ANNEX TO IMMUNIZATION AGENDA 2030

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance:

An action framework

Draft 17 Mar 2020

World Health Organization 2020
# Table of contents

25 Table of contents

26 Overview .................................................................................................................................. 3

27 Action framework – Table format .......................................................................................... 1

28 Background .............................................................................................................................. 1

29 The ability to prevent and effectively treat many infectious diseases is one of humanity’s greatest achievements .................................................................................................................. 1

30 Antimicrobial resistance: a major global health threat ............................................................... 1

32 A ‘One Health’ approach ......................................................................................................... 7

33 Prioritization of activities should be based on best available evidence .................................... 8

34 Reaching public health goals require investments, capacity, collaboration, political will, and public confidence. .................................................................................................................. 8

36 Strategic Vision .......................................................................................................................... 10

37 Goals, objectives and priority actions ...................................................................................... 10

38 Expanding use of licensed vaccines to maximize impact on AMR ............................................ 10

39 Developing new vaccines that contribute to prevention and control of AMR ............................ 15

40 Expanding and sharing knowledge of vaccine impact on AMR .................................................. 21

41 Conclusions ............................................................................................................................... 23

42 References .................................................................................................................................. 25

43 Abbreviations .............................................................................................................................. 28

44 Methodology .............................................................................................................................. 29

45 Target audience for this report ................................................................................................... 30

46 Useful links .................................................................................................................................. 32
Overview

There is increasing awareness of the significant threats to individual and public health represented by antimicrobial-resistant microbes. The development of multiple strategies to prevent infections and reduce the use of antimicrobial drugs is central to address the growing global burden of antimicrobial resistance (AMR). Vaccines are among the most effective tools to prevent infections, and they have the potential to make a major contribution to the control and prevention of AMR.

Vaccines protect people and communities by preventing infections and their onward transmission, whether antimicrobial resistant or not. Prevention of infections results in reduced use of antimicrobials for treatment, thereby reducing the selective pressures on microbial populations that drive the emergence of resistance.

This document presents a strategic vision for vaccines to contribute fully, sustainably and equitably to the prevention and control of AMR by preventing infections and reducing antimicrobial use. It identifies a series of priority actions to be taken by stakeholders in the fields of immunization and AMR, in three areas:

- Expanding use of licensed vaccines to maximize impact on AMR
- Developing new vaccines that contribute to prevention and control of AMR
- Expanding and sharing knowledge on the impact of vaccines on AMR.

Immunization Agenda 2030

This document complements the high-level global immunization strategy, the Immunization Agenda 2030: A Global Strategy to Leave No One Behind. It summarizes how, in addition to its public health benefit in directly preventing infection, immunization can also contribute to the control of antimicrobial resistance. It is of relevance to the following IA2030 strategic objectives:

SP1: Immunization programmes for primary health care and universal health coverage
SP3: Coverage and equity
SP4: Life course and integration
SP6: Supply and sustainability
SP7: Research and innovation
## Action framework – Table format

<table>
<thead>
<tr>
<th>GOALS</th>
<th>OBJECTIVES</th>
<th>ACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPANDING USE OF LICENSED VACCINES TO MAXIMIZE IMPACT ON AMR</td>
<td>1. Increase coverage of vaccines with impact on AMR.</td>
<td>1a Countries should implement existing vaccine-related recommendations of the Global Action Plan against AMR.¹&lt;br&gt;1b Donors, countries and other health payers should maintain and expand immunization financing and strengthen capacities, ensuring affordable supply, functional delivery systems and programmatic sustainability.¹,⁶</td>
</tr>
<tr>
<td></td>
<td>2. Update recommendations and normative guidance in both the vaccine and the AMR sectors to include the role of vaccines in control of AMR.</td>
<td>2a Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to specifically account for the use of vaccines to impact AMR.¹,³&lt;br&gt;2b AMR national action plans and international organizations dedicated to AMR control should consistently include vaccines in the armamentarium of interventions planned for use against AMR, and build capacity for the full realization of vaccine impact as individual or combined interventions.¹,³&lt;br&gt;2c Immunization programmes should be strengthened to reach children beyond the first year of life and immunization services broadened to support vaccination with impact on AMR throughout the life course.¹,²,³,⁶&lt;br&gt;2d In a ‘One Health’ perspective, bodies such as WHO, the FAO and OIE, in collaboration with the agricultural industry and animal health stakeholders, should update recommendations and regulations and develop an action plan to maximize the use of animal vaccines to reduce antibiotic use in animals.³,⁸</td>
</tr>
<tr>
<td></td>
<td>3. Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training</td>
<td>3a Countries, funders and other stakeholders should include the role of vaccines in limiting AMR in their communication materials used to present their related activities.=all&lt;br&gt;3b Institutions involved in the vaccine and AMR sector should develop communication, education and training materials about the role of vaccines in controlling AMR, targeting audiences ranging from the general public to infectious disease experts.=all</td>
</tr>
<tr>
<td>DEVELOPING NEW VACCINES THAT CONTRIBUTE TO PREVENTION AND</td>
<td>4. Bridge the funding gap for R&amp;D of new vaccines with potential for global AMR impact.</td>
<td>4a Funders, industry, governments, non-governmental and supranational organizations, academic institutions and researchers should increase investments in vaccine candidates with anticipated benefits for AMR.¹,³,⁴,⁵,⁶&lt;br&gt;4b Funders, including governments and non-governmental organizations, product development</td>
</tr>
</tbody>
</table>

--

¹ Commented [MH1]: numbers to be replaced by stakeholder specific icons
## CONTROL OF AMR

Sponsors and industry, should create novel financing mechanisms for late-stage vaccine evaluation, introduction, evaluation of new vaccine effectiveness and impact, and for ensuring sufficient manufacturing capacity exists to meet global needs for vaccines expected to reduce AMR.\(^{(1,4,6)}\)

### 5. Develop regulatory and policy mechanisms to accelerate approval and use of new vaccines that can reduce AMR

5a Vaccine development sponsors and regulatory authorities should systematically assess the potential to prevent and control AMR and related data packages generated in clinical development to expand assessment of investigational product risk–benefit balance.\(^{(1,3)}\)

5b Regulators and policymakers should develop means to accelerate access to vaccines of urgent medical need, including impacts on AMR, without jeopardizing the required confidence in safety and efficacy.\(^{(1,3)}\)

5c WHO, through its Product Development for Vaccines Advisory Committee (PDVAC) and Strategic Advisory Group of Experts (SAGE) on Immunization, and other stakeholders who shape progress in vaccine R&D should include evaluation of AMR impacts in their product landscape analyses and guidance.\(^{(3)}\)

5d Vaccine development sponsors and regulators should discuss clinical research requirements for regulatory labelling to include specifications about impact on AMR and antimicrobial use.\(^{(3,4,6)}\)

5e Sponsors of post-licensure vaccine evaluations, such as health-economic impact studies, should discuss with regulators and policymakers, during the approval process, when and how to include evaluation of vaccine’s potential to reduce antimicrobial use and AMR in these studies.\(^{(3,4,6)}\)

## EXPANDING AND SHARING KNOWLEDGE OF VACCINE IMPACT ON AMR

### 6. Improve methodologies and increase collection and analysis of data relevant to assess vaccine impact on AMR, including antimicrobial use

