

Annex to Immunization Agenda 2030

Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance:

An Action Framework



World Health
Organization

**Leveraging Vaccines
to Reduce Antibiotic
Use and Prevent
Antimicrobial
Resistance:**

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ISBN XXXXX-XXXXXX

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Suggested citation. Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework: World Health; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at xxxxxx

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Design and layout by Lushomo.

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Printed in Switzerland.

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Abbreviations

AMR	antimicrobial resistance
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
EDCTP	European & Developing Countries Clinical Trials Partnership
ETEC	Enterotoxigenic <i>Escherichia coli</i>
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
Gates MRI	Bill & Melinda Gates Medical Research Institute
Gavi	Gavi, the Vaccine Alliance
GBS	group B <i>Streptococcus</i>
Hib	<i>Haemophilus Influenzae</i> type b
IA2030	Immunisation Agenda 2030
LMICs	low- and middle-income countries
OIE	World Organisation for Animal Health
PCV	pneumococcal conjugate vaccine
PDVAC	Product Development for Vaccines Advisory Committee
R&D	research and development
RSV	respiratory syncytial virus
SAGE	Strategic Advisory Group of Experts on Immunization
SP	strategic priority
TB	tuberculosis
TCV	typhoid conjugate vaccine
UN	United Nations
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Target audience

This report is aimed at any individual or organization interested and/or active in the fields of vaccines and prevention of infectious diseases, antimicrobial resistance (AMR), vaccine research and development (R&D), funding of vaccines and AMR control, vaccine policy and regulatory decision-making, and immunization programmes. This covers sectors

such as academia, philanthropy, the private sector, government, supranational organizations, the United Nations (UN), and the general public. The following sectors that play a role in global health should consider the priorities presented here as they take actions related to vaccines and AMR:



governments, national immunization technical advisory groups, and agencies implementing national AMR action plans and immunization strategies, which can use the considerations presented here to prioritize and harmonize their plans, optimizing the role of vaccines;



health-care workers, professional medical associations, patient groups, civil society and sub-national organizations, whose decisions influence vaccine uptake, access and public perceptions;



regulators and policy-makers who assess evidence and health technologies, and through benefit-risk analyses recommend or implement public health interventions to protect individuals and populations;



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;



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;



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



media and educators, who can use these priority actions to frame communications and improve understanding of the role of vaccines in controlling AMR;



the agricultural and animal industry sectors, which need to consider the potential of vaccines to reduce antibiotic use in animals;



public health advocates, including many of the stakeholders named above, who can use the recommendations presented here to shape their message and strengthen their public outreach and education.

Methodology and acknowledgments

This Action Framework, intended to guide vaccine stakeholders in efforts to maximize the impact of vaccines in preventing and containing AMR, was generated through a consensus-building consultative process. While the role of vaccines in tackling AMR has been considered in the scientific literature and deliberations of international organizations, a comprehensive global Action Framework has not been proposed. In response, the World Health Organization (WHO), in collaboration with the Bill & Melinda Gates Foundation (BMGF), Wellcome and the Center for Disease Dynamics, Economics & Policy (CDDEP), undertook an effort to build on expert discussions and develop specific actions to strengthen 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: Anthony Fiore (Centers for Disease Control and Prevention, Atlanta, GA, USA), William P. Hausdorff (PATH, Washington, DC, USA), Mark Jit, (London School of Hygiene and Tropical Medicine (LSHTM), London, UK); Gagandeep Kang (Translational Health Science and Technology Institute, Faridabad, India), Marc Lipsitch (Harvard T.H. Chan School of Public Health, Boston, MA, USA), Angela Brueggemann (University of Oxford, Oxford, UK), Buddha Basnyat (Oxford University Clinical Research Unit, Kathmandu, Nepal), Gordon Dougan (University of Cambridge, Cambridge, UK), Francis Ndowa (Skin and GU Medicine Clinic, Harare, Zimbabwe), Iruka Okeke (University of Ibadan, Ibadan,

Nigeria), David Salisbury (Chatham House, London, UK), Anthony Scott (LSHTM, London, UK), JP Sevilla (Harvard T.H. Chan School of Public Health, Boston, MA, USA), Lone Simonsen (Roskilde University, Roskilde, Denmark) provided input throughout the process. The Action Framework was first drafted following a stakeholder consultation held in London on 26–27 February 2019. The document has been circulated widely for comment, including an opportunity for public review through the WHO website.

