459 million	257 million
SEAR	243 (25.2–734) million	136 (14.1–411) million	1393 million	780 million
AMR	64.4 (33–110) million	36 (18.5–61.6) million	136 million	76 million
WPR	19.2 (6.5–40) million	10.8 (3.6–22.4) million	306 million	171 million
GLOBAL	**1807** (973–3181) **million**	**1012** (545–1781) **million**	**3569 million**	**1999 million**

Mycobacterium tuberculosis (TB_2)

A vaccine against pulmonary *M.tuberculosis* disease given to 70% of children aged 10 years, with 10-year efficacy of 50% and subsequent boosting to ensure lifelong protection [TB_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Mycobacterium tuberculosis	**Children aged 10 years**	**10 years**	Efficacy: **50%** Coverage: **70%**	CRITICAL
Vaccine name: **TB_2**				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	43 000 (39 000–48 000)	13 500 (12 000–15 500)	1.9 (1.7–2.1) million	521 000 (455 000–595 000)
EUR	12 000 (11 000–13 000)	4098 (3614–4656)	504 000 (466 000–545 000)	170 000 (153 000–191 000)
EMR	19 500 (17 000–22 500)	6015 (5137–7222)	899 000 (776 000–1 million)	252 000 (206 000–308 000)
SEAR	116 000 (98 000–134 000)	40 000 (33 500–48 000)	4.1 (3.5–4.9) million	1.4 (1.2–1.7) million
AMR	2508 (2224–2829)	858 (733–995)	88 000 (78 000–99 500)	29 000 (25 000–33 500)
WPR	18 500 (16 500–21 000)	6380 (5600–7347)	632 000 (570 000–700 000)	209 000 (187 000–239 000)
GLOBAL	**211 000** (193 000–231 000)	**70 500** (64 000–78 000)	**8.1** (7.5–8.9) **million**	**2.6** (2.3–2.8) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	690 (670–700) million	230 (220–230) million
EUR	150 (150–160) million	52 (50–53) million
EMR	260 (250–270) million	84 (81–85) million
SEAR	1600 (1500–1600) million	520 (500–550) million
AMR	120 (120–120) million	42 (41–42) million
WPR	700 (680–720) million	240 (230–240) million
GLOBAL	**3500** (3400–3500) **million**	**1200** (1100–1200) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	32.2 (17.2–60.3) million	9.8 (5.2–18.4) million	451 million	133 million
EUR	1399 (690–2648) million	480 (237–909) million	824 million	280 million
EMR	49.7 (23.5–89.6) million	16 (7.5–28.5) million	459 million	136 million
SEAR	243 (25.2–734) million	83.2 (8.6–251) million	1393 million	470 million
AMR	64.4 (33–110) million	21.7 (11.1–37.1) million	136 million	45 million
WPR	19.2 (6.5–40) million	6.6 (2.2–13.9) million	306 million	101 million
GLOBAL	**1807** (973–3181) **million**	**617** (330–1089) **million**	**3569 million**	**1165 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.12 *Neisseria gonorrhoeae*

Pathogen and its epidemiology

N. gonorrhoeae is a gram-negative bacterium responsible for gonorrhoea, the second most common sexually transmitted bacterial infection globally, after *Chlamydia trachomatis* infection. Infection is primarily spread through sexual contact, although it can also be transmitted from mothers to neonates during childbirth. Infection can cause cervicitis symptoms in women, but it is often asymptomatic. Regardless of symptoms, untreated infection can progress to important reproductive health complications in women, such as pelvic inflammatory disease, infertility, ectopic pregnancy and chronic pelvic pain. Men commonly experience urethritis and occasionally epididymitis, and extragenital infections, such as pharyngitis and proctitis, are not uncommon, notably in men who have sex with men *(173)*. In 2020, WHO estimated 82.4 million new infections with *N. gonorrhoeae* among adults aged 15–49 years *(174)*.

The impact of gonorrhoea is unevenly distributed, with women, people living in low-resource settings, and underprivileged and marginalized populations in all settings bearing the brunt of gonorrhoea-associated disease. The WHO African Region reports the highest incidence rates, followed by the Region of the Americas and the Western Pacific Region *(174)*. Stigma and limited access to health care further exacerbate the situation in LMIC and for groups such as indigenous communities, men who have sex with men, sex workers and transgender women. The socioeconomic ramifications of infection may be significant, particularly for women with gonorrhoea-associated infertility, which can result in broader social and economic deprivation. Cultural beliefs regarding condom usage and the stigmatization of diseases play a pivotal role in the perpetuation and management of the infection, especially in LMIC *(175)*.

Treatment and prevention

Controlling the spread of *N. gonorrhoeae* involves a multipronged strategy. WHO recommends the use of injectable ceftriaxone as first-line treatment, or potentially cefixime (often combined with azithromycin) if ceftriaxone is unavailable. However, treatment should be tailored according to local antimicrobial susceptibility patterns *(176)*. A Phase 3 trial of a new drug, zoliflodacin, met the primary endpoint when compared with the combination of injectable ceftriaxone and oral azithromycin, offering hope for treatment of drug-resistant *N. gonorrhoeae* *(177)*. IPC measures are crucial; they include promoting safer sex practices, prompt evaluation of urethritis or cervicitis symptoms, screening for infection in some settings and prompt treatment *(173)*.

Antimicrobial resistance

WHO has classified the urgency of AMR in *N. gonorrhoeae* as high *(10)*. The pathogen has shown a remarkable ability to develop resistance to antibiotics, including to ceftriaxone, the last-resort medication. The WHO Gonococcal Antimicrobial Surveillance Programme found resistance or decreased susceptibility to ceftriaxone in 21 (31%) of 68 reporting countries, and resistance or decreased susceptibility to cefixime in 24 (47%) of 51 reporting countries. Resistance to azithromycin was reported by 51 (84%) of 61 countries, and resistance to ciprofloxacin by all 70 reporting countries *(178)*. Designated by the CDC as an urgent threat *(27)*, the rise of MDR and XDR strains of *N. gonorrhoeae* poses a global challenge, with some regions nearing the threshold for XDR categorization *(179)*.

Vaccines

There is no licensed vaccine against *N. gonorrhoeae*. However, several observational studies have shown that certain serogroup B meningococcal vaccines may have cross-protection against gonorrhoea, with demonstrated vaccine effectiveness of up to 40% *(180)*, and randomized controlled trials to further evaluate these findings are ongoing. This report evaluated the impact of a vaccine against *N. gonorrhoeae* infection given to 70% of adolescents, with 10-year efficacy of 70% (Table 4.12). Vaccine characteristics were identified using the WHO PPC for gonococcal vaccines *(181)*.

The model findings must be considered in the context of the epidemiology of AMR in

N. gonorrhoeae and the methods used to estimate the burden of disease due to the pathogen. There is considerable uncertainty about the burden of disease associated with *N. gonorrhoeae* infection and the proportion due to resistant strains. Most *N. gonorrhoeae* infections are still treatable with available first-line therapy; however, the number of gonococcal isolates showing reduced susceptibility to extended-spectrum cephalosporins is increasing, and the threat of untreatable infections due to AMR is high. The increasing resistance in *N. gonorrhoeae* is addressed in this report because it could lead to a sharp rise in AMR-related morbidity, including pelvic inflammatory disease, infertility and adverse pregnancy outcomes.

Other analyses of vaccine impact on AMR

In addition to the WHO-coordinated analyses, other researchers have modelled the potential impact of *N. gonorrhoeae* vaccines. One study *(182)* employed a mathematical model to assess the potential impact of a hypothetical gonorrhoea vaccine among heterosexuals in a high-prevalence setting, using South Africa as an example. The model, stratified by age and sex, predicted a significant reduction in *N. gonorrhoeae* prevalence. Key results showed that, with an annual vaccination uptake of 10%, vaccine efficacy against infection acquisition of 25% and a duration of protection of 5 years, *N. gonorrhoeae* prevalence could decrease by about 50% in the entire population of those aged 15–49 years within 10 years. If vaccination was limited to only those aged 15–24 years, the predicted reduction in prevalence was 25%. The study concluded that vaccinating only highly sexually active individuals was more efficient, requiring about three times fewer vaccinations to achieve a similar reduction in prevalence, compared with vaccinating the entire population.

Another study *(183)* used a stochastic transmission-dynamic model to evaluate the potential impact of a gonococcal vaccine, especially in the context of increasing gonorrhoea incidence and antibiotic resistance. The study, based on data from England, explored various scenarios for vaccine efficacy and duration of protection, and incorporating the emergence of XDR gonorrhoea. The results indicated that WHO's target of reducing gonorrhoea incidence by 90% by 2030 is achievable with a vaccine offering at least 52% protection for 6 years or more, even in the worst-case scenario of untreatable infection. A vaccine with 31% efficacy, similar to the MeNZB vaccine, and protection for 2–4 years could reduce incidence by 45% in the worst-case scenario and by 75% if most resistant gonorrhoea remained treatable. The study concluded that even a partially effective vaccine, if realistically targeted, could significantly reduce gonorrhoea incidence despite antibiotic resistance.

Neisseria gonorrhoeae

Table 4.12. A vaccine against *N. gonorrhoeae* infection given to 70% of adolescents, with 10-year efficacy of 70% [NG]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Neisseria gonorrhoeae	**Adolescents**	**10 years**	Efficacy: **70%** Coverage: **70%**	HIGH
				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	Not estimated	Not estimated	**10 000** (8158–13 500)	**1982** (1220–3162)
EUR	Not estimated	Not estimated	**3** (1–13)	**0** (0–3)
EMR	Not estimated	Not estimated	**4750** (4258–5700)	**956** (663–1468)
SEAR	Not estimated	Not estimated	**21 500** (17 000–27 000)	**3917** (2424–6239)
AMR	Not estimated	Not estimated	**2820** (2704–2920)	**457** (332–609)
WPR	Not estimated	Not estimated	**11 000** (9060–14 000)	**1466** (934–2527)
GLOBAL	**Not estimated**	**Not estimated**	**50 500** (45 000–58 000)	**8917** (6929–11 500)

AMR: antimicrobial resistance; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.13 *Plasmodium falciparum*

Pathogen and its epidemiology

Malaria, a vector-borne disease, is transmitted through the bite of female *Anopheles* mosquitoes carrying *Plasmodium* parasites. Five *Plasmodium* species naturally infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. The intensity of malaria transmission varies based on parasite prevalence, mosquito vector characteristics and environmental factors, such as temperature and humidity. Transmission often shows seasonal peaks influenced by rainfall *(184)*. Globally, malaria causes significant morbidity and mortality, with an estimated 249 million cases and 608 000 deaths in 2022 *(57)*. Most cases occur in sub-Saharan Africa, with a significant additional burden in South-East Asia and South America. Up to 95% of cases and deaths affect children aged under 5 years. *P. falciparum* is the most lethal of the *Plasmodium* species and is the predominant species in Africa, whereas *P. vivax* is more prevalent outside Africa. Progress in reducing cases and deaths has slowed since 2016, highlighting the need for new strategies and tools. The economic impact of malaria is profound, especially in endemic regions. Malaria impedes economic growth, with an estimated loss of 1.3% in GDP growth annually in countries with endemic malaria. The disease disproportionately affects people living in poverty, imposing significant financial challenges for families *(57, 184)*.

Treatment and prevention

Treatment depends on the *Plasmodium* species, disease severity and local resistance patterns. WHO recommends artemisinin-based combination therapies (ACTs) for uncomplicated *P. falciparum* malaria, with severe cases treated using intravenous or intramuscular artesunate, followed by oral ACTs *(185)*. Prevention strategies include insecticide-treated nets, indoor residual spraying, chemoprevention in high-transmission areas and prompt diagnosis and treatment. None of the recommended interventions prevent all malaria cases; for the highest impact, WHO recommends a mix of interventions based on subnational tailoring using local data *(185)*. Scale-up of malaria control interventions has significantly reduced malaria incidence and deaths since 2000, but this progress is being challenged by insecticide resistance and emerging drug resistance *(184)*.

Antimicrobial resistance

Resistance to antimalarials, particularly to drugs used in ACTs, is a growing concern. In the Greater Mekong subregion of South-East Asia, multidrug resistance has led to high treatment failure rates of certain ACT regimens for some *P. falciparum* strains. Continuous monitoring of resistance and drug efficacy is critical, along with development of new treatments. Although some regions show emerging resistance, efficacious treatments remain available. The experience of countries such as China in eliminating malaria despite resistance challenges offers hope *(186)*. The *WHO Strategy to respond to antimalarial drug resistance in Africa* has three objectives: improve the detection of resistance to ensure a timely response; delay the emergence of resistance to artemisinin and ACT partner drugs; and limit the selection and spread of resistant parasites where resistance has been confirmed *(187)*. WHO does not recommend the use of antibiotics for treating uncomplicated malaria *(185)*; however, in LMIC, antibiotics are prescribed for up to 60% of cases of acute febrile illness, of which malaria is the leading cause *(188)*.