6a Normative bodies should provide guidance for health technology assessment and evaluation of vaccine impact on AMR and antimicrobial use.\(^{(3)}\)

6b Funders and researchers should analyse existing datasets from epidemiologic studies, trials and routine surveillance in order to estimate vaccine impact on AMR.\(^{(4,5,6)}\)

6c When relevant, sponsors, funders and investigators conducting new trials and studies using existing and candidate vaccines should assess vaccine impact on AMR, including antimicrobial use.\(^{(4,5,6)}\)

6d Public health authorities at the global, national and subnational levels should enhance surveillance data systems to facilitate the linkage of vaccination data with antimicrobial use and resistance data, with the greatest practicable level of geographic and demographic granularity to enhance the ability to focus interventions on the most vulnerable. In resource-limited settings, building capacity for data collection and analysis should be included in immunization and AMR monitoring.\(^{(4,5,6)}\)
<table>
<thead>
<tr>
<th>Country action plans</th>
<th>6e Researchers should continue to generate new evidence about: (5,6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- how to use vaccines with the specific aim of controlling drug-resistant pathogens when highly prevalent or causing epidemics</td>
</tr>
<tr>
<td></td>
<td>- how vaccines can complement other infection control strategies and stewardship efforts to prolong or restore effective use of antibiotics against specific pathogens</td>
</tr>
<tr>
<td></td>
<td>- socio-economic and ethical aspects of vaccine impact on AMR</td>
</tr>
<tr>
<td></td>
<td>6f Researchers and their sponsors should ensure that new data and evidence are made rapidly and publicly available through prompt public posting and scientific publications, preprints, and data-sharing platforms. (4,5,6)</td>
</tr>
</tbody>
</table>

### 7. Develop estimates of vaccine value to avert the full public health and socioeconomic burden of AMR

<table>
<thead>
<tr>
<th>7a Research funders should support researchers to develop and improve methodologies for estimating impact of vaccines on AMR. (4,6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7b Health delivery payers and investors in R&amp;D should develop and use standard health technology assessments and value-attribution frameworks to inform the estimation of the full value of vaccines to prevent and control AMR. (1,4,6)</td>
</tr>
</tbody>
</table>
**Background**

The ability to prevent and effectively treat many infectious diseases is one of humanity’s greatest achievements.

Between the 19th and 21st centuries, infectious disease mortality – especially among children – dramatically decreased, initially in industrialized countries and later in low- and middle-income countries (LMICs).(1) The large decrease in deaths from infectious diseases was driven by several linked advances. Hygiene and improved infrastructure for wastewater management, clean water delivery, and economic and social development paved the way for better housing, education and nutrition. Basic science and the study of disease dynamics led to the discovery that microbes cause disease.

The discovery of modern antimicrobials, which first appeared in the 1930s, provided the extraordinary ability to treat and cure many diseases that were previously untreatable and often life-threatening. Vaccines, delivered through routine immunization programmes that often constituted the backbone of primary health care, helped to eliminate or vastly reduce many once-common viral diseases such as smallpox, polio and measles, as well as bacterial infections such as diphtheria, tetanus and pertussis.

More recently, countries that expanded immunization programmes to include childhood vaccination against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* have achieved substantial reductions in disease due to these bacterial pathogens.

**Antimicrobial resistance: a major global health threat**

Antimicrobial resistance now threatens to undermine the effectiveness of antimicrobials and partially undo progress made against infectious disease. Antimicrobials selectively kill or slow the growth of microbes by blocking crucial biochemical processes such as protein synthesis and genome replication. However, when a person takes an antimicrobial drug, the whole pool of microbes that individual carries in the gastrointestinal tract, on the skin and mucosae is exposed to that drug, in a ‘bystander’ effect. Microbes that are less susceptible to the drug are more likely to survive and pass that trait to their progeny, and be spread to other persons. Furthermore, mobile genetic elements such as plasmids, which carry genes that make the microbe drug-resistant, can be transferred to other strains and even other bacterial species, thus perpetuating resistance elements in multiple species.

AMR is now an alarming and growing global problem. Penicillin-resistant bacteria were noted shortly after penicillin was first introduced. Today, pathogens resistant to all classes of antimicrobials can be found throughout the world, and the incidence of resistant infections is growing sharply. As many as 700,000 people die from infections...
resistant to at least one antimicrobial agent every year (2), and many strains of
pathogens that cause common blood, skin, digestive and respiratory infections are
resistant to two or more classes of antibiotics. Some pathogens, such as the bacterium
that causes gonorrhoea, have evolved strains that can no longer be treated successfully
with any licensed antibiotic.

Unless these trends are reversed, many more pathogens will become resistant to first-
line antibiotics. The second- or third-line drugs used as replacements typically have
more side effects, are more expensive and sometimes can be administered only in
hospital; these factors make them less accessible to people living in LMICs, raising
questions of equity. Moreover, as more pathogens become resistant to multiple drugs,
patients undergoing now-routine surgical procedures will be at higher risk of contracting
drug-resistant infections.

In a connected world, AMR is a global problem, and the human and societal impact of
resistant pathogens is increasing. All countries have a stake in stemming the global
problem of AMR, and need to contribute through national and globally coordinated
actions. Unless there is a rapid and multifaceted response to prevent and control AMR,
very significant economic costs from lost productivity and social disruption by 2050 are
highly likely (3).

Addressing AMR will require concerted action in the human health, animal health, social
protection and environmental domains. The WHO, in collaboration with the Food and
Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE),
published the Global Action Plan on Antimicrobial Resistance in 2015, and in 2016 the
United Nations (UN) Secretary-General convened the Interagency Coordination Group
on AMR to explore how best to structure the global response. The group’s final report,
published in 2019, outlines an ambitious and comprehensive blueprint for the global
governance structures needed to drive progress against AMR (4).

Controlling AMR will require improvements in infection prevention, antimicrobial
stewardship, and antimicrobial discovery. Infection prevention reduces the need for
antibiotic treatment. Antimicrobial stewardship, ensuring more responsible use of
antimicrobials, reduces inappropriate use of treatments and minimises the selection
pressures that drive the development of resistance (figure 1).
The discovery and use of new antibiotics constitutes an increasingly complex economic and scientific challenge. While a long list of distinct classes of antibiotics were licensed for use before 1970, few have been developed in the last half-century (5). As for antibiotics developed in the past, resistant isolates in the bacterial population can emerge in the relatively short term, jeopardizing effective and sustainable use.

Vaccines contribute to the battle against AMR by preventing infections and by reducing antimicrobial use (figure 2).
Figure 2. The impact of vaccines on AMR: a schematic pathway
The most direct way in which vaccines contribute to prevention and control of AMR is by reducing the incidence of disease from resistant pathogens. Vaccines against *Streptococcus pneumoniae*, *Hib*, *Salmonella typhi*, *Bordetella pertussis*, tuberculosis, and *Neisseria meningitidis* can prevent morbidity and mortality due to these pathogens, including drug-resistant forms. By preventing people from transmitting infection, use of vaccines extends population protection by reducing the risk of infection among those who are not vaccinated—‘herd immunity’. For some of these vaccines the specific impact on resistant infection has been estimated, for example, *Streptococcus pneumoniae* (figure 3) (6) and Hib (7).