The Department of Immunization, Vaccines and Biologicals at WHO (WHO IVB) would like to thank the many individuals who contributed to the development of this document. We extend additional thanks to the following key contributors: Laetitia Bigger (International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland), Isabel Frost (CDDEP, New Delhi, India), Elizabeth J. Klemm (Wellcome Trust, London, UK), Ramanan Laxminarayan (CDDEP, New Delhi, India), Stefano Messori (World Organisation for Animal Health (OIE), Paris, France), Wilson Mok (Gavi, Geneva, Switzerland), Holly Prudden (International AIDS Society, Geneva, Switzerland), Padmini Srikantiah (BMGF, Seattle, WA, USA), Robert Taylor (Scientific Writer, Boston, MA, USA), the WHO IVB Secretariat, Geneva, Switzerland, the WHO AMR Secretariat, Geneva, Switzerland.

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Overview

There is increasing awareness of the significant threats to individuals and public health from the growing burden of antimicrobial-resistant microbes. Multiple approaches are needed to prevent infections and reduce the use of antimicrobial drugs. Among these, vaccines are 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 the use of licensed vaccines to maximize impact on AMR
- Developing new vaccines that contribute to the prevention and control of AMR
- Expanding and sharing knowledge on the impact of vaccines on AMR.

Table 1 summarizes the objectives and priority actions under each of these areas to achieve the AMR-related sections of the Immunization Agenda 2030. A full description of each of these elements is provided under the section Strategic vision of the Action Framework.

BOX 1

AMR-related objectives of the Immunization Agenda 2030

This document complements the high-level global immunization strategy, the Immunization Agenda 2030: A Global Strategy to Leave No One Behind (IA2030). It summarizes how, in addition to its public

health benefit in directly preventing infection, immunization can also contribute to the control of AMR. The current document is of particular relevance to the following IA2030 strategic priorities (SP):

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.

Table 1. Action Framework at a glance



GOAL

Expand use of licensed vaccines to maximize impact on AMR

OBJECTIVES

ACTIONS

AUDIENCE

1 Increase coverage of vaccines with impact on AMR.

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



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

- 2a.** Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to account specifically 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 the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO), 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 Improve awareness and understanding of the role of vaccines in limiting AMR through effective communication, education and training.

- 3a.** Countries, funders and other stakeholders should include the role of vaccines in limiting AMR in communication materials used to present their related activities.
- 3b.** Institutions involved in the vaccine and AMR sectors 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.



Key:

- governments, national immunization technical advisory groups, and agencies
- health-care workers, professional medical associations, patient groups, civil society and subnational organizations

- regulators and policy-makers
- the pharmaceutical industry
- academic researchers
- funders of research

- media and educators
- the agricultural and animal industry sectors
- public health advocates



GOAL

Develop new vaccines that contribute to prevention and control of AMR

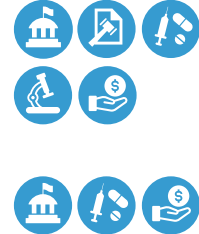
OBJECTIVES

ACTIONS

AUDIENCE

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

- 4a. Funders, industry, governments, nongovernmental and supranational organizations, academic institutions and researchers should increase investments in vaccine candidates with anticipated benefits for AMR.
- 4b. Funders, including governments and nongovernmental 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 to ensure sufficient manufacturing capacity to meet global needs for vaccines expected to reduce AMR.