Vaccines

There are two vaccines targeting *P. falciparum* that are WHO prequalified and recommended for use in malaria endemic settings: RTS,S/AS01 and R21/Matrix-M *(184, 189, 190)*. Given the scarcity of ACT resistance in the WHO African Region, this report estimated the potential impact of a malaria vaccine against *P. falciparum* on antibiotic use associated with treating malaria (Table 4.13).

Other analyses of vaccine impact on AMR

In addition to the WHO-coordinated analyses, Hamilton and colleagues developed a compartmental model estimating cases, drug-resistant cases and deaths averted from 2021 to 2030 with a vaccine against *P. falciparum* infection administered yearly to children aged 1 year in 42 African countries *(191)*. In a scenario where vaccine efficacy starts at 80% and drops 20 percentage points each year, the vaccine would avert 313.9 (UI: 249.8–406.6) cases per 1000 children, 0.9 (0.6–1.3) resistant cases per 1000 children and 0.9 (0.6–1.2) deaths per 1000 children *(191)*.

Plasmodium falciparum (malaria)

Table 4.13. A vaccine against clinical *P. falciparum* (malaria) infection given to 70% of infants, with 4-year efficacy of 40% [Malaria]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Plasmodium falciparum	**Infants**	**4 years**	Efficacy: **40%** Coverage: **70%**	*Not assessed*
				Feasibility of vaccine development and implementation: HIGH

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	87 (53–130) million	24 (15–37) million
EUR	1900 (770–4800)	540 (220–1300)
EMR	910 000 (160 000–2.9 million)	260 000 (46 000–810 000)
SEAR	130 000 (18 000–540 000)	36 000 (5200–150 000)
AMR	65 000 (11 000–270 000)	18 000 (3100–74 000)
WPR	69 000 (18 000–200 000)	19 000 (5100–56 000)
GLOBAL	**88** (53–130) **million**	**25** (15–37) **million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.14 *Pseudomonas aeruginosa*

Pathogen and its epidemiology

P. aeruginosa, a gram-negative bacterium, is recognized as a significant contributor to severe infections associated with health care, such as surgical site infections, UTIs, bloodstream infections and respiratory infections, including pneumonia *(192)*. It was estimated that, in 2019, the pathogen caused 559 000 deaths, up to 60% of which were associated with AMR *(2)*. Populations most vulnerable to *P. aeruginosa* infection include elderly people, immunocompromised individuals, patients with prolonged stays in hospital or intensive care units, people with burn injuries and those with cystic fibrosis or chronic lung conditions. Mortality rates are high in LMIC, where the hospital environment may lack stringent hygiene and infection control, leading to a higher prevalence of MDR strains *(193)*. The economic impact of these infections is substantial, with extended hospital stays and high health care costs that can devastate low-income families and strain health care resources in medically underresourced settings *(194)*.

Treatment and prevention

Treatment of *P. aeruginosa* infections typically involves antibiotics *(87)*. However, treatment is complicated by the pathogen's ability to form protective biofilms and its inherent resistance to several antibiotic classes *(78)*. Emerging therapies, including passive immunization and engineered bacteriophages, are in development but have not yet been widely adopted *(115)*. Prevention strategies are multifaceted, encompassing strict hygiene practices, patient isolation, public and health care provider education and stewardship programmes to improve antibiotic prescribing practices *(114)*.

Antimicrobial resistance

WHO classified the urgency of carbapenem-resistant *P. aeruginosa* as critical in 2017 *(9)* and high in 2024 *(10)*. With rising resistance to antibiotics that renders last-line treatments ineffective and the emergence of carbapenem-resistant strains, the situation is alarming. The CDC has categorized this resistance as a serious AMR threat *(27)*. The distribution of MDR and XDR strains is a global concern, with varied prevalences reported across continents and exceptionally high rates seen in specific patient populations. The International Network for Optimal Resistance Monitoring has documented substantial prevalence of XDR strains, underscoring the urgency of continued surveillance and intensified research for novel treatment strategies *(9, 195)*.

Vaccines

There is no vaccine against *P. aeruginosa*, and there are no vaccines in active clinical development *(33)*. This report evaluated the potential impact of two vaccines on AMR, with the vaccine characteristics identified by pathogen experts (Table 4.14).

Pseudomonas aeruginosa (PA_1)

Table 4.14. A vaccine against bloodstream and lower respiratory tract *P. aeruginosa* infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [PA_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Pseudomonas aeruginosa	**Infants and elderly**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name:				Feasibility of vaccine development and implementation
PA_1				MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	48 000 (44 500–54 000)	5898 (4676–7056)	3.1 (2.8–3.6) million	426 000 (339 000–546 000)
EUR	25 500 (23 000–28 500)	1577 (1114–2166)	580 000 (530 000–630 000)	40 500 (33 000–50 000)
EMR	26 000 (24 000–29 000)	2339 (1888–2880)	1.5 (1.3–1.7) million	148 000 (115 000–189 000)
SEAR	72 500 (66 000–80 500)	5781 (4328–7641)	3 (2.6–3.4) million	229 000 (179 000–290 000)
AMR	34 500 (32 000–37 500)	2381 (1797–3246)	879 000 (819 000–951 000)	71 500 (58 000–90 000)
WPR	35 500 (31 500–39 500)	2597 (1756–3715)	834 000 (757 000–903 000)	66 000 (53 500–82 500)
GLOBAL	**243 000** (233 000–254 000)	**20 500** (18 000–23 500)	**9.9** (9.3–10.6) **million**	**1.0** (0.9–1.1) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	25 (15–36) million	1.3 million (690 000–2.1 million)
EUR	34 (24–44) million	1.8 (1.2–2.4) million
EMR	36 (25–49) million	1.5 million (930 000–2.3 million)
SEAR	150 (130–170) million	6.8 (4.8–8.9) million
AMR	55 (43–64) million	2.8 (1.9–3.7) million
WPR	68 (59–77) million	3.3 (2.4–4.2) million
GLOBAL	**370** (330–410) **million**	**17** (13–22) **million**

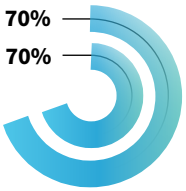
AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	175 (108–277) million	7.8 (4.5–12.8) million	1503 million	211 million
EUR	36 (27–4449) million	164 (106–245) million	1892 million	92 million
EMR	541 (323–867) million	23.9 (13.7–38.9) million	1738 million	165 million
SEAR	637 (231–1502) million	26.8 (8.3–63.1) million	2698 million	190 million
AMR	4365 (1944–8893) million	214 (92.7–439) million	2920 million	189 million
WPR	983 (491–1826) million	51.2 (24.7–98.4) million	1398 million	82 million
GLOBAL	**9707** (6746–14 389) **million**	**488** (337–725) **million**	**12 148 million**	**929 million**

Pseudomonas aeruginosa (PA_2)

A vaccine against bloodstream and lower respiratory tract *Pseudomonas aeruginosa* infection given to 70% of all people at risk of infection, with 5-year efficacy of 70% [PA_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Pseudomonas aeruginosa	**All people**	**5 years**	Efficacy: **70%** Coverage: **70%**	CRITICAL
Vaccine name: **PA_2**				Feasibility of vaccine development and implementation: LOW



AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	48 000 (44 500–54 000)	23 500 (21 000–27 500)	3.1 (2.8–3.6) million	1.5 (1.3–1.8) million
EUR	25 500 (23 000–28 500)	12 500 (11 500–14 500)	580 000 (530 000–630 000)	284 000 (258 000–313 000)
EMR	26 000 (24 000–29 000)	13 000 (11 500–14 500)	1.5 (1.3–1.7) million	713 000 (618 000–854 000)
SEAR	72 500 (66 000–80 500)	35 500 (32 000–40 000)	3 (2.6–3.4) million	1.5 (1.3–1.7) million
AMR	34 500 (32 000–37 500)	17 000 (15 500–19 000)	879 000 (819 000–951 000)	429 000 (395 000–471 000)
WPR	35 500 (31 500–39 500)	17 500 (15 500–19 500)	834 000 (757 000–903 000)	409 000 (367 000–450 000)
GLOBAL	**243 000** (233 000–254 000)	**119 000** (113 000–126 000)	**9.9** (9.3–10.6) **million**	**4.8** (4.5–5.3) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	25 (15–36) million	12 (7.2–18) million
EUR	34 (24–44) million	17 (12–22) million
EMR	36 (25–49) million	18 (12–24) million
SEAR	150 (130–170) million	74 (64–83) million
AMR	55 (43–64) million	27 (21–31) million
WPR	68 (59–77) million	33 (29–38) million
GLOBAL	**370** (330–410) **million**	**180** (160–200) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	175 (108–277) million	85.8 (53.2–136) million	1503 million	736 million
EUR	36 (27–4449) million	1473 (983–2180) million	1892 million	927 million
EMR	541 (323–867) million	265 (158–425) million	1738 million	851 million
SEAR	637 (231–1502) million	312 (113–736) million	2698 million	1322 million
AMR	4365 (1944–8893) million	2139 (952–4358) million	2920 million	1431 million
WPR	983 (491–1826) million	482 (241–895) million	1398 million	685 million
GLOBAL	**9707** (6746–14 389) **million**	**4756** (3306–751) **million**	**12 148 million**	**5953 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.15 Nontyphoidal *Salmonella*

Pathogen and its epidemiology

Nontyphoidal *Salmonella* (NTS) enterica serovars represent a significant public health challenge globally, causing two main disease phenotypes: diarrhoeal disease and invasive disease, such as bloodstream or focal infections. Among more than 2500 serovars, *S. Enteritidis* and *S. Typhimurium* are the most prevalent causes of invasive disease in humans *(196)*. NTS causes millions of diarrhoeal illnesses worldwide and was estimated to cause more than half a million invasive infections in 2019 *(2, 197)*. Globally, the mortality burden of NTS (both diarrhoeal and invasive) was estimated at 215 000 deaths in 2019, up to 13% of which were associated with AMR *(2)*. Sub-Saharan Africa bears the highest burden of invasive NTS disease, but high-quality representative data are limited, particularly from regions such as Asia and Latin America. The incidence of diarrhoeal disease is highest in South-East Asia and sub-Saharan Africa, with most cases being foodborne, and people of all ages are affected *(197)*. Populations vulnerable to invasive disease include infants and young children with health conditions (e.g. malaria, anaemia and malnutrition) and immunocompromised individuals *(198)*. Living conditions that increase the risk of diarrhoeal disease are those with poor sanitation and hygiene, proximity to animals and unsafe agricultural and food processing practices *(199)*. These factors are especially common in LMIC, exacerbating health outcomes and economic hardships *(200)*.

Treatment and prevention

Mild to moderate diarrhoeal illnesses caused by NTS in otherwise healthy individuals might not necessitate antibiotic treatment, with management instead focusing on rehydration and electrolyte replacement. Antibiotic treatment is required for invasive infections and may include AWaRe 'Watch' antibiotics, such as ciprofloxacin and ceftriaxone, depending on local antimicrobial susceptibility profiles *(87, 103)*. However, NTS is often associated with empirical antimicrobial prescribing *(103, 201, 202)*. Prevention strategies for NTS are multifaceted and include food chain hygiene from production to preparation. In high-income countries, measures such as improved hygiene, vaccination in the poultry industry and educational interventions have been implemented *(201)*.

Antimicrobial resistance

AMR associated with NTS is a critical issue, with MDR strains having a global distribution. WHO has classified the AMR threat from fluoroquinolone-resistant *Salmonella* as high *(9)*, and the CDC categorizes drug-resistant NTS as a serious AMR threat *(27)*. NTS infections associated with AMR have been shown to result in higher mortality and a higher requirement for hospitalization than infections caused by susceptible strains in high-income countries *(203)*. Although data on AMR in NTS strains associated with invasive infections are limited, MDR strains (with co-resistance to ampicillin, trimethoprim–sulfamethoxazole and chloramphenicol) are widespread in sub-Saharan Africa *(204)*. XDR strains (MDR plus third-generation cephalosporin and azithromycin resistance) with the addition of decreased susceptibility to ciprofloxacin have been described *(205)*. The high prevalence of AMR in NTS increases the risk of invasive infections becoming untreatable, particularly in LMIC. Maintaining vigilance through enhanced surveillance of pathogen incidence and resistance patterns, and developing new diagnostic, treatment and prevention strategies are imperative to manage and contain this pathogen effectively.