Figure 3. The impact of pneumococcal vaccine on rates of drug resistant Invasive Pneumococcal Disease in the USA (8)

The importance of protecting against resistant strains of *Salmonella typhi* led WHO in 2018 to recommend use of such vaccines in children 6 months of age or older in countries where typhoid is endemic, with priority given to countries with a high typhoid burden or high levels of AMR (9). In late 2019, one country, Pakistan, embarked on a phased introduction campaign with a typhoid conjugate vaccine (TCV) in all children from 9 months to age 15 years to help control the spread of extensively drug-resistant typhoid disease (10) (figure 4).
Figure 4. The estimated impact of the typhoid vaccine on drug sensitive and drug resistant typhoid in Pakistan

The estimated number of typhoid cases over 10 years without vaccination, and the estimated number of typhoid cases averted over 10 years after vaccine introduction was calculated assuming vaccine efficacy of 82% at 1 year of follow-up (11). The estimated number of extensive drug resistant typhoid cases over 10 years without vaccination, and the estimated number of extensive drug resistant typhoid cases averted over 10 years after vaccine introduction was calculated assuming that 70.4% of reported cases in Pakistan are extensively drug resistant (XDR) (12). Note that multi-drug resistant typhoid cases are not reported, and the vaccine impact could be underestimated.

In the future, vaccines may play a major role in the realisation of public health goals against tuberculosis, malaria, gonorrhoea, shigella or other infections with an important AMR burden.

Another key benefit is reduction of antibiotic use. Since the clinical presentations of many infections, such as fevers, respiratory infections or diarrhoea, do not appreciably differ whether caused by bacteria or viruses, and antibiotic use is often empiric (when syndromes are treated without any aetiiological diagnosis), vaccines that prevent syndromic disease also reduce antibiotic use.

For example, influenza vaccines can reduce the frequently inappropriate use of antibiotics in patients with respiratory symptoms. Moreover, several viral infections,
such as influenza, measles and respiratory syncytial virus (RSV), predispose to secondary bacterial infections, which then require antibiotic treatment.

Vaccines that reduce the incidence of antibiotic use can contribute to reducing selection for AMR in the target pathogen (for bacterial vaccines) as well as in bystander bacterial species, often present in the normal flora, that can be transmitted, and cause disease in specific circumstances, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* and *Staphylococcus aureus*.

Some vaccines have the potential to reduce antibiotic use to an extent that exceeds the causal fraction of the disease syndrome due to the vaccine target pathogen. This could occur when a single bacterial pathogen constitutes the primary reason for antibiotic treatment of a clinical syndrome that can also be caused by other pathogens that do not require antibiotics. For example, many viruses cause sore throat, but prevention of the adverse consequences of group A *Streptococcus* pharyngitis is about the only reason one would appropriately treat sore throat with antibiotics. A vaccine effective against group A streptococcus would greatly reduce the need for presumptive antibiotic treatment for pharyngitis. These considerations show that single or combination vaccines effective against key pathogens causing a given clinical syndrome might ultimately result in synergistic effects on antimicrobial use and therefore resistance. In this way, vaccines become a tool to reinforce policies of antibiotic stewardship.

Another benefit from reducing antibiotic use will be to decrease dysbiosis, perturbation of the healthy microbiome that can result from antibiotic exposure. For example, genital or oral candidiasis and *Clostridium difficile* infections are frequently triggered by antibiotic treatment. A group B *Streptococcus* (GBS) vaccine for maternal immunization during pregnancy could reduce the frequent preventive use of antibiotics perinatally, and not only reduce the risk of invasive GBS disease but also protect the normal development of the neonatal microbiome.

**A ‘One Health’ approach**

Antimicrobials used in animals are identical or related to those used in humans. The role of veterinary vaccines in preventing AMR burden in humans needs to be better characterized. OIE vaccine development priorities for chicken, swine, sheep, goat, bovine and fish diseases have been expressed, targeted to address bottlenecks and market barriers across the product life cycle, from fundamental research to registration and equitable and affordable access and stewardship(13). As expressed in the Global Action Plan on AMR(14) and in a 2019 report to the UN Secretary General(4), recommendations for industry practices need to be renewed, strengthened and implemented.
Prioritization of activities should be based on best available evidence

Efforts are ongoing to expand the knowledge base on the epidemiology of AMR (15). In addition, understanding the impact of vaccines is essential to inform the value proposition, justify the need for investment and define the potential use case, recognizing the current and future health impacts of AMR in all populations and all parts of the world. There is a strong theoretical rationale for a role of vaccines in reducing AMR. Evidence on the magnitude of this effect is compelling for some vaccines, suggestive for others, and uncertain for still others.

Health technology assessment and informed decision-making require evidence on the existing impact on AMR and the potential to expand that impact through better use of vaccines. Impact estimates are also needed for not-yet-licensed vaccines. Where available, evidence on the role of other interventions should be used to assess the comparative value of investments in alternative approaches, for example, innovative drug discovery versus development of novel vaccines. Continuous efforts to expand the evidence base on these effects are therefore needed. Economic, social and equity effects of vaccines and alternatives on AMR must be assessed to understand their value, and be promptly and transparently disseminated, to input into rational investment, regulatory and policy decision-making.

While better evidence will enhance confidence in decisions, the urgency of the AMR threat, combined with the long time lag for some types of investments to pay off, demands that we make decisions and investment based on currently available data.

Reaching public health goals require investments, capacity, collaboration, political will, and public confidence.

Maximizing the potential of vaccines to reduce AMR will require innovative research, informed planning, and substantial investment of resources over a long period. Increasing the use of existing vaccines and meeting uptake targets are essential short-term goals. In the long term, new vaccines are needed to protect against disease due to resistant pathogens and to reduce antimicrobial use. Bringing new vaccines from basic discovery to regulatory approval, policy decision for use, and financing availability and global use is a long process. It requires a collaborative endeavour involving both the public and private sectors, and equitable access will depend on sustained investments, capacity strengthening, collaboration, political will and public confidence.
Wellcome’s assessment of vaccine priorities for targeting of WHO AMR priority bacteria

In 2016, the World Health Assembly directed WHO to create a list of antibiotic-resistant bacteria for which new antibiotics were most urgently needed, to help set funding priorities and facilitate global coordination of antibiotic R&D strategies against AMR (Lancet Infect Dis. 2018 Mar;18(3):318-327. doi: 10.1016/S1473-3099(17)30753-3). Following an extensive consultation and review process, using a systematic methodology taking into accounts factors such as overall mortality, availability of effective therapy, health-care burden, and increasing drug resistance, pathogens were classified into three categories. It is important to note that this exercise focused on drug-resistant pathogens, and did not consider the value of vaccines in reducing antimicrobial use, including viral vaccines.

Priority 1: CRITICAL
Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae (Klebsiella pneumoniae, Escherichia coli, Enterobacter spp., Serratia spp., Proteus spp., Providencia spp, Morganella spp). Mycobacterium tuberculosis was not included in this prioritization exercise, but is also a recognized priority pathogen.

Priority 2: HIGH
Enterococcus faecium, Staphylococcus aureus, Helicobacter pylori, Campylobacter, Salmonella spp., Neisseria gonorrhoeae.

Priority 3: MEDIUM
Streptococcus pneumoniae, Haemophilus influenzae, Shigella spp.

Subsequently, Wellcome and the Boston Consulting Group carried out a prioritization exercise on the role of vaccines targeting WHO AMR priority pathogens (https://vaccinesforamr.org). Prioritization was based on potential for health impact, probability of R&D success and probability of uptake. This assessment identified pathogen clusters for which different interventions are required.