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 knowledge of investigational product risk-benefit balance.
- 5b. Regulators and policy-makers 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.
- 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 labeling 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 policy-makers, during the approval process, when and how to include evaluation of a vaccine's potential to reduce antimicrobial use and AMR in these studies.



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GOAL

Expand and share knowledge of vaccine impact on AMR

OBJECTIVES

ACTIONS

AUDIENCE

6 Improve methodologies and increase collection and analysis of relevant data 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.
- 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 systems to link vaccination data with antimicrobial use and resistance data, with the greatest practical level of geographic and demographic granularity to enable interventions that focus 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 on:
 - 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;
 - socioeconomic 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.



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

- 7a. Funders should support researchers to develop and improve methodologies for estimating impact of vaccines on AMR.
- 7b. Health delivery payers and investors in R&D should develop and use standardized health technology assessments and value-attribution frameworks to inform the estimation of the full value of vaccines to prevent and control AMR.

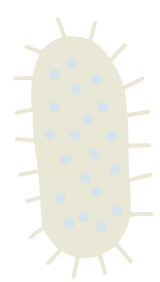
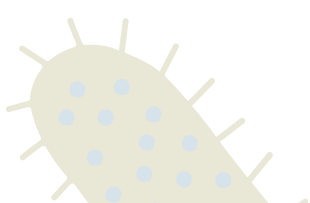
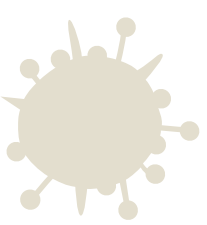
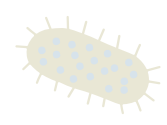
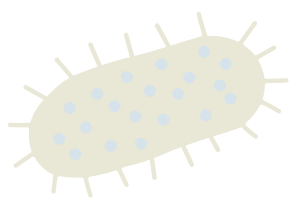
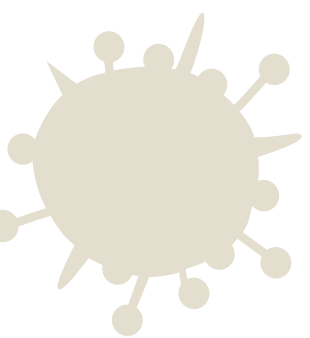
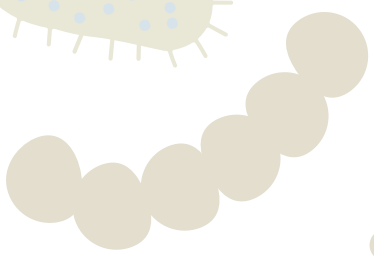
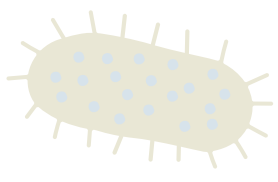
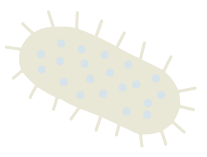
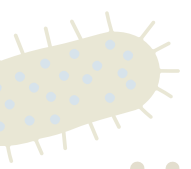
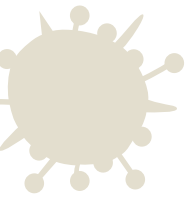


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1. Background

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 reduction 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 diseases. 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 the individual carries in the gastrointestinal tract, on the skin and in mucosae is exposed to that drug, in a “bystander” effect. Microbes that are less susceptible to the drug are more likely to survive, and in so doing will pass

that trait to their progeny, and to 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 of the same species and even other bacterial species, thus propagating resistance.

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. In some countries, more than 40% of infections are resistant,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.

The risk of AMR infection has increased in clinical care settings, where the use of antibiotics is frequent and infections sometimes transmitted from one patient to another. This threatens the continuity of safe access to routine care, including surgical procedures.

Unless current 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 settings; these factors make them less accessible to people living in LMICs, raising questions of equity.

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 this global problem, 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

¹ Gapminder [Internet]. [cited 2020 Feb 26]. Available from: www.gapminder.org/data/

² OECD. Stemming the Superbug Tide Just A Few Dollars More. OECD Publ. 2018.