Vaccines

There is no licensed vaccine against NTS, but three vaccine candidates for preventing invasive NTS disease are in clinical development *(206)*. This report evaluated the impact on AMR of a vaccine against NTS diarrhoeal and invasive infections given to 70% of infants, with 5-year efficacy of 80% (Table 4.15), based on advice from pathogen experts. The report did not evaluate the impact of a combined NTS vaccine with other *Salmonella* vaccines; however, such a vaccine would be expected to further increase the impact on AMR.

Nontyphoidal *Salmonella*

Table 4.15. A vaccine against nontyphoidal *Salmonella* infection given to 70% of infants, with 5-year efficacy of 80% [NTS]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Nontyphoidal *Salmonella*	**Infants**	**5 years**	Efficacy: **80%** Coverage: **70%**	HIGH
				Feasibility of vaccine development and implementation: MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**1419** (1153–1846)	**342** (231–540)	**99 500** (76 500–134 000)	**30 500** (19 500–50 000)
EUR	**232** (197–282)	**2** (1–3)	**1024** (558–1811)	**572** (272–1097)
EMR	**1329** (1036–1772)	**161** (102–265)	**88 000** (65 500–128 000)	**13 500** (8225–23 500)
SEAR	**23 000** (20 000–27 000)	**1118** (772–1941)	**1.1 million** (905 000–1.3 **million**)	**106 000** (68 000–180 000)
AMR	**156** (132–186)	**14** (8–23)	**5292** (3818–7508)	**1752** (985–3045)
WPR	**3815** (3303–4430)	**140** (99–208)	**231 000** (193 000–291 000)	**22 500** (14 500–40 000)
GLOBAL	**30 000** (26 500–34 000)	**1820** (1412–2624)	**1.5** (1.3–1.8) **million**	**178 000** (134 000–253 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**670 000** (370 000–1.1 **million**)	**380 000** (210 000–620 000)
EUR	**110 000** (63 000–210 000)	**64 000** (35 000–120 000)
EMR	**700 000** (410 000–1.1 **million**)	**390 000** (230 000–600 000)
SEAR	**500 000** (320 000–720 000)	**280 000** (180 000–410 000)
AMR	**180 000** (97 000–300 000)	**100 000** (55 000–170 000)
WPR	**200 000** (120 000–300 000)	**110 000** (66 000–170 000)
GLOBAL	**2.4** (1.6–3.3) **million**	**1.3 million** (870 000–1.9 million)

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**75.8** (44.3–128) **million**	**12.1** (6.7–21.4) **million**	**34 million**	**9 million**
EUR	**4581** (2743–7723) **million**	**489** (281–852) **million**	**9 million**	**1 million**
EMR	**221** (130–378) **million**	**30.3** (18.3–50) **million**	**62 million**	**9 million**
SEAR	**1764** (825–3675) **million**	**135** (66.4–266) **million**	**500 million**	**53 million**
AMR	**315** (186–511) **million**	**34.4** (21.2–54.9) **million**	**17 million**	**3 million**
WPR	**9126** (3343–20 691) **million**	**856** (318–1939) **million**	**186 million**	**20 million**
GLOBAL	**1683** (9534–27 684) **million**	**1556** (930–2636) **million**	**809 million**	**94 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.16 *Salmonella* Paratyphi A

Pathogen and its epidemiology

Salmonella enterica serovar Paratyphi A is a gram-negative bacterium responsible for paratyphoid fever, a disease with clinical manifestations that are virtually identical to those of typhoid fever, such as high fever, lethargy, gastrointestinal symptoms, diarrhoea or constipation and headache. In 2019, there were about 3.8 million cases of paratyphoid fever worldwide, caused predominantly by the serovar Paratyphi A, and 23 000 deaths, almost 87% of which were associated with AMR *(2)*. The highest incidence rates were reported in the WHO South-East Asia Region and Eastern Mediterranean Region *(2)* and in people aged 15–25 years *(207)*. However, data on pathogen burden and AMR profile are limited. In regions with constrained resources, including many LMIC, particularly in south and south-east Asia, paratyphoid fever emerges as a disease of poverty, predominantly affecting children in communities with poor sanitation and inadequate access to microbiologically safe water *(207)*. Its economic impact is profound; families that are often already impoverished face financial strain when wage-earners fall ill or must tend to sick relatives. The disease also propagates cultural stigmatization, especially among displaced populations, further exacerbating social and economic burdens *(208)*.

Treatment and prevention

Approaches to containing *S.* Paratyphi A encompass treatment with antibiotics, such as fluoroquinolones and, in cases of resistant strains, third-generation cephalosporins or azithromycin, with carbapenems being a therapy of last resort *(207)*. Prevention strategies centre on improving access to clean water, sanitation and hygiene practices, given the faecal–oral route of transmission. Nevertheless, overdiagnosis and overtreatment with antibiotics are widespread, underscoring the need for enhanced diagnostic methods, education on antibiotic stewardship and comprehensive training of health care workers *(207)*.

Antimicrobial resistance

The threat of AMR adds urgency to the management of *S.* Paratyphi A. WHO has classified the AMR threat from fluoroquinolone-resistant *Salmonella* as high *(9)*. Research in Bangladesh has shown a relatively stable susceptibility to major antibiotics, such as ampicillin, chloramphenicol, co-trimoxazole, ceftriaxone and azithromycin, over a 23-year period, with greater than 99% susceptibility to azithromycin. Nevertheless, there has been a notable decrease in susceptibility to ciprofloxacin *(209)*. In contrast, data from Pakistan show a decrease in MDR strains of *S.* Paratyphi A, but an increase in fluoroquinolone resistance *(210)*. Global trends indicate significant regional variation in AMR, with south and south-east Asia experiencing a rise in fluoroquinolone-resistant strains, underscoring the need for continuous monitoring and region-specific treatment guidelines, especially in the absence of a paratyphoid vaccine *(211)*. Although XDR strains have not yet been reported, the current trajectory indicates a pressing need for global action to mitigate this escalating AMR threat *(207)*.

Vaccines

Unlike its close relative *S.* Typhi, there is no licensed vaccine against *S.* Paratyphi A, but there are three vaccines in active clinical development. Vaccines against *S.* Paratyphi A that are being developed are often considered for inclusion in combination vaccines against other *Salmonella* serovars *(206)*. This report evaluated the impact on AMR of a monovalent vaccine against *S.* Paratyphi A infection given to 70% of infants, with 5-year efficacy of 70%, as informed by pathogen experts (Table 4.16).

Salmonella Paratyphi A

Table 4.16. A vaccine against *S.* Paratyphi A infection given to 70% of infants in countries with a high typhoid burden, with 5-year efficacy of 70% [SPara]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
***Salmonella* Paratyphi A**	**Infants**	**5 years**	Efficacy: **70%** Coverage: **70%**	HIGH
				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	99 (62–173)	15 (5–42)	6348 (4180–10 500)	1114 (589–2161)
EUR	12 (9–17)	0 (0–0)	0 (0–0)	0 (0–0)
EMR	5757 (4416–7848)	405 (204–866)	411 000 (291 000–587 000)	34 500 (17 000–77 500)
SEAR	15 500 (11 500–21 500)	978 (448–2155)	1.1 million (797 000–1.6 million)	85 000 (42 000–177 000)
AMR	5 (4–5)	0 (0–0)	0 (0–0)	0 (0–0)
WPR	283 (205–380)	23 (10–57)	18 000 (13 000–25 500)	2145 (962–4271)
GLOBAL	**22 000** (18 000–28 000)	**1463** (853–2793)	**1.5** (1.2–2.1) **million**	**128 000** (74 500–224 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	110 000 (36 000–300 000)	53 000 (18 000–150 000)
EUR	13 000 (2900–51 000)	6500 (1400–25 000)
EMR	2.9 million (310 000–7.0 million)	1.4 million (150 000–3.4 million)
SEAR	870 000 (150 000–2.9 million)	430 000 (73 000–1.4 million)
AMR	8300 (2800–20 000)	4100 (1400–10 000)
WPR	61 000 (11 000–180 000)	30 000 (5500–87 000)
GLOBAL	**4.0 million** (710 000–7.9 **million**)	**1.9 million** (350 000–3.8 **million**)

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	786 000 (439 000–1.3 million)	47 000 (26 000–79 500)	3 million	<1 million
EUR	3.5 (2.4–5.1) million	134 000 (84 500–212 000)	1 million	<1 million
EMR	27.6 (11.3–58.2) million	845 000 (344 000–1.8 million)	453 million	30 million
SEAR	145 (59–304) million	5.4 (2.2–11.4) million	877 million	53 million
AMR	4.7 (2.2–8.9) million	86 500 (38 500–168 000)	1 million	<1 million
WPR	10.9 (5.9–19.5) million	458 000 (236 000–848 000)	44 million	4 million
GLOBAL	**192** (102–355) **million**	**7** (3.7–13.1) **million**	**1378 million**	**87 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.17 *Salmonella* Typhi

Pathogen and its epidemiology

S. enterica serovar Typhi (*S.* Typhi) is a virulent gram-negative bacterium responsible for typhoid fever, a significant public health concern. Individuals infected with *S.* Typhi experience a range of symptoms, including fever, fatigue, abdominal pain and sometimes a distinctive rose-coloured skin rash. If not properly treated, the infection can lead to serious complications, including intestinal perforation, which has a mortality rate of 1–5% in hospitalized patients. *S.* Typhi infections often result in outbreaks, including outbreaks of MDR and XDR *S.* Typhi. There were seven confirmed outbreaks between 2017 and 2022 in China, Pakistan, the Philippines and Zimbabwe *(212)*. In 2019, *S.* Typhi is estimated to have caused about 182 000 deaths, up to 70% of which were associated with AMR *(2)*; however, incidence has shown a falling trend since 1990 *(213)*. Typhoid fever affects populations in LMIC, with significant incidence and frequent disease outbreaks among those aged 5–19 and 20–24 years in south and south-east Asia, the eastern Mediterranean, sub-Saharan Africa and various island nations in Oceania *(48)*. It is a disease of poverty, disproportionately affecting children in overpopulated urban and periurban settings with inadequate sanitation and limited access to microbiologically safe water *(213)*. Marginalized groups, such as pastoralists, who often lack sanitation infrastructure, are at heightened risk *(214)*. Cultural practices, such as consuming unwashed produce or using microbiologically unsafe water, can exacerbate the spread of disease. Economically, typhoid fever imposes a heavy burden, with affected families facing income loss due to illness or caregiving and communities grappling with strained health care resources. These economic impacts are further compounded by cultural stigma and the social isolation of affected individuals *(208)*.

Treatment and prevention

Containment of *S.* Typhi hinges on a multifaceted approach that includes vaccination, improved sanitation, access to microbiologically safe water and proper hygiene practices. Antibiotic treatment is the mainstay for managing infections, with fluoroquinolones, third-generation cephalosporins, azithromycin and, in severe cases, steroids being used. XDR strains may require last-resort therapies, such as carbapenems *(213)*. Although not unique to typhoid infections, overuse of antibiotics, a common problem in many regions, necessitates improved diagnostic tools, better prescribing practices and public education to curb the unnecessary use of these medicines. Furthermore, as *S.* Typhi exclusively infects humans, transmission control focuses on interrupting the faecal–oral transmission pathway by enhancing community sanitation and hygiene *(213)*. Although there are vaccines available to prevent typhoid fever, managing the disease remains complex, especially because of challenges with diagnostics (e.g. a lack of reliable point-of-care contact testing and the requirement for well-performing microbiology laboratories) and emerging MDR strains *(213)*.

Antimicrobial resistance

WHO has classified the AMR threat from fluoroquinolone-resistant *Salmonella* as high *(9)*. The pathogen has developed resistance to multiple drug classes, especially in Asia, where MDR and XDR strains have caused significant outbreaks. Resistance to commonly used drugs, such as fluoroquinolones and third-generation cephalosporins, is increasing, with resistance rates rising to over 80% in some regions *(215)*. The CDC classifies *S.* Typhi as a serious AMR threat, emphasizing the need for global attention and coordinated action *(27)*. The pathogen's AMR profile not only heightens the challenge of treating

infections but also increases morbidity and mortality rates, particularly among children, highlighting the need for urgent advancements in vaccine development and distribution, especially to reach the most vulnerable and hard-to-access populations.