The “increase uptake” cluster is composed of pathogens with effective licensed vaccines. Hib vaccines and PCV population uptake are globally at ~70% and 40%, respectively. A new, conjugated Salmonella typhi vaccine has recently been pre-qualified by the WHO and is supported by Gavi for introduction. Continued efforts are needed to maintain and expand uptake.

The “bring to market” cluster is composed of pathogens with significant health impact and sufficiently advanced R&D to recommend concentrating on accelerating vaccines through clinical development to market. The high antigenic diversity of Escherichia coli (enteric) is a challenge for vaccine development, but inclusion of heat labile toxoid and fimbrial antigens in a potential vaccine may help cover 70-80% of strains. A non-typhoidal Salmonella vaccine appears technically promising and potentially impactful, given high disease burden in Africa. A vaccine against Shigella would represent a major opportunity in this segment due to high incidence and significant associated mortality, particularly in LMICs.

Mycobacterium tuberculosis was included in the “advance early R&D” cluster. Since this report was published, phase 2 trial data of protection against progression to pulmonary TB disease justified its inclusion in the ‘bring to market’ cluster.

The “advance early R&D” cluster is composed of pathogens with significant health impact but unclear R&D feasibility, where more investment in early-stage R&D is needed to advance a robust pipeline of vaccine candidates. The case for development of a vaccine targeting Neisseria gonorrhoeae is strong due to high incidence, high morbidity, and current circulation of resistant strains. Although significant development challenges remain, evidence of Neisseria meningitidis B vaccine to cross-protect against Neisseria gonorrhoeae has fostered fresh optimism in the expert community. The incidence of extraintestinal Escherichia coli infections is high and constitute an important target for vaccination, but antigen selection remains a challenge. Vaccine development for Pseudomonas aeruginosa is attractive for high-risk patient groups, such as cystic fibrosis patients, but vaccine development is difficult because the target population is predominantly composed of immunocompromised patients. Morbidity and mortality from Staphylococcus aureus in high-income countries means the market for a vaccine is attractive, with significant commercially-driven activity. However, there are significant gaps in understanding disease burden and identifying vaccine targets and animal models have limited predictive capability.

The “collect data, explore alternatives” cluster is composed of pathogens for which significant outstanding epidemiological questions remain, or alternative control strategies may be preferable. Salmonella paratyphi has low incidence and low associated mortality and morbidity. Uptake of a standalone vaccine is unlikely and combination vaccines with Salmonella typhi should be contemplated. More data is needed on Campylobacter in LMICs, particularly to understand transmission pathways and whether animal vaccination would be a preferred approach. A better understanding of the link between Helicobacter pylori and gastric cancer, and better understanding of how AMR is likely to evolve due to relative current treatability of the pathogen, is necessary. Klebsiella pneumoniae has a higher burden than most other hospital-acquired infections, but more data are needed to help determine whether there are predictable sub-populations to target for clinical development and vaccine delivery. Enterobacteriaceae, Acinetobacter baumannii and Enterococcus faecium have comparatively low incidence. These pathogens cause hospital-acquired infections in small, immunocompromised target populations. These characteristics present particularly challenging hurdles for vaccine strategies. Alternatives, such as passive immunization, should be explored.
Strategic Vision

For vaccines to contribute fully, sustainably and equitably to the prevention and control of antimicrobial resistance by preventing infections and reducing antimicrobial use.

Goals, objectives and priority actions

Specific objectives and priority actions in three goal areas will significantly enhance the contribution of vaccines to the control of AMR. These goals are:

- Expanding use of licensed vaccines to maximize impact on AMR
- Developing new vaccines that contribute to prevention and control of AMR
- Expanding and sharing knowledge of vaccine impact on AMR

Expanding use of licensed vaccines to maximize impact on AMR

Expanding the use of licensed vaccines will require reaching uptake targets for licensed vaccines, and setting and achieving ambitious coverage targets as new vaccines are approved. Reduction in the incidence of infection through effective sanitation, hygiene and infection prevention measures, including immunization, is an integral part of the Global Action Plan on AMR (Objective 3)(14). The framework for action on AMR urges all Member States to have national action plans defining priorities and activities.

For currently licensed vaccines, there is significant room for improvement in coverage. Recent data from WHO and UNICEF show that more than 1 in 10 children missed out on life-saving vaccines in 2018, with most unvaccinated children living in LMICs. Out of six world regions, four failed to meet vaccine uptake targets included in the Decade of Vaccine’s Global Vaccine Action Plan 2011-2020. The Immunization Agenda 2030(16) will play an essential role in ensuring that all people, at all ages, everywhere enjoy the full benefits of vaccines, including through prevention and control of AMR.

Objective 1. Increase coverage of vaccines with impact on AMR.
Maximizing the impact of immunization on AMR will depend on the successful implementation of a global strategy with an integrated action framework linking immunization to primary health care and universal health coverage.

**Priority actions**

1a **Countries should implement existing vaccine-related recommendations of the Global Action Plan against AMR.**

Priority should be given to completion of the full basic series for pneumococcal conjugate vaccine (PCV), Hib vaccine, rotavirus vaccine, measles-containing vaccines as well as increasing coverage for influenza and typhoid conjugate vaccine (TCV).

### Recommended use of selected licensed vaccines and potential impact on AMR

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>WHO recommendation</th>
<th>Global coverage in 2018(17)</th>
<th>WHO coverage target(18)</th>
<th>Vaccine impact on AMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal conjugate vaccines (PCV)</td>
<td>All children, through routine immunization</td>
<td>47% 90% nationally, 80% at district level</td>
<td>Reduces resistant and non-resistant pneumococcal disease; reduces antibiotic use in children(6).</td>
<td></td>
</tr>
<tr>
<td>Typhoid conjugate vaccine (TCV)</td>
<td>In endemic countries, programmatic delivery to children 9 months old or in the second year of life and catch-up campaign in children up to 15 years of age</td>
<td>NA Access to be prioritized in settings with high endemicity and high levels of AMR</td>
<td>Modelling suggests vaccine use will proportionally reduce incidence of resistant and non-resistant typhoid, including number of chronic typhoid carriers.(11)</td>
<td></td>
</tr>
<tr>
<td>Hib vaccine</td>
<td>All children, through routine immunization</td>
<td>72% 90% nationally, 80% at district level</td>
<td>Reduces resistant and non-resistant Hib disease; may have reduced overall proportion of resistant strains. Some evidence that Hib introduction modestly reduced antibiotic prescriptions among children &lt;5 years.(6).</td>
<td></td>
</tr>
<tr>
<td>Influenza vaccines</td>
<td>All pregnant women, children 6-59 months, adults ≥65 years, people with chronic medical conditions and healthcare workers</td>
<td>NA Varies according to risk group</td>
<td>Good evidence that influenza vaccine reduces antibiotic use by reducing misuse of antibiotics and treatment of secondary bacterial infections.(19).</td>
<td></td>
</tr>
</tbody>
</table>
Donors, countries and other health payers should maintain and expand immunization financing and strengthen capacities, ensuring affordable supply, functional delivery systems and programmatic sustainability.