³ de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? PLoS Med. 2016; 13(11).

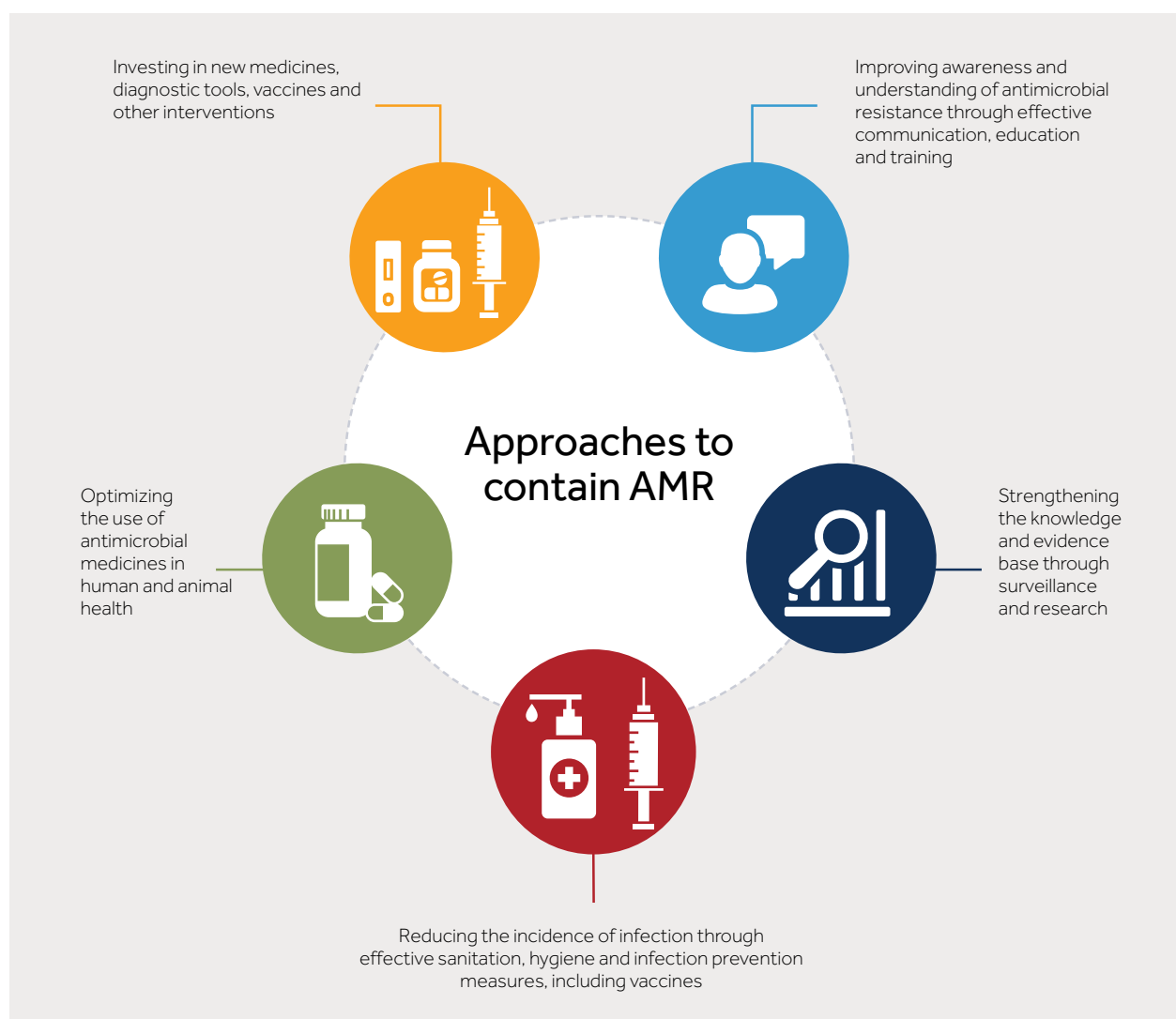
Addressing AMR will require concerted action in the human health, animal health, and agricultural, economic and environmental domains. WHO, in collaboration with FAO and OIE, published the Global Action Plan on Antimicrobial Resistance in 2015,⁴ and in 2016 the UN Secretary-General convened the Interagency 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 global stakeholders to drive progress against AMR.⁵