Vaccines

Three types of typhoid vaccines are prequalified by WHO: TCV, Vi polysaccharide vaccine and live attenuated Ty21a vaccine. Additional vaccines are licensed in selected countries. TCV has been recommended by WHO since 2008 and Vi polysaccharide vaccine since 2018 for the control of typhoid in high-burden and epidemic settings *(213, 216)*. Of the available typhoid vaccines, TCV is preferred for all age groups in view of its improved immunological properties, suitability for use in younger children and expected longer duration of protection. WHO encourages routine programmatic administration of TCV at the same time as other vaccination visits at nine months of age or in the second year of life. In addition to licensed and prequalified vaccines, there are five vaccine candidates in clinical development *(33)*. This report evaluated the impact on AMR of a monovalent vaccine against *S.* Typhi infection given to 70% of infants in countries with a high typhoid burden, with 15-year efficacy of 85% (Table 4.17), with the vaccine characteristics being based on the licensed TCV. Recent analyses from Malawi suggest, however, that vaccine efficacy might be lower in children aged under 2 years *(217)*. The report did not evaluate the impact of a combination vaccine targeting *S.* Typhi and other *Salmonella* serovars; however, such a combination is expected to further increase the impact on AMR.

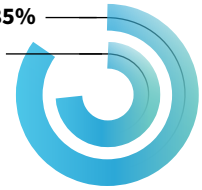
Other analyses of vaccine impact on AMR

In addition to the WHO-led analyses, a modelling study estimated the potential impact of typhoid vaccination on reducing antimicrobial-resistant typhoid fever across 73 countries supported by Gavi, the Vaccine Alliance *(218)*. The approach assumed routine vaccination at 9 months of age, complemented by a catch-up campaign extending to individuals aged up to 15 years, with the vaccine's initial efficacy ranging from 80% to 95%. The findings suggested that this strategy could prevent between 46% and 74% of all typhoid fever cases in the 73 Gavi-supported countries. It was anticipated that vaccination would lower the relative occurrence of antimicrobial-resistant typhoid fever by 16% (95% prediction interval [PI]: 0–49). The introduction of TCV, along with a catch-up campaign, was estimated to avert 42.5 million (95% PI: 24.8–62.8 million) cases and 506 000 (95% PI: 187 000–1.9 million) deaths from typhoid fever that is not susceptible to fluoroquinolones, and 21.2 million (95% PI: 16.4–26.5 million) cases and 342 000 (95% PI: 135 000–1.5 million) deaths from MDR typhoid fever during the decade after the vaccine's introduction *(218)*.

Salmonella Typhi

Table 4.17. A vaccine against *S.* Typhi infection given to 70% of infants in countries with a high typhoid burden, with 15-year efficacy of 85% [ST]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
***Salmonella* Typhi**	**Infants**	**15 years**	Efficacy: **85%** Coverage: **70%**	HIGH
				Feasibility of vaccine development and implementation: HIGH



AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**44 500** (36 500–53 000)	**8436** (5708–12 000)	**3.4** (2.7–4.3) **million**	**684 000** (500 000–1.0 **million**)
EUR	**702** (571–867)	**22** (16–31)	**21 000** (17 500–25 500)	**778** (625–939)
EMR	**27 500** (22 500–34 000)	**7413** (4970–11 000)	**2** (1.7–2.5) **million**	**586 000** (439 000–851 000)
SEAR	**57 500** (44 500–74 000)	**17 500** (11 000–26 500)	**4.1** (3.1–5.2) **million**	**1.4 million** (959 000–2.2 **million**)
AMR	**1028** (866–1214)	**50** (37–72)	**50 000** (40 500–62 500)	**3942** (2894–5851)
WPR	**2664** (2224–3219)	**555** (363–871)	**167 000** (135 000–216 000)	**46 500** (31 500–70 000)
GLOBAL	**135 000** (119 000–152 000)	**34 500** (26 000–44 000)	**9.8 (8.5–11.4) million**	**2.8 (2.2–3.6) million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**11** (3.6–29) **million**	**6.4** (2.1–17) **million**
EUR	**240 000** (36 000–990 000)	**140 000** (21 000–590 000)
EMR	**50** (5.5–120) **million**	**30** (3.3–72) **million**
SEAR	**12** (2.1–43) **million**	**7.3** (1.2–26) **million**
AMR	**130 000** (46 000–300 000)	**76 000** (28 000–180 000)
WPR	**2 million** (290 000–6.2 **million**)	**1.2 million** (170 000–3.7 **million**)
GLOBAL	**76** (18–150) **million**	**45** (11–88) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**77.2** (54–116) **million**	**15.8** (10.4–24.7) **million**	**1497 million**	**335 million**
EUR	**16.4** (12–22.8) **million**	**631 000** (388 000–1.1 **million**)	**82 million**	**6 million**
EMR	**97.2** (59.1–164) **million**	**21.6** (12.4–37.9) **million**	**2301 million**	**691 million**
SEAR	**242** (110–493) **million**	**73.7** (32.7–151) **million**	**3407 million**	**1149 million**
AMR	**23.1** (14.4–36.8) **million**	**668 000** (411 000–1.1 **million**)	**157 million**	**13 million**
WPR	**23.1** (15.6–33.8) **million**	**4.4** (3–6.6) **million**	**419 million**	**107 million**
GLOBAL	**479** (327–727) **million**	**117** (71.5–192) **million**	**7864 million**	**2301 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.18 *Shigella* spp.

Pathogen and its epidemiology

Shigella species, comprising *S. sonnei*, *S. flexneri*, *S. boydii* and *S. dysenteriae*, are highly contagious pathogens responsible for severe bacterial gastroenteritis. Annually, these pathogens cause about 113 000 deaths, predominantly through acute diarrhoea accompanied by dysentery, fever and possible grave complications, such as sepsis and haemolytic uraemic syndrome. Almost 26% of deaths from *Shigella* are expected to be associated with AMR *(2)*. *Shigella* infections are also associated with long-term morbidity, such as wasting, stunting or impaired cognitive development *(219)*. In the absence of an approved vaccine, the disease's spread is a significant concern in both temperate and tropical regions. *S. flexneri* is predominantly associated with low-income settings, whereas *S. sonnei* is more prevalent in other areas. *S. boydii* is mostly seen in south Asia and, historically, *S. dysenteriae* has been linked with large outbreaks *(220)*. The burden of *Shigella* disproportionately affects underprivileged and marginalized populations, especially in LMIC, where inadequate sanitation exacerbates its transmission. Its economic impact is severe, affecting health care systems and hindering children's educational prospects because of long recovery times and associated stunted growth and cognitive impairment *(220)*.

Treatment and prevention

Containment of *Shigella* relies on a multifaceted approach, given its transmission through direct contact or via contaminated food and water. Although mild cases in healthy individuals may not require intervention, antibiotic treatment is essential for severe infections. The treatment regimen is guided by local antibiotic resistance patterns, with fluoroquinolones being a common choice (but not recommended for young children), and alternatives including azithromycin and ceftriaxone. One Health aspects underline the importance of a coordinated approach involving public education, improved prescribing practices and the exploration of microbiome-based treatments *(220)*.

Antimicrobial resistance

WHO has classified fluoroquinolone-resistant *Shigella* spp. as a medium threat for AMR *(9)*. MDR strains are widespread, and XDR strains have emerged globally. The development of PDR strains has not yet been reported but looms as a potential threat. *Shigella*'s resistance amplifies the disease's impact on morbidity and mortality and underscores the need for global vigilance and proactive measures. Among clinically attended diarrhoea cases in the Global Enteric Multicenter Study, *Shigella* was found to be a leading driver of antibiotic use in infants and children aged under 5 years *(221)*. Continuous surveillance for resistance patterns and development of innovative treatment options are crucial steps in curtailing this public health challenge *(220)*.

Vaccines

There is no licensed vaccine against *Shigella* spp., but there are eight vaccine candidates in clinical development *(33)*. This report evaluated the impact on AMR of a vaccine against moderate to severe *Shigella* infection given to 70% of infants, with 5-year efficacy of 60% (Table 4.18). The vaccine characteristics were those listed in the WHO PPCs for vaccines against *Shigella (222)*.

Shigella

Table 4.18. A vaccine against moderate to severe diarrhoea caused by *Shigella* infection given to 70% of infants, with 5-year efficacy of 60% [*Shigella*]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Shigella	**Infants**	**5 years**	Efficacy: **60%** Coverage: **70%**	MEDIUM
				Feasibility of vaccine development and implementation: MEDIUM

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**10 500** (7926–15 500)	**2598** (1517–4511)	**842 000** (567 000–1.3 **million**)	**232 000** (130 000–401 000)
EUR	**96** (70–131)	**7** (3–17)	**2186** (900–6207)	**741** (285–2137)
EMR	**2658** (1934–3740)	**488** (257–907)	**189 000** (122 000–284 000)	**44 000** (23 500–79 000)
SEAR	**17 500** (13 500–25 000)	**911** (473–1729)	**685 000** (504 000–980 000)	**81 500** (38 500–154 000)
AMR	**193** (150–265)	**21** (12–38)	**7176** (4592–13 000)	**1969** (1163–3812)
WPR	**341** (263–460)	**35** (20–63)	**39 000** (30 000–53 500)	**4985** (2760–9034)
GLOBAL	**31 500** (26 500–41 000)	**4133** (2765–6132)	**1.8** (1.4–2.3) **million**	**369 000** (242 000–553 000)

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**14** (7.6–23) **million**	**5.8** (3.2–9.5) **million**
EUR	**2.1 million** (930 000–4.2 **million**)	**870 000** (390 000–1.8 **million**)
EMR	**15** (8–24) **million**	**6.4** (3.4–10) **million**
SEAR	**7.4** (4.7–11) **million**	**3.1** (2–4.5) **million**
AMR	**3.6** (1.7–6) **million**	**1.5 million** (690 000–2.5 **million**)
WPR	**3.8** (2.2–6) **million**	**1.6 million** (930 000–2.5 **million**)
GLOBAL	**46** (30–64) **million**	**19** (13–27) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**808** (210–2160) **million**	**87.3** (22.2–238) **million**	**267 million**	**74 million**
EUR	**4994** (1768–11 377) **million**	**251** (88.5–582) **million**	**7 million**	**2 million**
EMR	**8748** (2162–25 126) **million**	**515** (146–1458) **million**	**117 million**	**30 million**
SEAR	**4195** (802–12 868) **million**	**155** (30.2–474) **million**	**290 million**	**42 million**
AMR	**7926** (231–23 202) **million**	**302** (100–771) **million**	**20 million**	**5 million**
WPR	**5614** (1035–16 947) **million**	**338** (59.1–122) **million**	**23 million**	**5 million**
GLOBAL	**32 286** (17 415–57 883) **million**	**1649** (911–2872) **million**	**723 million**	**158 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.19 *Staphylococcus aureus*

Pathogen and its epidemiology

S. aureus, a gram-positive bacterium, is a member of the usual human microbiota. It is notorious for its ability to cause a spectrum of diseases, ranging from an array of infections, including skin and soft tissue infections, bloodstream infections and joint infections, to severe conditions such as pneumonia and toxic shock syndrome. It is estimated that the pathogen was responsible for a staggering 1.1 million deaths in 2019, up to 68% of which were associated with AMR *(2)*. *S. aureus* infections particularly affect hospitalized patients, with the greatest risks seen in LMIC, where hospital conditions may be suboptimal. Overcrowding, inadequate sanitation and a lack of antibiotic stewardship elevate the risk of MDR strains; for example, high proportions of health care workers in Nepalese intensive care units are carriers of both *S. aureus* and methicillin-resistant *S. aureus* (MRSA), signifying a high potential for nosocomial transmission *(223)*. Cultural practices, such as insufficient hand hygiene among doctors *(224)* or limited knowledge of prescribing practices *(225)*, contribute to the spread and development of resistance in *S. aureus*. Economically, the infection leads to prolonged hospital stays, affecting patients' ability to work and participate in daily activities; this is further exacerbated by MDR strains that require even longer and more costly treatment regimens *(75, 226)*.

Treatment and prevention

S. aureus can infect any organ or tissue in the human body. Managing and preventing acute infections is challenging because of the dual nature of *S. aureus* as both a commensal and pathogenic entity. Effective management involves quickly tackling the infection's source and any secondary infection sites, coupled with the use of suitable antibiotics (chosen based on the infection's location, its severity and local patterns of antibiotic resistance). Further studies are needed to ascertain the most effective method, duration and type of antimicrobial treatment for *S. aureus* infections in children. Topical antibiotics are widely used in both health care and outpatient settings to eliminate *S. aureus* colonization and prevent further infections. Potential new preventive and treatment options (e.g. lytic agents, vaccines, probiotics, microbiota transplants and phage therapy) present promising directions for future research *(227)*. A One Health approach underscores the importance of recognizing the interconnectedness of human, animal and environmental health, given that reservoirs of *S. aureus* include both humans and animals, and the bacteria can persist on various surfaces *(228)*.