Public and private sector partnerships are important to help ensure equitable access to quality-assured products and technologies, through fair pricing and donations for the poorest populations. Global financing mechanisms need to support procurement, access and delivery, and sustainable functioning of health systems, including mechanisms for surveillance and vaccine safety and effectiveness monitoring.

Objective 2. Update recommendations and normative guidance in both the vaccine and the AMR sectors to include the role of vaccines in control of AMR.

In addition to the objectives and indicators set out in the Global Action Plan on Antimicrobial Resistance and existing WHO recommendations, new activities are needed to expand the impact of vaccines on AMR. Expanding the benefits of immunization throughout the life course will play a major role. When research and epidemiologic data emerge that justify changes in optimal vaccine use, revised recommendations should be developed. This may include situations where vaccines are used to protect the effectiveness of antimicrobials.

For instance, increased TCV use may help contain the emergence of multidrug-resistant Salmonella typhi. In some geographical areas, azithromycin is the only oral typhoid treatment available. As azithromycin is also being used in mass campaigns for trachoma, TCV deployment might be useful in protecting azithromycin effectiveness. As another example, if evidence accumulates on the potential for influenza and PCV vaccines to reduce antibiotic use in specific population groups, recommendations for vaccine use in such populations should be strengthened.

Specific vaccine use recommendations could also be developed for vulnerable groups who, for medical reasons, use antibiotics chronically or frequently, or are at increased risk of exposure to drug-resistant microbes, such as healthcare workers.

Priority actions

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Target Population</th>
<th>Coverage</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus vaccine</td>
<td>All children, through routine immunization</td>
<td>35%</td>
<td>Expected to reduce antibiotic use but no confirmatory data available.</td>
</tr>
<tr>
<td>Measles vaccine</td>
<td>All children, through routine immunization</td>
<td>69%</td>
<td>Expected to reduce antibiotic use against secondary complications, no confirmatory data available.</td>
</tr>
</tbody>
</table>
2a Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to specifically account for the use of vaccines to impact AMR.

2b AMR national action plans and international organizations dedicated to AMR control should consistently include vaccines in the armamentarium of interventions planned for use against AMR, and build capacity for the full realization of vaccine impact as individual or combined interventions.

2c Immunization programmes should be strengthened to reach children beyond the first year of life and immunization services broadened to support vaccination with impact on AMR throughout the life course.

2d In a ‘One Health’ perspective, bodies such as WHO, the FAO and OIE, in collaboration with the agricultural industry and animal health stakeholders, should update recommendations and regulations and develop an action plan to maximize the use of animal vaccines to reduce antibiotic use in animals.

Objective 3. Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training

The value of vaccines in prevention of disease at the individual and population levels is incompletely understood in parts of the public and professional communities. This has contributed to low and decreasing coverage and confidence in vaccines in some areas. Communicating the additional benefit of the use of vaccines to fight AMR requires the development of carefully constructed and evaluated communication strategies and tools. Vaccination should not be presented as a panacea for all AMR, but its potential to deliver public health benefits should be communicated when relevant. Such communication may be delivered within the broader context of building confidence in vaccines.

Priority actions

3a Countries, funders and other stakeholders should include the role of vaccines in limiting AMR in their communication materials used to present their related activities.

3b Institutions involved in the vaccine and AMR sector should develop communication, education and training materials about the role of vaccines in controlling AMR, targeting audiences ranging from the general public to infectious disease experts.
Visuals from International Vaccine Institute’s advocacy campaign about the contribution of vaccines in the fight against AMR (20)
Developing new vaccines that contribute to prevention and control of AMR

New vaccine R&D of is an integral part of the Global Action Plan on AMR (14). Addressing AMR will require new tools and technologies to complement currently available strategies and interventions (21). Few new antimicrobials have been developed recently or are anticipated to be available soon, and all are threatened by the emergence of resistance (22). In contrast, vaccines have traditionally had sustainable impact, and there has been little or no evidence of escape from immunity.

The vaccine pipeline includes many early-stage candidates, but few in clinical studies. However, technologies supporting vaccine discovery and development are expanding. Progress in structural and systems biology, genomics and reverse vaccinology, adjuvants, monoclonal antibody development, and nucleic acid vaccines offer promise for next-generation vaccines targeting a variety of pathogens.

The development and use of new or improved vaccines is of particular importance to prevent diseases that are becoming difficult to treat or are untreatable owing to antimicrobial resistance. For some resistant infections, technologies such as phage-based medicine or microbiome interventions offer promise. Pathogen areas to be prioritized for investments into vaccine R&D should be informed by public value and feasibility assessments, taking into account alternative options.

Objective 4. Bridge the funding gap for R&D of new vaccines with potential for global AMR impact

Investment in the development of new vaccines to impact global health is often impeded by market failures and decades-long development, licensure and implementation timelines, making them frequently unattractive business investments.

Funding of research to bring candidates to regulatory submission can be costly. The large-scale randomized trials and complex regulatory review that products must undergo are time-consuming, labour-intensive and expensive, and even after a vaccine is approved, further evaluation can be necessary to support decision-making on implementation. In addition, further investment is required to ensure manufacturing supply at scale, procurement and affordable access according to medical need, and delivery through functional health systems. Surveillance systems also need to be in place to monitor safety and effectiveness of newly introduced vaccines and demonstrate population-level impact.

New mechanisms are needed to overcome these obstacles and encourage renewed investment in R&D of new vaccines for use in LMICs. Innovative financing mechanisms channelling substantial public-sector funding and private-sector investment will be
needed to support new vaccine development, and to bring candidates from discovery through pre-clinical and clinical testing to licensure, adoption and implementation.

Related activities should be monitored and evaluated, in line with the Global Action Plan monitoring and evaluation framework for new products and funding instruments.

**Selected WHO priority disease areas for which vaccines are critically needed and available evidence supports a favourable technical feasibility assessment and potential impact on AMR.**

<table>
<thead>
<tr>
<th>Target pathogen and disease</th>
<th>Burden</th>
<th>AMR-related impact</th>
<th>Vaccine outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium tuberculosis</em>, tuberculosis</td>
<td>A quarter of global population latently infected(23); in 2018, 10 million people fell ill with TB and 1.45 million died(24).</td>
<td>Resistant TB rising sharply. There were half a million rifampicin resistant diagnoses in 2018, 78% of which were resistant to more than one drug; 214,000 people died with drug-resistant TB infections(24).</td>
<td>A highly effective vaccine likely feasible: most infected people do not develop disease and the existing BCG vaccine protects children against severe disease. Recent phase 2B trial of candidate M72/AS01 in adults with latent infection reduced progression to active pulmonary TB by around 50% over 3 years follow-up(25).</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em>, pelvic inflammatory disease, infertility</td>
<td>78 million new cases per year among people aged 15-49 years(26); can cause infertility and other severe sequelae</td>
<td>Once universally susceptible to antibiotics, strains resistant to every current class of antibiotic have emerged; complete treatment failure has been reported(27).</td>
<td><em>Neisseria gonorrhoeae</em> shares 80–90% of its genetic sequence with <em>Neisseria meningitidis</em>, a common cause of meningitis. There is some evidence that type B <em>Neisseria meningitidis</em> vaccine partially protects against some <em>Neisseria gonorrhoea</em>, suggesting a vaccine is feasible(28).</td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em>, malaria</td>
<td>228 million cases worldwide in 2018, 405,000 deaths(29). Important driver of antibiotic use for undocumented febrile illness, in high endemicity areas.</td>
<td>Artemisinin resistance emerged in SE Asia in early 2000s; several artemisinin combination therapies now failing(29). Potential to reduce malaria-driven antibiotic use.</td>
<td>RTS,S/AS01 vaccine provides partial protection in young children, showing that a vaccine is feasible(30). RTS,S/AS01 is being implemented in pilot projects in Ghana, Kenya and Malawi. Other candidates continue to be developed.</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV), respiratory disease</td>
<td>A very common respiratory tract infection that affects all ages; most severe in early childhood. Important driver of antibiotic use for undocumented respiratory illness,</td>
<td>Potential to reduce RSV-driven antibiotic use.</td>
<td>Proof of concept is established for the potential of vaccines delivered to pregnant women to prevent severe RSV disease early in life. RSV vaccine candidates aiming to provide longer protection to children and adults are in the pipeline.</td>
</tr>
</tbody>
</table>
Enterotoxigenic Escherichia coli (ETEC) and Shigella