Controlling AMR will require improvements in infection prevention, antimicrobial stewardship, and antimicrobial discovery. Infection prevention reduces

the need for antibiotic treatment. Antimicrobial stewardship encourages more responsible use of antimicrobials and minimizes the selection pressures that drive the development of resistance (Fig. 1).

The discovery and use of new antibiotics constitute an increasingly complex economic and scientific challenge. While numerous distinct classes of antibiotics were licensed for use before 1970, few have been developed in the last half-century.⁶ 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.

Fig. 1. Strategic objectives of the Global Action Plan on Antimicrobial Resistance

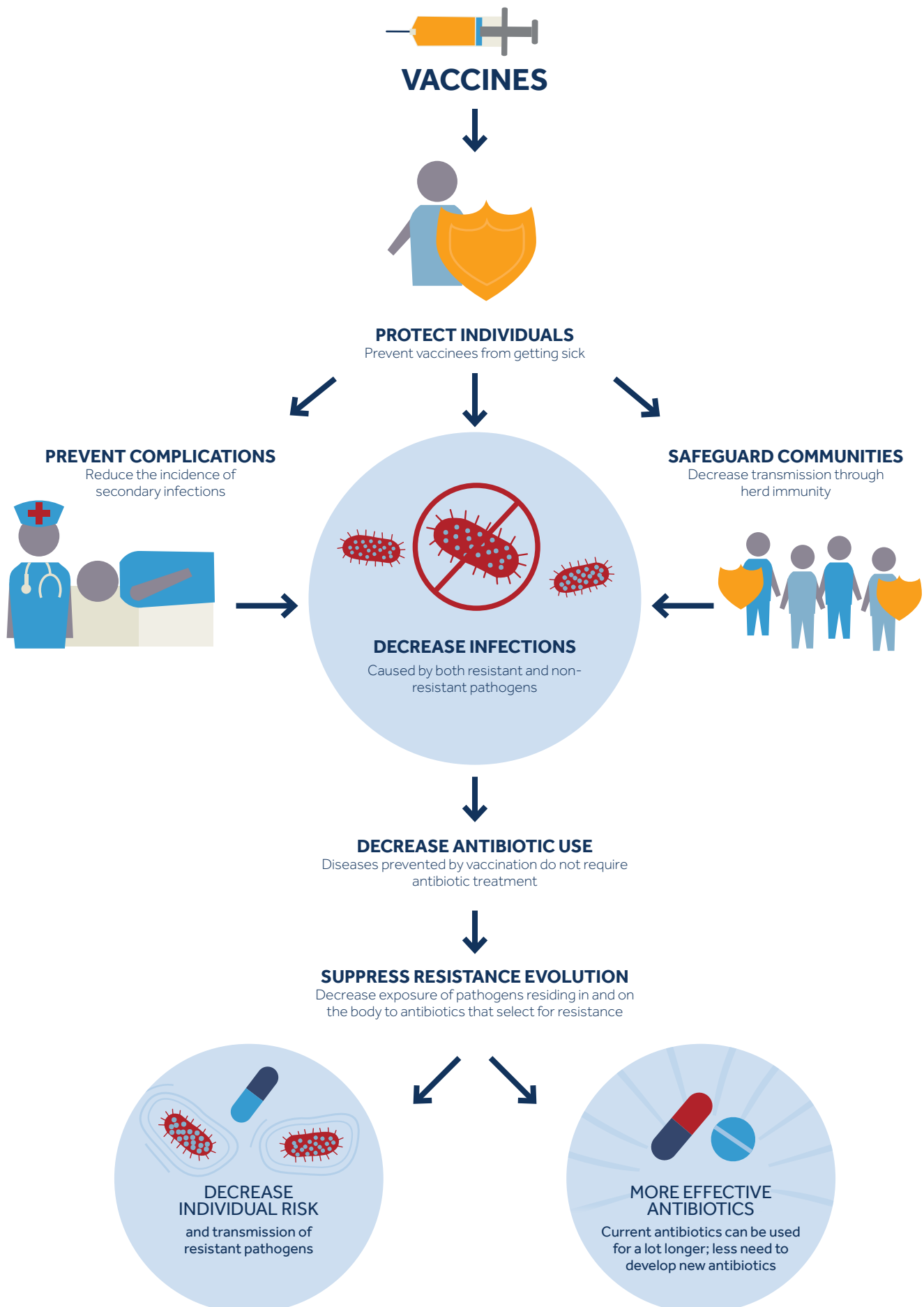


⁴ World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.