Antimicrobial resistance

The emergence of MRSA shortly after the introduction of methicillin, and subsequent resistance to other antibiotics, has been alarming. WHO has classified MRSA and vancomycin-intermediate and vancomycin-resistant *S. aureus* as a high AMR priority *(9)*. The CDC classifies MRSA as a serious AMR threat *(27)*. Resistance in MRSA is not limited to one drug but often extends across multiple antibiotic classes, contributing to its MDR status. Although MRSA prevalence varies globally, its resistance impacts are profound, necessitating a concerted global effort in surveillance, reporting and management to contain this adaptable and persistent pathogen *(9)*.

Vaccines

There is no vaccine against *S. aureus*, but there are two vaccine candidates in clinical development *(33)*. This report evaluated the impact on AMR of two vaccines (Table 4.19). Vaccine characteristics were identified through analysis of the clinical pipeline, considering challenges to developing *S. aureus* vaccines, and consultation with pathogen experts.

Staphylococcus aureus (SA_1)

Table 4.19. A vaccine against *S. aureus* infection given to 70% of infants and elderly people, with 5-year efficacy of 60% [SA_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Staphylococcus aureus	**Infants and elderly**	**5 years**	Efficacy: **60%** Coverage: **70%**	HIGH
Vaccine name:				Feasibility of vaccine development and implementation
SA_1				LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	138 000 (129 000–147 000)	17 000 (14 000–20 500)	7.7 (7.1–8.5) million	1.2 million (974 000–1.5 million)
EUR	85 000 (80 000–92 000)	4265 (3293–5680)	1.7 (1.6–1.9) million	97 000 (81 500–120 000)
EMR	65 500 (62 000–70 500)	5821 (4911–7015)	3.2 (2.9–3.6) million	354 000 (289 000–450 000)
SEAR	162 000 (152 000–174 000)	11 500 (9151–14 000)	5.7 (5.4–6.2) million	445 000 (371 000–551 000)
AMR	126 000 (119 000–134 000)	7143 (5727–8912)	2.9 (2.7–3.0) million	188 000 (158 000–221 000)
WPR	182 000 (169 000–197 000)	10 500 (7801–14 500)	4 (3.7–4.3) million	243 000 (202 000–304 000)
GLOBAL	**760 000** (737 000–782 000)	**56 000** (51 000–62 500)	**25.3** (24.3–26.3) **million**	**2.6** (2.3–2.9) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	210 (150–290) million	17 (11–25) million
EUR	300 (220–410) million	14 (9.9–19) million
EMR	190 (120–300) million	12 (6.2–20) million
SEAR	510 (380–640) million	25 (17–34) million
AMR	300 (200–410) million	16 (10–22) million
WPR	250 (200–310) million	14 (10–18) million
GLOBAL	**1800** (1500–2100) **million**	**97** (79–120) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	3962 (2402–6197) million	456 (275–698) million	3188 million	479 million
EUR	37 015 (23 380–55 283) million	1710 (188–2505) million	5159 million	180 million
EMR	10 570 (6381–16 733) million	822 (489–1295) million	4410 million	456 million
SEAR	9372 (3913–19 501) million	614 (244–1303) million	5696 million	377 million
AMR	44 528 (2223–82 466) million	2283 (1202–4002) million	9950 million	444 million
WPR	32 218 (17 996–54 350) million	2451 (1318–4169) million	8057 million	299 million
GLOBAL	**137 664** (104 596–186 432) **million**	**8337** (6407–11 085) **million**	**36 460 million**	**2235 million**

Staphylococcus aureus (SA_2)

A vaccine against *S. aureus* infection given to 70% of all people at risk of infection, with 5-year efficacy of 60% [SA_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Staphylococcus aureus	**All people**	**5 years**	Efficacy: **60%** Coverage: **70%**	HIGH
Vaccine name:				Feasibility of vaccine development and implementation
SA_2				LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**138 000** (129 000–147 000)	**58 000** (53 500–63 500)	**7.7** (7.1–8.5) **million**	**3.3** (2.9–3.7) **million**
EUR	**85 000** (80 000–92 000)	**35 500** (33 000–39 500)	**1.7** (1.6–1.9) **million**	**729 000** (675 000–795 000)
EMR	**65 500** (62 000–70 500)	**27 500** (25 500–30 000)	**3.2** (2.9–3.6) **million**	**1.4** (1.2–1.6) **million**
SEAR	**162 000** (152 000–174 000)	**68 000** (63 500–74 500)	**5.7** (5.4–6.2) **million**	**2.4** (2.2–2.7) **million**
AMR	**126 000** (119 000–134 000)	**52 500** (48 500–57 000)	**2.9** (2.7–3.0) **million**	**1.2** (1.1–1.3) **million**
WPR	**182 000** (169 000–197 000)	**76 500** (69 500–85 000)	**4** (3.7–4.3) **million**	**1.7** (1.5–1.8) **million**
GLOBAL	**760 000** (737 000–782 000)	**319 000** (307 000–331 000)	**25.3** (24.3–26.3) **million**	**10.6** (10.1–11.2) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**210** (150–290) **million**	**88** (65–120) **million**
EUR	**300** (220–410) **million**	**130** (94–170) **million**
EMR	**190** (120–300) **million**	**81** (49–120) **million**
SEAR	**510** (380–640) **million**	**210** (160–270) **million**
AMR	**300** (200–410) **million**	**130** (85–170) **million**
WPR	**250** (200–310) **million**	**100** (84–130) **million**
GLOBAL	**1800** (1500–2100) **million**	**740** (630–880) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**3962** (2402–6197) **million**	**1664** (19–2603) **million**	**3188 million**	**1339 million**
EUR	**37 015** (23 380–55 283) **million**	**15 546** (9820–23 219) **million**	**5159 million**	**2167 million**
EMR	**10 570** (6381–16 733) **million**	**4439** (2680–7028) **million**	**4410 million**	**1852 million**
SEAR	**9372** (3913–19 501) **million**	**3936** (1644–8191) **million**	**5696 million**	**2392 million**
AMR	**44 528** (2223–82 466) **million**	**18 702** (9250–34 636) **million**	**9950 million**	**4179 million**
WPR	**32 218** (17 996–54 350) **million**	**13 531** (7558–22 827) **million**	**8057 million**	**3384 million**
GLOBAL	**137 664** (104 596–186 432) **million**	**57 819** (43 930–78 302) **million**	**36 460 million**	**15 313 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.20 *Streptococcus pneumoniae*

Pathogen and its epidemiology

S. pneumoniae is a gram-positive bacterium responsible for a myriad of infections, such as pneumonia, meningitis, sinusitis and acute otitis media. It predominantly inhabits the upper respiratory tract and is associated with a high degree of morbidity and mortality. *S. pneumoniae* is also notorious as a leading cause of lower respiratory tract infection worldwide, resulting in an estimated 829 000 deaths in 2019, up to 72% of which were associated with AMR *(2)*. The existence of more than 100 pneumococcal serotypes poses challenges, although vaccines targeting 10–13 serotypes are available and widely used *(229)*. Vaccines targeting a higher number of serotypes are available but not yet widely used. The burden of *S. pneumoniae* infections falls heavily on underprivileged populations and LMIC, with disproportionate morbidity in regions such as Africa and Asia. Vulnerable groups – for example, young children, elderly people and immunocompromised individuals, especially those in LMIC – face the highest risk of infection. Economic impacts are profound, with infections resulting in significant financial loss, inability to work and long-term care needs, which are often exacerbated by AMR strains. Cultural beliefs and disparities in vaccine uptake further compound these challenges, with suboptimal vaccination rates in many disadvantaged communities *(229)*.

Treatment and prevention

Antibiotics, especially penicillins such as penicillin V and G and amoxicillin, remain the cornerstone of treatment. Nonetheless, antimicrobial stewardship, enhanced diagnostics, public awareness and health care protocols are essential to reduce the misuse of antibiotics. In addition, implementing IPC measures in medical facilities (e.g. contact-free cleaning and rigorous hand hygiene) is crucial to prevent the transmission of disease *(229)*.

Vaccination strategies using PCVs and pneumococcal polysaccharide vaccines have proven effective in lowering infection rates and reducing the need for antibiotics. The current PCVs are both safe and effective, with expanded serotype coverage significantly advancing progress in combating pneumococcal disease, especially in LMIC. Consequently, WHO recommends the incorporation of PCVs into global childhood immunization programmes *(229)*.

Routine vaccination for elderly people is not widely implemented, and in situations where it is implemented, coverage is often inadequate. LMIC in particular lack sufficient data on disease burden and vaccine impact to guide policy-making for pneumococcal vaccination in older populations. WHO advises prioritizing the integration of PCV into national childhood immunization schemes and maintaining high coverage among children. For countries with well-established childhood programmes, the extension to adult vaccination should consider local epidemiology and cost–effectiveness *(230)*.

Antimicrobial resistance

WHO has classified the AMR threat posed by penicillin-non-susceptible *S. pneumoniae* as medium *(9)*, and the CDC has categorized it as a serious threat *(27)*. The AMR threat is underscored by data from the SENTRY Antimicrobial Surveillance Program, which found susceptibility to penicillin ranging from 52.4% to 70.7% across regions *(231)*. The emergence of MDR and XDR strains, particularly in the Asia-Pacific region, where nearly half of the isolates are MDR, exacerbates the challenge.

Vaccines

PCVs are widely available and, by 2022, reached global coverage of about 60% *(232, 233)*. They target many serotypes traditionally responsible for most invasive disease in children and have proven highly effective for reducing both resistant infections and antibiotic consumption. The impact of vaccines on the reduction of drug-resistant strains of *S. pneumoniae* and antibiotic use has been shown in multiple clinical trials and observational studies in all income settings. The evidence was recently summarized in a One Health

Trust report *(17)*. A systematic review and meta-analysis found reductions in the proportions of pneumococci showing non-susceptibility to penicillin (11.5%; 95% CI: 8.6–14.4), sulfamethoxazole–trimethoprim (9.7%; 4.3–15.2) and third-generation cephalosporins (7.5%; 3.1–11.9) over the 10 years after implementation of any PCV product *(234)*. In addition to the existing vaccines, there are multiple other vaccines against *S. pneumoniae*, with vaccines targeting 20 or more serotypes in development *(33)*.

This report evaluated the impact on AMR of existing pneumococcal vaccines [SP_1] and the same vaccines if WHO global coverage targets were met [SP_2], the incremental impact of these vaccines if they were to be used in elderly people [SP_3], and the impact of a potential new vaccine with increased efficacy against lower respiratory tract infections [SP_4] (Table 4.20).

Other analyses of vaccine impact on AMR

In addition to the WHO-coordinated analyses, Lewnard and colleagues estimated the impact of pneumococcal vaccines under current and expanded coverage *(235)*. At current vaccine coverage, they estimated that PCV10/13 prevents 23.8 million (range: 4.2–52.0 million) episodes of antibiotic-treated acute respiratory infection (ARI) annually among children aged 24–59 months in LMIC. This figure accounts for 42.4% (32.7–47.5) of all such ARI episodes that would occur in the absence of PCV10/13. Expanding PCV10/13 coverage to include all children aged 24–59 months in LMIC could prevent an additional 21.7 million (3.8–47.5 million) episodes of antibiotic-treated ARI, representing 38.7% (30.0–43.4) of all episodes attributable to vaccine-serotype pneumococci in this age group *(235)*.