- ETEC caused 51,186 deaths globally, and 18,669 deaths in children under 5 years old in 2016 (31). Shigella caused 212,438 deaths globally, and 63,713 in children under 5 years old in 2016 (31). Contributors to long-term morbidity such as malnutrition and stunting.

| Enterotoxigenic Escherichia coli (ETEC) and Shigella | ETEC caused 51,186 deaths globally, and 18,669 deaths in children under 5 years old in 2016 (31). Shigella caused 212,438 deaths globally, and 63,713 in children under 5 years old in 2016 (31). Contributors to long-term morbidity such as malnutrition and stunting. | High and growing rates of multidrug resistance. | Several candidate vaccines are in development. Controlled infection models may be able to accelerate clinical development. |

Priority actions

4a Funders, industry, governments, non-governmental and supranational organizations, academic institutions and researchers should increase investments in vaccine candidates with anticipated benefits for AMR.
4b Funders, including governments and non-governmental organizations, product development sponsors and industry, should create novel financing mechanisms for late-stage vaccine evaluation, introduction, evaluation of new vaccine effectiveness and impact, and for ensuring sufficient manufacturing capacity exists to meet global needs for vaccines expected to reduce AMR.
Objective 5. Develop regulatory and policy mechanisms to accelerate approval and use of new vaccines that can reduce AMR

Most vaccines are developed for use in a large target population, although some are for more restricted use in specific groups at risk. Vaccines are usually given to large numbers of healthy people, and are subject to strict regulatory oversight, with licensure requiring a favourable risk–benefit assessment. In-country use is based on policy decisions that, in addition, consider health-economic questions and public value more broadly.

In the field of global health, WHO recommendations inform decision-making at multiple levels, including international financing bodies supporting vaccine procurement and distribution. Regulators and policymakers engage in discussions with funders and vaccine developers to prioritize disease areas, product development, investments and activities, and create scientific consensus. Throughout, specific modalities should be adopted to consider and facilitate vaccine impact on AMR, all along regulatory and policymaking pathways.

Priority actions

5a Vaccine development sponsors and regulatory authorities should systematically assess the potential to prevent and control AMR and related data
packages generated in clinical development to expand assessment of investigational product risk–benefit balance.

5b Regulators and policymakers should develop means to accelerate access to vaccines of urgent medical need, including impacts on AMR, without jeopardizing the required confidence in safety and efficacy.

Accelerated approval pathways similar to those being developed for some epidemic vaccines may be appropriate for AMR-reducing vaccines, such as those involving controlled infectious challenge models, use of immune correlates of protection, and animal protection data, when pre-licensure clinical efficacy trials are not feasible or highly problematic. Indirect evidence can lead to conditional approvals pending confirmation of effectiveness through early introduction studies. Some related regulatory mechanisms exist:

The FDA’s Priority Review Vouchers

The US Congress created the priority review voucher programme in 2007 to encourage the development of products for neglected diseases. The developer benefits from an accelerated review by the Food and Drug Administration (FDA) for the product in question, and a voucher for a faster review of a different drug. The developer can sell the voucher, which has potentially large commercial value.

Conditional marketing authorization

Several regulatory authorities have provisions aiming to accelerate access to products that meet an urgent medical need, when early assessments of benefit–risk balances are positive, and plans are agreed for post-approval investigations.

5c WHO, through its Product Development for Vaccines Advisory Committee (PDVAC) and Strategic Advisory Group of Experts (SAGE) on Immunization, and other stakeholders who shape progress in vaccine R&D should include evaluation of AMR impacts in their product landscape analyses and guidance.

5d Vaccine development sponsors and regulators should discuss clinical research requirements for regulatory labelling to include specifications about impact on AMR and antimicrobial use.

5e Sponsors of post-licensure vaccine evaluations, such as health-economic impact studies, should discuss with regulators and policymakers, during the approval process, when and how to include evaluation of vaccine’s potential to reduce antimicrobial use and AMR in these studies.
Expanding and sharing knowledge of vaccine impact on AMR

Continuing research is needed to strengthen the knowledge base on the potential role of vaccines in prevention and control of AMR, and this knowledge disseminated to stakeholders. Better estimates of impact will improve policymaking and rational prioritization of investments. Data on immunization should inform formulation of policy for prevention and control of AMR, and data on AMR should inform decision-making in the immunization field.

Decision-making and evidence generation should be an iterative process whereby new evidence generated informs existing recommendations and investments, and vaccine prioritization is updated. National governments, intergovernmental organizations, agencies, professional organizations, nongovernmental organizations, industry and academia have important roles in generating such knowledge. Knowledge dissemination to the general public is essential to build public trust and increase vaccine confidence.

Objective 6. Improve methodologies and increase collection and analysis of data to assess vaccine impact on AMR, including antimicrobial use

Many types of data and study results are required to understand the impact of vaccines on AMR. Unfortunately, few data are currently available. There is an urgent need to increase data collection and analysis(19). This is particularly relevant to settings where issues of both access to antibiotics and excessive use of antibiotics are important public health concerns.

Priority actions

6a Normative bodies should provide guidance for health technology assessment and evaluation of vaccine impact on AMR and antimicrobial use.

6b Funders and researchers should analyse existing datasets from epidemiologic studies, trials and routine surveillance in order to estimate vaccine impact on AMR.

6c When relevant, sponsors, funders and investigators conducting new trials and studies using existing and candidate vaccines should assess vaccine impact on AMR, including antimicrobial use.

6d Public health authorities at the global, national and subnational levels should enhance surveillance data systems to facilitate the linkage of vaccination data with antimicrobial use and resistance data, with the greatest practicable level of geographic and demographic granularity to enhance the ability to focus interventions on the most vulnerable. In resource-limited settings, building
capacity for data collection and analysis should be included in immunization and AMR country action plans.

6e Researchers should continue to generate new evidence about:

- how to use vaccines with the specific aim of controlling drug-resistant pathogens when highly prevalent or causing epidemics
- how vaccines can complement other infection control strategies and stewardship efforts to prolong or restore effective use of antibiotics against specific pathogens
- socio-economic and ethical aspects of vaccine impact on AMR

6f Researchers and their sponsors should ensure that new data and evidence are made rapidly and publicly available through prompt public posting and scientific publications, preprints, and data-sharing platforms.