⁵ Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. 2019.

⁶ Kallberg C, Ardal C, Blix HS, Klein E, Martinez EM, Lindbæk M, et al. Introduction and geographic availability of new antibiotics approved between 1999 and 2014. PLoS One. 2018; 13(10).

Fig. 2. Impact of vaccines on AMR: a schematic pathway



Vaccines contribute to the battle against AMR by preventing infections and by reducing antimicrobial use

The most direct way in which vaccines contribute to prevention and control of AMR is by reducing the incidence of disease from resistant pathogens (Fig. 2). Vaccines against *S. pneumoniae*, Hib, *Salmonella* Typhi, *Bordetella pertussis*, tuberculosis (TB), 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 *S. pneumoniae* (Fig. 3)⁷ and Hib.⁸

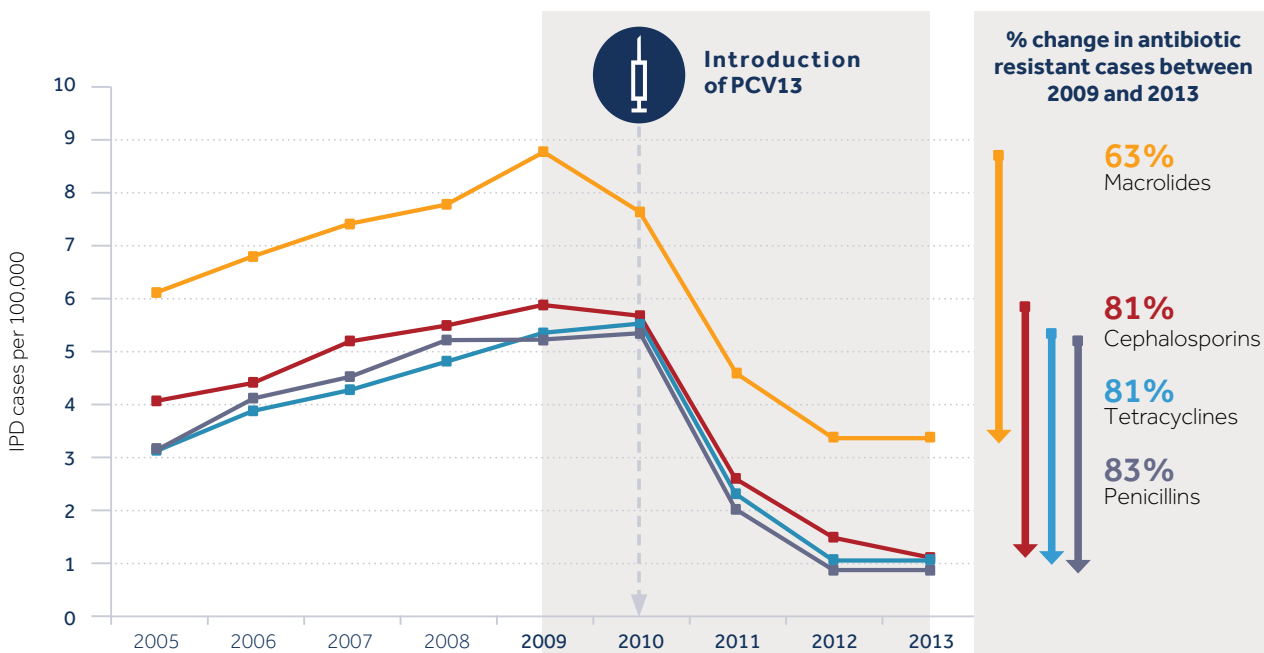
The importance of protecting against resistant strains of *S. Typhi* led WHO in 2018 to recommend