Streptococcus pneumoniae (SP_1)

Table 4.20. A serotype-specific vaccine against *S. pneumoniae* infection given to 51% of infants (2019 coverage), with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_1]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Streptococcus pneumoniae	**Infants**	**5 years**	**Efficacy** LRI: **25%** IPD caused by any serotype: **58%** **Coverage: 51%**	MEDIUM
Vaccine name: **SP_1**				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**226 000** (206 000–250 000)	**29 000** (22 000–36 000)	**16.3** (14.5–18.2) **million**	**2.5** (2–3.1) **million**
EUR	**41 000** (38 500–44 000)	**1015** (777–1317)	**1.2** (1.2–1.3) **million**	**87 500** (66 000–110 000)
EMR	**66 500** (60 500–73 000)	**7613** (5748–10 000)	**4.6** (4.1–5.2) **million**	**674 000** (538 000–864 000)
SEAR	**136 000** (127 000–147 000)	**1955** (1395–2670)	**6.7** (6.1–7.4) **million**	**170 000** (125 000–227 000)
AMR	**59 000** (56 500–62 000)	**2141** (1651–2677)	**2** (1.8–2.1) **million**	**187 000** (145 000–239 000)
WPR	**116 000** (109 000–124 000)	**2418** (1896–2968)	**3.3** (3.1–3.5) **million**	**212 000** (163 000–275 000)
GLOBAL	**646 000** (618 000–672 000)	**44 500** (37 000–51 500)	**34** (32–36.2) **million**	**3.8** (3.3–4.5) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**95** (36–196) **million**	**3.5** (1.4–6.4) **million**
EUR	**186** (58–500) **million**	**7.2** (2.9–17) **million**
EMR	**141** (52–255) **million**	**4.5** (1.9–7.9) **million**
SEAR	**93** (33.4–231) **million**	**720 000** (300 000–1.5 **million**)
AMR	**143** (57–289) **million**	**4.9** (2.4–10) **million**
WPR	**58** (27.2–113) **million**	**1.8** (1–3.3) **million**
GLOBAL	**720** (328–1500) **million**	**23** (11–43) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**554** (307–947) **million**	**22.4** (13.1–36.4) **million**	**5295 million**	**689 million**
EUR	**6192** (3898–9773) **million**	**116** (72.7–188) **million**	**3286 million**	**223 million**
EMR	**2687** (1221–5287) **million**	**80.1** (39.5–146) **million**	**5006 million**	**604 million**
SEAR	**2178** (901–4697) **million**	**8.7** (3.8–18.1) **million**	**5687 million**	**145 million**
AMR	**14 044** (5873–28 746) **million**	**279** (125–546) **million**	**6724 million**	**527 million**
WPR	**8571** (3651–16 811) **million**	**119** (51.8–234) **million**	**6837 million**	**457 million**
GLOBAL	**34 226** (23 165–50 356) **million**	**626** (433–911) **million**	**32 834 million**	**2645 million**

Streptococcus pneumoniae (SP_2)

A serotype-specific vaccine against *S. pneumoniae* infection given to 90% of infants, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_2]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Streptococcus pneumoniae	**Infants**	**5 years**	**Efficacy** LRI: **25%** IPD caused by any serotype: **58%** **Coverage: 90%**	MEDIUM
Vaccine name: **SP_2**				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**226 000** (206 000–250 000)	**36 000** (27 500–44 500)	**16.3** (14.5–18.2) **million**	**3.1** (2.4–3.8) **million**
EUR	**41 000** (38 500–44 000)	**1020** (784–1341)	**1.2** (1.2–1.3) **million**	**88 000** (66 500–111 000)
EMR	**66 500** (60 500–73 000)	**8745** (6693–12 000)	**4.6** (4.1–5.2) **million**	**775 000** (619 000–993 000)
SEAR	**136 000** (127 000–147 000)	**8035** (5924–11 000)	**6.7** (6.1–7.4) **million**	**695 000** (515 000–931 000)
AMR	**59 000** (56 500–62 000)	**2299** (1747–2910)	**2** (1.8–2.1) **million**	**201 000** (155 000–261 000)
WPR	**116 000** (109 000–124 000)	**3083** (2416–3844)	**3.3** (3.1–3.5) **million**	**272 000** (210 000–347 000)
GLOBAL	**646 000** (618 000–672 000)	**59 000** (50 000–69 000)	**34** (32–36.2) **million**	**5.1** (4.5–6.0) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**95** (36–196) **million**	**4.3** (1.7–7.9) **million**
EUR	**186** (58–500) **million**	**7.3** (2.9–17.1) **million**
EMR	**141** (52–255) **million**	**5.2** (2.2–9.1) **million**
SEAR	**93** (33.4–231) **million**	**3.1** (1.2–7.2) **million**
AMR	**143** (57–289) **million**	**5.2** (2.6–10.7) **million**
WPR	**58** (27.2–113) **million**	**2.3** (1.2–4.1) **million**
GLOBAL	**720** (328–1500) **million**	**27.6** (13–53) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**554** (307–947) **million**	**27.7** (16.2–45) **million**	**5295 million**	**852 million**
EUR	**6192** (3898–9773) **million**	**117** (73.2–189) **million**	**3286 million**	**224 million**
EMR	**2687** (1221–5287) **million**	**92.4** (45.6–168) **million**	**5006 million**	**696 million**
SEAR	**2178** (901–4697) **million**	**42** (18.4–87.8) **million**	**5687 million**	**600 million**
AMR	**14 044** (5873–28 746) **million**	**300** (134–586) **million**	**6724 million**	**569 million**
WPR	**8571** (3651–16 811) **million**	**158** (68.4–309) **million**	**6837 million**	**585 million**
GLOBAL	**34 226** (23 165–50 356) **million**	**737** (522–156) **million**	**32 834 million**	**3524 million**

Streptococcus pneumoniae (SP_3)

A serotype-specific vaccine against *S. pneumoniae* infection given to 90% of infants and elderly people, with 5-year efficacy of 25% for lower respiratory tract infections and 58% for invasive pneumococcal disease caused by any serotype [SP_3]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Streptococcus pneumoniae	**Infants and elderly**	**5 years**	**Efficacy** LRI: **25%** IPD caused by any serotype: **58%** **Coverage: 90%**	MEDIUM
Vaccine name: **SP_3**				Feasibility of vaccine development and implementation: HIGH

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**226 000** (206 000–250 000)	**37 500** (29 500–46 500)	**16.3** (14.5–18.2) **million**	**3.1** (2.5–3.8) **million**
EUR	**41 000** (38 500–44 000)	**2164** (1697–2741)	**1.2** (1.2–1.3) **million**	**106 000** (84 000–132 000)
EMR	**66 500** (60 500–73 000)	**9436** (7294–12 500)	**4.6** (4.1–5.2) **million**	**787 000** (630 000–1 **million**)
SEAR	**136 000** (127 000–147 000)	**11 500** (9109–14 500)	**6.7** (6.1–7.4) **million**	**745 000** (563 000–979 000)
AMR	**59 000** (56 500–62 000)	**3896** (3153–4691)	**2** (1.8–2.1) **million**	**225 000** (176 000–283 000)
WPR	**116 000** (109 000–124 000)	**6884** (5576–8716)	**3.3** (3.1–3.5) **million**	**328 000** (262 000–408 000)
GLOBAL	**646 000** (618 000–672 000)	**71 500** (62 500–81 500)	**34** (32–36.2) **million**	**5.3** (4.7–6.1) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**95** (36–196) **million**	**5.1** (2–9.4) **million**
EUR	**186** (58–500) **million**	**7.3** (2.9–17.3) **million**
EMR	**141** (52–255) **million**	**5.9** (2.5–10.3) **million**
SEAR	**93** (33.4–231) **million**	**6** (2.4–13.4) **million**
AMR	**143** (57–289) **million**	**5.6** (2.7–11.4) **million**
WPR	**58** (27.2–113) **million**	**2.9** (1.6–5.2) **million**
GLOBAL	**720** (328–1500) **million**	**33** (15.7–64) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**554** (307–947) **million**	**30.8** (18.0–50.3) **million**	**5295 million**	**852 million**
EUR	**6192** (3898–9773) **million**	**226** (140–362) **million**	**3286 million**	**224 million**
EMR	**2687** (1221–5287) **million**	**107** (51.8–197) **million**	**5006 million**	**696 million**
SEAR	**2178** (901–4697) **million**	**58.3** (25.7–121) **million**	**5687 million**	**600 million**
AMR	**14 044** (5873–28 746) **million**	**441** (196–868) **million**	**6724 million**	**569 million**
WPR	**8571** (3651–16 811) **million**	**270** (118–529) **million**	**6837 million**	**585 million**
GLOBAL	**34 226** (23 165–50 356) **million**	**1132** (795–1621) **million**	**32 834 million**	**3524 million**

Streptococcus pneumoniae (SP_4)

A non-serotype-specific vaccine against *S. pneumoniae* infection given to 90% of infants and elderly people, with 5-year efficacy of 50% for lower respiratory tract infections and 70% for invasive pneumococcal disease [SP_4]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Streptococcus pneumoniae	**Infants and elderly**	**5 years**	**Efficacy** LRI: **50%** IPD caused by any serotype: **70%** **Coverage: 90%**	MEDIUM
Vaccine name: **SP_4**				Feasibility of vaccine development and implementation: LOW

AMR health burden

WHO region	Deaths associated with resistance in 2019 (95% UI)	Deaths associated with resistance averted by a vaccine in 2019 (95% UI)	DALYs associated with resistance in 2019 (95% UI)	DALYs associated with resistance averted by a vaccine in 2019 (95% UI)
AFR	**226 000** (206 000–250 000)	**62 500** (50 500–76 000)	**16.3** (14.5–18.2) **million**	**5.2** (4.3–6.6) **million**
EUR	**41 000** (38 500–44 000)	**3395** (2868–4213)	**1.2** (1.2–1.3) **million**	**177 000** (146 000–212 000)
EMR	**66 500** (60 500–73 000)	**15 500** (12 500–20 000)	**4.6** (4.1–5.2) **million**	**1.3** (1.1–1.7) **million**
SEAR	**136 000** (127 000–147 000)	**19 500** (15 500–24 500)	**6.7** (6.1–7.4) **million**	**1.3** (1.0–1.6) **million**
AMR	**59 000** (56 500–62 000)	**6322** (5258–7555)	**2** (1.8–2.1) **million**	**367 000** (298 000–464 000)
WPR	**116 000** (109 000–124 000)	**11 500** (9367–14 000)	**3.3** (3.1–3.5) **million**	**560 000** (457 000–677 000)
GLOBAL	**646 000** (618 000–672 000)	**119 000** (104 000–135 000)	**34** (32.0–36.2) **million**	**9.0** (7.9–10.3) **million**

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	**95** (36–196) **million**	**8.6** (3.3–16) **million**
EUR	**186** (58–500) **million**	**15** (5.8–37) **million**
EMR	**141** (52–255) **million**	**11** (4.4–20) **million**
SEAR	**93** (33.4–231) **million**	**8.1** (3.4–18) **million**
AMR	**143** (57–289) **million**	**11** (5.3–23) **million**
WPR	**58** (27.2–113) **million**	**5.1** (2.8–9.3) **million**
GLOBAL	**720** (328–1500) **million**	**60** (28–120) **million**

AMR economic burden

WHO region	Hospital costs associated with resistance in 2019, US dollars (95% UI)	Hospital costs associated with resistance averted by a vaccine in 2019, US dollars (95% UI)	Productivity losses associated with resistance in 2019, US dollars	Productivity losses associated with resistance averted by a vaccine in 2019, US dollars
AFR	**554** (307–947) **million**	**51.9** (29.2–85.8) **million**	**5295 million**	**1449 million**
EUR	**6192** (3898–9773) **million**	**410** (254–661) **million**	**3286 million**	**388 million**
EMR	**2687** (1221–5287) **million**	**193** (91.4–362) **million**	**5006 million**	**1192 million**
SEAR	**2178** (901–4697) **million**	**106** (46.4–223) **million**	**5687 million**	**1060 million**
AMR	**14 044** (5873–28 746) **million**	**807** (356–1587) **million**	**6724 million**	**941 million**
WPR	**8571** (3651–16 811) **million**	**493** (214–970) **million**	**6837 million**	**1012 million**
GLOBAL	**34 226** (23 165–50 356) **million**	**262** (1438–2970) **million**	**32 834 million**	**6041 million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.21 Influenza

Influenza is caused by influenza A and B viruses, which are part of the *Orthomyxoviridae* family and have a single-stranded, segmented RNA genome. These viruses, transmitted through respiratory droplets, aerosols and occasionally fomites, lead to seasonal epidemics and sporadic cases worldwide. Influenza infections can range from asymptomatic to severe, potentially resulting in death. Annually, an estimated 1 billion cases occur, with 3–5 million being severe and leading to 290 000 to 650 000 respiratory-related deaths *(236)*. Antibiotics are often inappropriately prescribed to treat influenza symptoms. Particularly vulnerable groups include older adults, pregnant women, young children, people with chronic health conditions and health care workers *(236)*.

Both inactivated and live attenuated vaccines are available in trivalent (covering two A subtypes and one B virus lineage) and quadrivalent (covering two A and two B virus lineages) formulations, offering moderate protection against the most prevalent seasonal influenza strains for about 6 months *(236, 237)*. A systematic review and meta-analysis found high-certainty evidence that influenza vaccination reduces antibiotic use among healthy adults *(72)*. This report evaluated the impact on antibiotic use of a seasonal maternal influenza vaccine to protect neonates for 1 year [Influenza_1]; however, recent data suggest that vaccine effectiveness is closer to 6 months *(238)*. The impact of a universal influenza vaccine given to people at high risk of severe influenza infection [Influenza_2] was also evaluated (Table 4.21).