Objective 7. Develop estimates of vaccine value to avert the full public health and socioeconomic burden of AMR

In a context of resource constraints, prioritization of investments should be informed by estimates of the value of existing and future vaccines in their ability to prevent and control AMR. Mathematical modelling, multi-criteria decision analysis and other methodologies including empirical approaches can be used to inform investment decision-making.

Beyond cost–effectiveness analyses, the full scope of investments needed and societal impact should be considered (direct medical costs, social care costs, loss in productivity, impact on education, consumption, leisure, savings and wealth, financial risk, impact on caregivers and households, and macroeconomic effects). Such analyses should inform both private and public funders, manufacturers, regulators and policymakers, ministry of health, finance and agriculture, global AMR control and vaccine-financing bodies. Through an iterative process, modelling estimates should be regularly refined as empirical data emerge.

Priority actions

7a Research funders should support researchers to develop and improve methodologies for estimating impact of vaccines on AMR.

Factors such as individual protection, herd immunity, transmission patterns, pathogen carriage rates, bacterial population dynamics, vaccine-driven reductions in antibiotic use and the various molecular drivers of resistance should be considered. Models should
account for replacement of vaccine-preventable serotypes by other serotypes of the targeted pathogen where applicable.

**7b Health delivery payers and investors in R&D should develop and use standard health technology assessments and value-attribution frameworks to inform the estimation of the full value of vaccines to prevent and control AMR.**

Value can be articulated in terms of mortality and morbidity prevention, reduction of antibiotic use, economic and societal impact, and impact on equity, taking into account potential vaccine-preventable AMR-related social exclusion, poverty and disproportionate negative impacts on vulnerable groups.

**Conclusions**

Vaccines are already contributing to the battle against AMR, through prevention of infections and associated reduction of antibiotic use. They offer a complementary approach to other AMR-reduction efforts. Further efforts are needed to fully realize their potential for the benefit of people and society, in a sustainable and equitable way. The priority activities outlined above provide the opportunity for the realization of this strategic vision.

Increased investments from the private, philanthropic and public sectors are needed to support implementation of existing vaccines to reach higher coverage, as well as development of new vaccines.

Guidance provided to both the AMR and immunization communities should be updated and strengthened to reflect the vision expressed here. Regulatory and policy frameworks should be adapted to support efficient decision-making and to maximize vaccine-related opportunities and impact.

Among available vaccines, increased uptake of Hib, PCV and TCV should be prioritized for impact on AMR. Increased coverage of flu vaccines should be prioritized to reduce antibiotic use. Among disease areas for which vaccines are not available but proof-of-concept evidence suggests that vaccine development is technically feasible, tuberculosis constitutes a major public health emergency and priority for investment. Vaccines against gonococcal disease and enteric diseases due to *Shigella,* *E. coli* and non-typhoidal *Salmonella* also constitute priority R&D opportunities.

Development should be accelerated of next-generation vaccines providing expanded strain coverage and durable protection against influenza and pneumococcus, as well as new vaccines against malaria, HIV, RSV and group A *Streptococcus.* It may be possible to develop vaccines against other important AMR pathogens, including *Staphylococcus*
aureus, Pseudomonas aeruginosa, E. coli, Campylobacter, Helicobacter pylori, Klebsiella pneumoniae, Enterobacteriaceae, Acinetobacter baumannii, Enterococcus faecium, Clostridium difficile, Chlamydia and Candida, but confidence in feasibility needs to be built.

Across disease areas, there is a need further develop innovative technologies, accelerated testing pathways, effectiveness evaluation through pilot implementation, new opportunities for immunization along the life course, access to high-risk groups and market shaping, to maximize impact, including for the sake of controlling AMR.

Decisions should be based on evidence, and investments based on careful value-based prioritization. More and better collection and analysis of data about the role of vaccines against AMR is needed. Evidence is needed across a variety of microbiological, health and economic sectors. Modelling provide important opportunities to estimate the full value of vaccines against AMR, across a range of relevant criteria for prioritization.

Health interventions and policies depend on public confidence. Advocacy and targeted communication can contribute to increased knowledge and catalyse the action needed to better protect all against infections and curb the threat that AMR poses to individuals, societies and global health.
References


Leave No One Behind. 2020.


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>BMGF</td>
<td>Bill and Melinda Gates Foundation</td>
</tr>
<tr>
<td>CARB-X</td>
<td>Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator</td>
</tr>
<tr>
<td>CaT</td>
<td>Coalition against Typhoid</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDDEP</td>
<td>The Center for Disease Dynamics, Economics &amp; Policy</td>
</tr>
<tr>
<td>EDCTP</td>
<td>European &amp; Developing Countries Clinical Trials Partnership</td>
</tr>
<tr>
<td>ETEC</td>
<td>Enterotoxigenic Escherichia coli</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agriculture Organization of the United Nations</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GATES MRI</td>
<td>Gates Medical Research Institute</td>
</tr>
<tr>
<td>GAVI</td>
<td>Gavi, The Vaccine Alliance</td>
</tr>
<tr>
<td>GBS</td>
<td>Group B Streptococcus</td>
</tr>
<tr>
<td>GLASS</td>
<td>Global Antimicrobial Resistance Surveillance System</td>
</tr>
<tr>
<td>Hib</td>
<td>Haemophilus influenzae b</td>
</tr>
<tr>
<td>IACG</td>
<td>The Interagency Coordination Group (IACG) on Antimicrobial Resistance</td>
</tr>
<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceuticals Manufacturers &amp; Associations</td>
</tr>
<tr>
<td>JPIAMR</td>
<td>The Joint Programming Initiative on Antimicrobial Resistance</td>
</tr>
<tr>
<td>LMICs</td>
<td>Low-and middle-income countries</td>
</tr>
<tr>
<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OIE</td>
<td>World Organisation for Animal Health</td>
</tr>
<tr>
<td>PCV</td>
<td>Pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PDVAC</td>
<td>Product Development for Vaccines Advisory Committee</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>SAGE</td>
<td>The Strategic Advisory Group of Experts on Immunization</td>
</tr>
<tr>
<td>TCV</td>
<td>Typhoid Conjugate Vaccine</td>
</tr>
<tr>
<td>TyVAC</td>
<td>Typhoid Vaccine Acceleration Consortium</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
<tr>
<td>UNICEF</td>
<td>The United Nations Children's Fund</td>
</tr>
<tr>
<td>VIS</td>
<td>Vaccine Investment Strategy</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Methodology

This action framework, intended to guide vaccine stakeholders in efforts to maximize the impact of vaccines for a better contribution to the effort of preventing and containing AMR, was generated through a consensus-building consultative process. The role of vaccines in tackling AMR has been considered in the scientific literature and deliberations from international organizations about how best to tackle AMR, but a comprehensive, global action framework has not been proposed. In response, the WHO, in collaboration with the Wellcome Trust, the Bill & Melinda Gates Foundation and the Center for Disease Dynamics, Economics and Policy, undertook to build on those discussions and propose a set of specific actions aimed at strengthening the use of vaccines for prevention and control of the devastating consequences of AMR, with a long term view. To gather information and opinions, WHO consulted experts from academic research institutions, country representatives, nongovernmental organizations, and the pharmaceutical industry. A formally constituted WHO expert working group provided suggestions all along the development of the present document. A stakeholder consultation meeting was organized in London on February, 26-27, 2019. The document was drafted after that meeting and circulated widely for comment, including an opportunity for public review through the WHO website.
Target audience for this report

This report is aimed at any individual or organization interested and/or active in the fields of vaccines and prevention of infectious diseases, AMR, vaccine research and development, funding of vaccines and AMR control, vaccine policy and regulatory decision-making, and immunization programmes. This includes sectors such as academia, philanthropy, the private sector, government, supranational organizations, the United Nations, and the general public.