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 15 years old to help control the spread of extensively drug-resistant typhoid disease (Fig. 4).¹⁰

In the future, vaccines may play a major role in the realization of public health goals against TB, malaria, gonorrhoea, *Shigella* or other infections with an important AMR burden.

Another key benefit of vaccines is reduction of antibiotic use. Since the clinical presentations of many infections, such as fever, respiratory infection or diarrhoea, do not appreciably differ whether caused by bacteria or viruses, and antibiotic use is often empiric

Fig. 3. Impact of pneumococcal vaccine on rates of drug-resistant invasive pneumococcal disease (IPD) in the United States of America^{a, b}



IPD: invasive pneumococcal disease; PCV: pneumococcal conjugate vaccine.

^a Jansen KU, Knirsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. *Nat Med*. 2018;24(1):10-9.

^b Tomczyk S, Lynfield R, Schaffner W, Reingold A, Miller L, Petit S, et al. Prevention of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease with the 13-Valent Pneumococcal Conjugate Vaccine. *Clin Infect Dis*. 2016; 62(9).

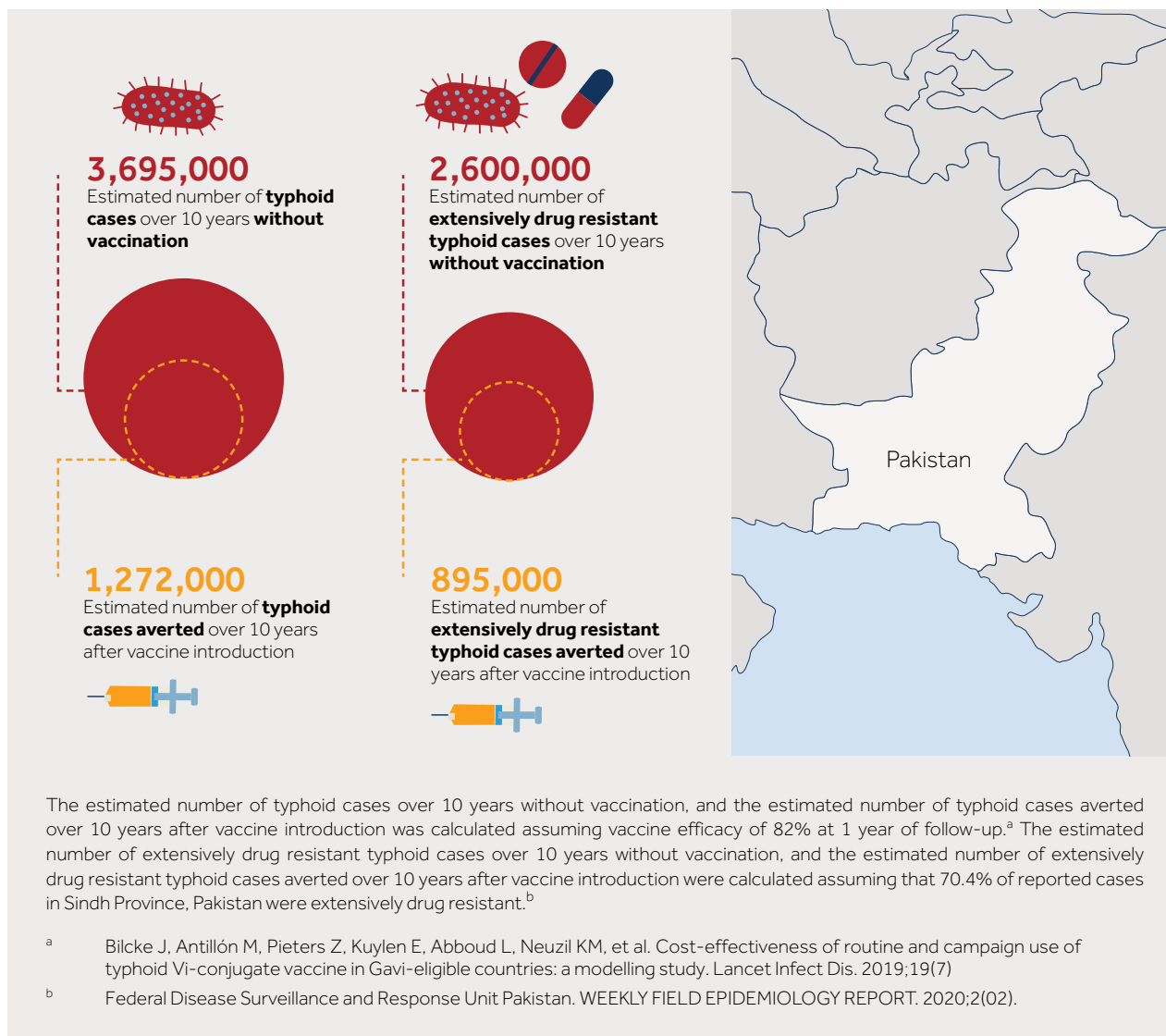
⁷ Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. *Proceedings of the National Academy of Sciences of the United States of America*. 2018;115(51).