Influenza (Influenza_1)

Table 4.21. A seasonal maternal vaccine against influenza infection given to 70% of pregnant women to protect neonates and infants, with 1-year efficacy of 70% [Influenza_1]

Target pathogen: **Influenza**	Targeting: **Infants**	Duration: **1 year**	Usage scenario: Efficacy: **70%** Coverage: **70%**	WHO AMR priority: *Not assessed*
Vaccine name: **Influenza_1**				Feasibility of vaccine development and implementation: HIGH

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	29 (17–55) million	2.9 (1.1–6.4) million
EUR	21 (10–34) million	1.1 million (380 000–2.5 million)
EMR	44 (28–64) million	3.7 (2.1–6.1) million
SEAR	17 (7.8–31) million	650 000 (200 000–1.6 million)
AMR	17 (9.6–29) million	950 000 (420 000–2.1 million)
WPR	14 (8.8–24) million	670 000 (310 000–1.5 million)
GLOBAL	**140** (100–200) **million**	**10** (5.1–18) **million**

Influenza (Influenza_2)

A universal vaccine against type A influenza infection given to 70% of infants and elderly people, with 5-year efficacy of 70% [Influenza_2]

Target pathogen: **Influenza**	Targeting: **Infants and elderly**	Duration: **5 years**	Usage scenario: Efficacy: **70%** Coverage: **70%**	WHO AMR priority: *Not assessed*
Vaccine name: **Influenza_2**				Feasibility of vaccine development and implementation: LOW

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	29 (17–55) million	14 (8.3–27) million
EUR	21 (10–34) million	10 (5–17) million
EMR	44 (28–64) million	22 (14–31) million
SEAR	17 (7.8–31) million	8.5 (3.8–15) million
AMR	17 (9.6–29) million	8.5 (4.7–14) million
WPR	14 (8.8–24) million	7 (4.3–12) million
GLOBAL	**140** (100–200) **million**	**70** (50–97) **million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.22 Norovirus

Norovirus, belonging to the *Caliciviridae* family, is an RNA virus that causes significant morbidity as a human enteric pathogen in both health care and community settings. Its high transmissibility is due to factors such as its small infectious dose, prolonged viral shedding and environmental resilience. Asymptomatic infection is common, especially in children, with frequent faecal excretion of the virus. Norovirus is the leading cause of acute gastroenteritis, characterized mainly by vomiting and diarrhoea and typically resolving within 1–3 days. It accounts for about one in every five cases of acute gastroenteritis globally, leading to significant health care burden and economic costs. Annually, norovirus causes an estimated 685 million cases of gastroenteritis, including 200 million among children aged under 5 years and resulting in about 50 000 child deaths, predominantly in developing countries. The economic impact is substantial, with annual costs estimated at US$ 60 billion in health care expenses and lost productivity. Norovirus outbreaks are more prevalent in cooler months, with most occurring from November to April in the northern hemisphere and May to September in the southern hemisphere. However, in equatorial regions, its occurrence may be less seasonal *(239–241)*.

There is no available vaccine against norovirus, but there are four vaccines in clinical development *(241)*. In this report, the potential impact of an infant norovirus vaccine on antibiotic use was evaluated (Table 4.22).

Norovirus

Table 4.22. A vaccine against norovirus infection given to 70% of infants, with 5-year efficacy of 50% [Norovirus]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Norovirus	**Infants**	**5 years**	Efficacy: **50%** Coverage: **70%**	*Not assessed*
				Feasibility of vaccine development and implementation MEDIUM

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	5.7 (2.7–10) million	2.0 million (940 000–3.7 million)
EUR	880 000 (370 000–1.8 million)	310 000 (130 000–620 000)
EMR	6.4 (2.7–12) million	2.2 million (940 000–4.3 million)
SEAR	3.1 (1.5–5.6) million	1.1 million (530 000–1.9 million)
AMR	1.5 million (590 000–2.7 million)	510 000 (210 000–960 000)
WPR	1.6 million (740 000–3.1 million)	550 000 (260 000–1.1 million)
GLOBAL	**19** (10–33) **million**	**6.6** (3.6–12) **million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.23 Rotavirus

Rotaviruses, characterized by their triple-layered structure and double-stranded RNA genome, primarily infect mature enterocytes in the small intestine, leading to severe diarrhoea and dehydration. Before the introduction of vaccines in 2006, most children were infected by rotavirus by the age of 3–5 years, making it the leading cause of severe diarrhoea in children aged under 5 years. This resulted in more than 500 000 childhood deaths and more than 2 million hospitalizations in 2000. The introduction of rotavirus vaccines has significantly reduced the global burden of severe rotavirus gastroenteritis, yet rotavirus continues to cause substantial morbidity and mortality. In 2013, rotavirus was responsible for about 3.4% of all child deaths, predominantly in sub-Saharan Africa. Between 2013 and 2017, annual child deaths due to rotavirus ranged from 122 000 to 215 000, a decline of 59–77% since 2000 *(242)*. Rotavirus transmission occurs mainly via the faecal–oral route, directly from person to person or indirectly through contaminated fomites. In the pre-vaccine era, rotavirus showed intense circulation with year-round transmission in low-income countries, and distinct winter seasonality in high-income temperate countries. Vaccine introduction has led to reduced and delayed seasonality in some regions *(242)*.

The available rotavirus vaccines are live, oral attenuated strains of human or animal origin. These vaccines replicate in the human intestine to induce an immune response. This report evaluated the potential impact of rotavirus vaccines on antibiotic use, assuming that the WHO-recommended goal for vaccine coverage was reached (Table 4.23).

Other analyses of vaccine impact on AMR

In addition to the WHO-coordinated analyses, Lewnard and colleagues estimated the potential impact of rotavirus vaccines under current and expanded coverage *(235)*. By examining data from extensive household studies, they estimated that the direct effects of rotavirus vaccination currently prevent 13.6 million (range: 3.6–23.7 million) episodes of antibiotic-treated diarrhoea annually among children aged 0–23 months in LMIC. This accounts for 31.0% (17.7–35.2) of all the antibiotic-treated diarrhoea episodes that rotavirus could cause annually in this age group in the absence of vaccination. Further, they projected that universal vaccine coverage could prevent an additional 18.3 million (4.2–32.6 million) episodes of antibiotic-treated diarrhoea annually among children aged 0–23 months. This would represent 42.1% (14.6–50.7) of all antibiotic use attributable to rotavirus in this demographic *(235)*.

Rotavirus

Table 4.23. An oral, live attenuated vaccine against rotavirus infection given to 90% of infants, with 2-year efficacy of 60% [Rotavirus]

Target pathogen:	Targeting:	Duration:	Usage scenario:	WHO AMR priority
Rotavirus	**Infants**	**2 years**	Efficacy: **60%** Coverage: **90%**	*Not assessed*
				Feasibility of vaccine development and implementation: HIGH

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	15 (8.4–22) million	4.6 (2.6–7) million
EUR	2.4 (1.1–4.8) million	1.1 million (480 000–2.1 million)
EMR	15 (8–24) million	4.4 (2.3–7) million
SEAR	7 (4.2–9.8) million	2.8 (1.7–3.9) million
AMR	3.4 (1.7–5.8) million	480 000 (240 000–820 000)
WPR	3.7 (2.2–6) million	2 (1.2–3.2) million
GLOBAL	**46** (30–63) **million**	**15** (10–21) **million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

4.24 Respiratory syncytial virus

Respiratory syncytial virus (RSV) is the primary cause of acute lower respiratory tract infection (ALRI) in young children globally, leading to millions of episodes of illness and hospitalization and significant fatalities each year. In 2019, an estimated 33 million RSV-induced ALRI episodes were recorded in children aged under 5 years, resulting in 3.6 million hospitalizations and 26 500 in-hospital deaths. Overall, there were about 101 000 RSV-related deaths, mainly in LMIC. Infants aged 6 months or younger face a higher risk of severe RSV outcomes, with substantial mortality both in and outside hospital settings in LMIC *(243)*.

Palivizumab, a short-acting monoclonal antibody (mAb), has been licensed for prevention of severe RSV-induced lower respiratory tract disease since the late 1990s. However, its use has been limited to very premature infants in high-income countries because of practical and cost constraints. A maternal vaccine has recently been approved by several regulatory agencies in high-income and upper middle-income countries for pregnant women in the late second or early third trimester (24–36 weeks of gestational age in the European Union, and 32–36 weeks in the United States of America) to protect infants against severe RSV outcomes from birth to 6 months. Policy deliberations for recommendations in LMIC are awaited. Additionally, nirsevimab, a long-acting infant mAb, has been authorized for all infants in some countries. These antibodies, distinct from vaccines, are laboratory-made proteins that emulate the immune system's response to viruses. For adults aged 60 years and over, two approved vaccines, Abrysvo and Arexvy, are available to prevent RSV-related lower respiratory tract disease. Several other vaccines are in development, highlighting ongoing efforts to mitigate the significant global health burden of RSV, particularly among young children and infants *(243, 244)*.

This report evaluated the potential impact on antibiotic use of two vaccines: a maternal vaccine to protect neonates [RSV_1] and an infant vaccine [RSV_2] (Table 4.24). The impact of long-acting mAbs given to neonates and preventing a similar disease endpoint is expected to be similar; however, there are unique technical challenges in developing and using mAbs at scale in LMIC.

Other analyses of vaccine impact on AMR

In addition to the WHO-coordinated analyses, Lewnard and colleagues analysed data from a Phase 3 RSV vaccine trial *(245)*. In a double-blind study conducted in 11 countries, infants born to mothers who were randomly selected to receive a trial vaccine against RSV had a 12.9% (95% CI: 1.3–23.1) reduction in antimicrobial prescriptions during their first 3 months of life, compared with infants whose mothers received a placebo. The vaccine's effectiveness in reducing antimicrobial prescriptions for ALRI was 16.9% (95% CI: 1.4–29.4). In the first 3 months, vaccination of mothers resulted in 3.6 fewer antimicrobial prescription courses per 100 infants in high-income countries and 5.1 fewer courses per 100 infants in LMIC. This reduction equates to 20.2% and 10.9% of all antimicrobial prescriptions in these respective settings *(245)*.

Respiratory syncytial virus (RSV_1)

Table 4.24. A vaccine against severe RSV infection given to 70% of infants through maternal vaccination, with 6-month efficacy of 70 % [RSV_1]

Target pathogen: **Respiratory syncytial virus**	Targeting: **Infants**	Duration: **6 month**	Usage scenario: Efficacy: **70%** Coverage: **70%**	WHO AMR priority: *Not assessed*
Vaccine name: **RSV_1**				Feasibility of vaccine development and implementation: HIGH

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	11 (3.7–22) million	1.5 million (330 000–3.7 million)
EUR	4.2 (1.5–9.5) million	640 000 (160 000–1.5 million)
EMR	5.2 (1.4–13) million	670 000 (130 000–1.8 million)
SEAR	3.2 million (800 000–6.8 million)	360 000 (74 000–890 000)
AMR	3.0 million (750 000–6.7 million)	400 000 (90 000–1.1 million)
WPR	2.3 million (630 000–4.6 million)	290 000 (54 000–700 000)
GLOBAL	**29** (9.8–62) **million**	**3.9 million** (870 000–8.7 **million**)

Respiratory syncytial virus (RSV_2)

A vaccine against severe RSV infection given to 70% of infants, with 2-year efficacy of 70% [RSV_2]

Target pathogen: **Respiratory syncytial virus**	Targeting: **Infants**	Duration: **2 years**	Usage scenario: Efficacy: **70%** Coverage: **70%**	WHO AMR priority: *Not assessed*
Vaccine name: **RSV_2**				Feasibility of vaccine development and implementation: LOW

Antibiotic use

WHO region	Pathogen-associated antibiotic use in 2019, DDD (95% UI)	Pathogen-associated antibiotic use averted by a vaccine in 2019, DDD (95% UI)
AFR	11 (3.7–22) million	5.4 (1.8–11) million
EUR	4.2 (1.5–9.5) million	2.0 million (710 000–4.6 million)
EMR	5.2 (1.4–13) million	2.6 million (710 000–6.4 million)
SEAR	3.2 million (800 000–6.8 million)	1.5 million (390 000–3.3 million)
AMR	3.0 million (750 000–6.7 million)	1.5 million (370 000–3.3 million)
WPR	2.3 million (630 000–4.6 million)	1.1 million (310 000–2.3 million)
GLOBAL	**29** (9.8–62) **million**	**14** (4.8–30.0) **million**

AMR: antimicrobial resistance; DDD: defined daily doses; UI: uncertainty interval; WHO: World Health Organization.

Regions: AFR: WHO African Region; AMR: WHO Region of the Americas; EMR: WHO Eastern Mediterranean Region; EUR: WHO European Region; SEAR: WHO South-East Asia Region; WPR: WHO Western Pacific Region.

5. Conclusions and recommendations

5.1 Conclusions

Vaccines play a critical, yet underrecognized, role in reducing AMR. They reduce infections and transmission of pathogens (both drug sensitive and drug resistant); they also reduce antibiotic use, which in turn slows down the evolution of resistant genes. Nevertheless, the impact of vaccines on AMR is often overlooked in policy-making and decision-making processes. This report highlights the significant benefits that vaccines offer in the fight against AMR, emphasizing the need for greater recognition and integration of vaccines into AMR mitigation strategies, and of AMR into vaccine decision-making.