Institutions from various sectors playing a role in global health should consider priorities presented here as they take actions related to vaccines and AMR, including:

- Governments, National Immunization Technical Advisory Groups, and agencies implementing national AMR action plans and immunization strategies, which can use considerations presented here to prioritize and harmonize these plans, optimizing the role of vaccines. (1)

- Health care workers, professional medical associations, patient groups, civil society and subnational organizations whose decisions influence vaccine uptake, access and public perceptions. (2)

- Regulators and policymakers who assess evidence and health technologies, and through benefit–risk analyses recommend or implement public health interventions to protect individuals and populations. (3)

- The pharmaceutical industry, which can identify new investment avenues and initiate new product development partnerships, and help generate data relevant to vaccine impact on AMR. (4)

- Academic researchers, who can focus on topics of scientific interest and potential public health impact in areas such as antigen discovery, epidemiologic research, health economic impact assessment, and determinants of vaccine confidence and health-seeking behaviours. (5)

- Funders of research on product development and use of interventions, from the private, philanthropic and public sectors, which can direct resources to address priority actions to achieve greater impact, address bottlenecks, accelerate discovery and remove barriers to implementation. (6)

- Media and educators, which can use these priority actions to frame communications and improve understanding of the role of vaccines in controlling AMR. (7)

- The agricultural and animal industry sector, which needs to consider the potential of vaccines to reduce antibiotic use in animals. (8)
Public health advocates, including many of the stakeholders named above, who can use recommendations presented here to shape their message and strengthen their public outreach and education. (9)
Bill & Melinda Gates Foundation (BMGF) is a global funder of health research with a focus on reducing mortality in children under five years old.

CARB-X
https://carb-x.org/
CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), a global non-profit partnership dedicated to accelerating antibacterial research to tackle the rising global threat of drug-resistant bacteria. Among the products that CARB-X funds are candidate vaccines against antimicrobial resistant pathogens.

CDC
Centers for Disease Control and Prevention (CDC) website that summarises key information, challenges, research areas, policy, and funding in the AMR sector.

CDDEP
https://cddep.org/research-area/antibiotic-resistance/
The Center for Disease Dynamics, Economics & Policy (CDDEP) produces independent, multidisciplinary research to advance the health and wellbeing of human populations around the world, with a focus on antimicrobial resistance.

Chatham House
https://www.chathamhouse.org/about/structure/global-health-security/antimicrobial-resistance-project
Chatham House, a not-for-profit organisation whose mission is to analyse and promote the understanding of major international issues and current affairs. This website summarises its current work and perspectives in the AMR field.

COMBACTE
https://www.combacte.com/
COMBACTE battles antimicrobial resistance by speeding up the development of new antibiotics.

FAO
The Food and Agriculture Organization of the United Nations website summarises key challenges and workstreams around the use of antimicrobials in agriculture.

Global AMR R&D Hub
https://globalamrhub.org/
Global AMR R&D Hub aims to plan, design, build and implement a dynamic online dashboard that will present all AMR R&D investments globally from public and private sources across the One Health continuum.

IFPMA
https://www.ifpma.org/subtopics/antimicrobial-resistance/
International Federation of Pharmaceuticals Manufacturers & Associations (IFPMA) represents research based biopharmaceutical companies to advocate policies and practices that encourage the discovery and access to life-saving and life-enhancing medicines and vaccines, for people everywhere. The website is a summary of IFPMA’s perspectives and workstreams on AMR.

LSHTM AMR Centre
https://www.lshtm.ac.uk/research/centres/amr/
The London School of Hygiene and Tropical Medicine (LSHTM) brings together inspiring innovation in AMR research through interdisciplinary and international engagements.

OECD
https://www.oecd.org/health/health-systems/antimicrobial-resistance.htm
The Organisation for Economic Cooperation and Development (OECD) provides a forum for discussion and provides countries with the evidence to implement effective and cost-effective policies to tackle AMR, promote effective use of antimicrobials and incentivise research and development in the antibiotic sector.

OIE
The World Organisation for Animal Health (OIE) website describes the coordinated actions between the human and animal health as well as environmental sectors to ensure responsible and prudent use of antibiotics to safeguard their efficacy.

PATH

PATH's article that describes the potential of vaccines to combat AMR, the need to expand the reach of existing vaccines, and highlights the urgency to produce vaccines for emerging threats.

ReAct

Created in 2005 ReAct is one of the first international independent networks to articulate the complex nature of antibiotic resistance and its drivers. ReAct was initiated with the goal to be a global catalyst, advocating and stimulating for global engagement on antibiotic resistance by collaborating with a broad range of organisations, individuals and stakeholders.

REPAIR Impact Fund

Novo Holdings established the REPAIR Impact Fund commissioned by the Novo Nordisk Foundation in February 2018 with a total budget of USD 165 million to invest in companies involved in discovering and the early-stage development of therapies targeting resistant microorganisms. The purpose of the REPAIR Impact Fund is to increase humanity's therapeutic arsenal in the fight against antimicrobial resistance.

The AMR Control

The AMR Control, a publication which brings together high-level contributors from around the world to monitor and analyse the worrying challenge of AMR, as well as providing its readership with a coherent picture of the latest thinking on developments, solutions and policy.

The Coalition against Typhoid

The Coalition against Typhoid (CaT) and the Typhoid Vaccine Acceleration Consortium (TyVAC) work on improving water, sanitation, and hygiene interventions to reduce the burden and impact of typhoid fever.

The European Commission

The European Commission provides funding opportunities in key research areas, including AMR, globally.

The Joint Programming Initiative on Antimicrobial Resistance

The Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), established by the European Commission, is a global collaborative platform and has engaged 28 nations to curb AMR with a One Health approach.

The Government of the United Kingdom

A five year action plan of the UK government that articulates the ambitions and actions to tackle AMR for the years 2019-2024.

UNICEF

This technical note reflects UNICEF’s response to the growing global threat of AMR to child survival, growth and development. It identifies UNICEF’s AMR-specific and AMR-sensitive actions in reducing infections, promoting access to and optimal use of antimicrobials, and increasing AMR awareness and understanding.

Vaccines Europe

Vaccines Europe represents major innovative research-based vaccine companies as well as small and medium-sized enterprises operating in Europe.

Vaccines for AMR

https://vaccinesforamr.org/
The report commissioned by Wellcome Trust: "Vaccines to tackle drug resistant infections. An evaluation of R&D opportunities".

WHO and AMR
https://www.who.int/antimicrobial-resistance/en/

The WHO website is the key source of information on antimicrobial resistance. It contains fact sheets, global action plan on antimicrobial resistance, data collection platforms such as Global Antimicrobial Resistance Surveillance System (GLASS), and WHO resolutions regarding antimicrobial resistance.

WHO and IACG

The Interagency Coordination Group (IACG) on Antimicrobial Resistance brings together partners across the UN, international organizations and individuals with expertise across human, animal and plant health, as well as the food, animal feed, trade, development and environment sectors, to formulate a blueprint for the fight against antimicrobial resistance.