The upcoming 79th Session of the UN General Assembly, which includes AMR, presents a prime opportunity for increased recognition of vaccines in the selection of strategies and tools to reduce AMR. This event can promote the inclusion of vaccines in national action plans and AMR strategies, advocating for their broader implementation and integration. To achieve appropriate inclusion of vaccines in the AMR agenda, the immunization and AMR communities must strengthen their joint understanding of the evidence and enhance collaboration. By assuring that the value of vaccines in AMR prevention and reduction is fully understood by relevant stakeholders, more impact can be achieved through cohesive strategies that fully incorporate effective use of vaccines in the fight against AMR. This will require greater communication and partnership between AMR constituencies and the broader vaccine and immunization community. Such cooperation can help to bridge gaps, align goals and ensure that vaccine programmes are fully leveraged to combat the growing threat of AMR.

It is vital to introduce, use and monitor the impact of existing vaccines, as highlighted in the report. Pneumococcal, rotavirus and typhoid vaccines are examples of interventions with demonstrated efficacy in reducing infections that are often treated with antibiotics. The analysis presented here shows that increasing coverage of bacterial vaccines can significantly lower antibiotic use, and the deaths and DALYs associated with AMR. Additionally, the report emphasizes the importance of robust research studies to monitor the ongoing impact of vaccines on colonization and infection by resistant pathogens, providing data that are crucial for informing and refining policy decisions.

It is important to prepare for vaccine introduction, and the report gives insights to ensure that new vaccines are ready for deployment. Including AMR endpoints in clinical trials will provide essential data on vaccine impact, validating modeling estimates and informing comprehensive cost–effectiveness analyses. The report also underscores the need for developing regulatory frameworks and processes that facilitate the inclusion of AMR endpoints in vaccine labels, to improve understanding and appreciation of the role of vaccines in combating AMR.

Enabling vaccine development, delivery and implementation is essential for addressing the current and future challenges posed by AMR. The report emphasizes the importance of developing PPCs for vaccines from the early stages of development to mid-clinical, outlining the attributes required for impactful vaccines. Creating research roadmaps for vaccines facing significant development challenges, as suggested here, can guide efforts to overcome obstacles and expedite the availability of vaccines, particularly in LMIC.

Understanding the role of vaccines alongside other approaches for reducing AMR is crucial for a comprehensive strategy. The report emphasizes that vaccines should be integrated into broader AMR containment efforts (e.g. infection prevention, access to essential health services, accurate diagnosis and appropriate treatment). Enhancing surveillance platforms to collect data on the burden of resistant pathogens will inform the development and implementation of effective vaccination strategies and other AMR interventions.

Vaccines are a vital, yet underused, tool in the fight against AMR, and can reach millions of children through existing immunization programmes. Recognizing their full potential requires concerted efforts to integrate vaccine strategies into AMR policies, enhance collaboration between stakeholders, and prioritize research and surveillance. The upcoming UN General Assembly on AMR is an opportunity to advance these goals and highlight the indispensable role of vaccines in reducing AMR globally. The analyses presented in this report provide a strong foundation for the proposed recommendations, underscoring the multifaceted benefits of vaccines in the ongoing battle against AMR.

5.2 Recommendations

This section gives the full set of recommendations from this report. Introduce, scale the use of and monitor the impact of the existing vaccines

Introduce existing vaccines

- *Cost–effectiveness studies:* In vaccine cost–effectiveness studies, include the impact on AMR and reduced antimicrobial prescribing, to ensure comprehensive understanding of vaccine benefits through standardized and validated frameworks. Ensure that all cost–effectiveness studies include the additional health loss, loss of productivity and cost of treating resistant pathogens (as has been outlined in this report), and explore ways to capture the impact of vaccines on the longer term consequences of AMR (e.g. reduced transmission of resistant strains and potentially prolonged efficacy of antibiotics in the future).
- *Policy updates:* Ensure that vaccine policy updates reflect vaccine impact on AMR and antimicrobial use (from data that are either modelled or collected during clinical development), ensuring that policy decisions are informed by the latest data.
- *Decision-making and strategic planning:* Incorporate the impact of vaccines on AMR in country-level decision-making processes, including as part of strategic planning in national immunization strategies (NIS), to ensure that the full benefits of vaccines are considered and that national health strategies are aligned with goals for AMR mitigation.
- *Typhoid vaccines:* Accelerate the introduction of typhoid vaccines in countries with a high burden of typhoid, to limit the spread of typhoid infections and reduce the use of antibiotics.

Scale vaccine use

- *National action plans:* Consider the use of vaccines as a tool to combat AMR in national action plans on AMR and ensure complementarity with NIS; also, align with other AMR mitigation strategies, in line with guidance in the people-centred approach to addressing AMR in human health *(7)*.

- *Pneumococcal vaccines:* Introduce pneumococcal vaccines in countries that have not yet done so, and increase coverage to meet the IA2030 target of 90% global coverage for the last dose of pneumococcal vaccine *(246)*, to combat pneumococcal diseases and their resistance to treatment.

- *Rotavirus vaccines:* Introduce rotavirus vaccines in countries that have not yet done so, and increase coverage to meet the IA2030 target of 90% global coverage for the last dose of rotavirus vaccines *(246)*, to reduce antibiotic use and the prevalence of AMR in bacteria.

- *Influenza vaccines:* Immunization stakeholders in a country should consider expanding the seasonal influenza immunization to high-risk groups (e.g. health workers, individuals with comorbidities and underlying conditions, older adults, pregnant women and children) to reduce the spread and impact of influenza *(236)*.

Monitor vaccine impact

- *Research studies:* Conduct research studies to assess the ongoing impact of vaccines on colonization and infection by resistant pathogens, and the role of vaccines in reducing the use of antimicrobial medicines (including those acquired outside regulated markets), health care encounters, productivity losses and health system costs *(14)*. Analyse and report the impact of vaccines on AMR, including on antimicrobial prescription. Use these data to inform regulatory decisions, policy-making and strategies for vaccine introduction and uptake in countries.

- *Malaria drug efficacy and resistance surveillance:* Strengthen surveillance of antimalarial drug efficacy and resistance of *Plasmodium* species to recommended treatments, to track and respond to the evolving threat of malaria resistance.

- *Pneumococcal and* Haemophilus influenzae *type b (Hib) surveillance:* Monitor the resistance patterns of circulating pneumococcal and Hib strains, so that vaccine products and vaccination strategies can be adapted accordingly.

- *Typhoid fever surveillance:* Expand the existing surveillance networks – such as the WHO Global Antimicrobial Resistance Surveillance System (GLASS) – to include typhoid fever diagnostics, especially in Africa. This will improve understanding of the burden and support development of effective vaccination and treatment strategies, among other AMR interventions.

5.2.1 Prepare for vaccine introduction

- *Regulatory frameworks for AMR endpoints:* Encourage regulators to develop frameworks that encourage the inclusion of vaccine impact on AMR endpoints in product labels, enhancing the understanding of vaccine benefits in combating AMR.

- *Evidence Consideration for Vaccine Policy (ECVP):* Follow the WHO ECVP framework *(247)* to consider AMR-related evidence that it is anticipated will be required to inform WHO vaccine policy and global health strategies.

- *Malaria vaccine supply and analysis:*

    - *Reduce costs:* Reduce the price of malaria vaccines, to enable the introduction and optimization of vaccine use across various malaria transmission settings, to effectively combat the emergence of drug-resistant *P. falciparum*.

    - *Analyse impact data:* Analyse existing datasets to understand the impact of malaria vaccines on the use of antimicrobials; this information can guide future vaccine development and deployment strategies.

- *Deployment of new TB vaccines:* Identify and establish pathways to enable and accelerate broad and rapid deployment of novel TB vaccines, particularly for adults and adolescents (who are responsible for the majority of transmission). Vaccine readiness will be critical in addressing this major infectious disease and its associated AMR challenges.

5.2.2 Enable vaccine development, delivery and implementation

- *Inclusion of AMR endpoints in clinical trials:* Where feasible, ensure that vaccine clinical trials include AMR endpoints (e.g. reduction in antimicrobial prescribing, or vaccine efficacy against infections or colonization with drug-resistant pathogens). This will provide crucial data about the impact of vaccines on AMR; help to validate the modelling estimates; inform the full value of vaccine assessments, cost–effectiveness analyses and policy decisions; and influence decisions to introduce vaccines to countries' immunization programmes. Develop comprehensive guidelines to inform the selection and feasibility of measuring AMR endpoints in clinical trials.

- *Assessment of vaccine characteristics:* For vaccines in early to mid-clinical development with a high potential impact on AMR, especially in LMIC, develop PPCs to summarize the minimum and optimum sets of attributes required for a vaccine to make an impact in target countries *(248)*.

- *Research roadmaps for challenging vaccine development:* For vaccines that have a high impact on AMR but are facing significant development challenges, develop research roadmaps outlining critical questions that need to be answered, to facilitate vaccine development, pathways to licensure, investment case or enablers for vaccine access, implementation and use.

- *Access for diverse and high-risk population groups:* For vaccines targeting high-risk groups that are diverse, poorly defined or difficult to immunize (e.g. hospital patients), develop pathways for identification and timely immunization.

- *Approaching regulatory agencies for pathogens with low to moderate incidence:* For vaccines targeting pathogens with low to moderate disease incidence and high mortality due to AMR, for which conducting large clinical trials is challenging, engage with regulatory agencies to understand the pathway to licensure. This includes exploring correlates of protection or human infection studies as alternatives to traditional efficacy trials.

- *Combining vaccines for synergistic effects:* Where the impact of individual vaccines alone may be insufficient, consider combining vaccines that target the same syndrome, geographical region, delivery platform or route of delivery. Use analytical tools (e.g. mathematical modelling) to estimate the impact of combination vaccines on cost–effectiveness, uptake and potentially a synergistic impact on reducing AMR.

- *Vaccines against pathogens with non-human reservoirs:* For pathogens with non-human reservoirs, consider the development and use of vaccines for targeted use in animals, as recommended by the One Health approach, to mitigate AMR transmission between animals and humans.

5.2.3 Understand the role of vaccines alongside other approaches to reduce AMR

- *Alternative AMR containment approaches:* For all infections, and particularly for those caused by pathogens with no vaccine candidates or in early development stages, use a comprehensive package of interventions to reduce AMR. Consider interventions documented in the people-centred approach to addressing AMR in human health: prevention of infections; access to essential health services; timely, accurate diagnosis; and appropriate, quality-assured treatment *(7)*.

- *Surveillance platforms:* Establish new surveillance platforms and enhance existing platforms to collect burden data for pathogens where such data are lacking, particularly in LMIC. This will aid in understanding the broader impact of these pathogens and the potential role of vaccines.

- *Increasing awareness of pathogens:* For vaccines targeting highly resistant pathogens for which there is low awareness, increase awareness among researchers, funders and country stakeholders through new and enhanced surveillance. Implement educational campaigns for clinicians and caregivers, to improve knowledge of and response to these pathogens.

- *Health burden of AMR:* For vaccines with an estimated high impact on AMR health burden, use new and enhanced surveillance platforms to collect data before and after vaccine introduction on the prevalence and incidence of resistant infections. Where feasible, collect data on the impact of a vaccine on AMR health burden during clinical development (see prior recommendation *"Inclusion of AMR endpoints in clinical trials"*), to inform analyses of the long-term impact of the vaccine on AMR health burden.

- *Economic burden of AMR:* For vaccines with an estimated high impact on AMR economic burden, collect data on the economic aspects of AMR before and after introduction of the vaccine (e.g. on hospital costs, length of stay in health facilities, and treatment costs for both drug-susceptible and drug-resistant infections). Where feasible, collect data on the impact of a vaccine on these endpoints during clinical development, to collectively estimate the long-term impact of the vaccine on the economic burden of AMR.

- *Impact on antibiotic use:* For vaccines with an estimated significant impact on antibiotic use, gather data on the pathogen-associated or syndrome-associated antimicrobial use. Where feasible, collect data on the impact of the vaccine on antimicrobial use during clinical development and after the introduction of the vaccine. For antibiotics, align data collection with the WHO AWaRe (Access, Watch, Reserve) classification of antibiotics *(1)*. Estimate the vaccine's impact on reducing antimicrobial usage.

- *Assessment of vaccine value:* For vaccines in early to mid-clinical development with a high potential impact on AMR, develop comprehensive assessments of the full value of the vaccines, including reduction of AMR, while accounting for pathogen epidemiology, transmission and vaccine herd effects. Consider expanding the assessment to include additional criteria such as impact on equity and social justice, and how vaccines can enable other health care interventions.

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