⁸ Jorgensen JH, Doern G V., Maher LA, Howell AW, Redding JS. Antimicrobial resistance among respiratory isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in the United States. *Antimicrob Agents Chemother*. 1990;34(11).

⁹ World Health Organization. Typhoid vaccine: WHO position paper - March 2018. *Wkly Epidemiol Rec*. 2018;37(2)

¹⁰ World Health Organization (WHO). Pakistan first country to introduce new typhoid vaccine into routine immunization programme [Internet]. 2019 [cited 2020 Feb 26]. Available from: <http://www.emro.who.int/pak/pakistan-news/pakistan-first-country-to-introduce-new-typhoid-vaccine-into-routine-immunization-programme.html>

Fig. 4. Estimated impact of typhoid vaccine on drug-sensitive and -resistant typhoid in Pakistan



(i.e., syndromes are treated without any etiological diagnosis), vaccines that reduce the incidence of syndromic diseases may also reduce antibiotic use.

For example, influenza vaccines can reduce the frequently inappropriate use of antibiotics among 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, which can in turn be transmitted and cause

disease in specific circumstances, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* and *S. 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 a 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 not only reduce the frequent preventive use of antibiotics perinatally and 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 further characterized. OIE vaccine development priorities for chicken, swine, sheep, goat, bovine and fish diseases have been expressed. They aim to address bottlenecks and market barriers across the product life cycle, from fundamental research to registration and equitable and affordable access and stewardship.^{11,12} As expressed in the Global Action Plan on AMR¹³ and in a 2019 report to the UN Secretary-General,¹⁴ recommendations for industry practices need to be renewed, strengthened and implemented.

Prioritization of activities: based on best available evidence

Efforts are ongoing to expand the knowledge base on the epidemiology of AMR.¹⁵ In addition, understanding the full potential impact of vaccines is essential to inform the value proposition, justify the need for investment and define the use case, in all populations and all parts of the world. 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. Economic, social and equity effects of vaccines and alternatives on AMR must be assessed to understand their value, and be promptly and transparently disseminated in order to inform rational investment, and 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. Equitable access will depend on sustained investments, capacity strengthening, collaboration, political will and public confidence.

¹¹ World Organisation for Animal Health (OIE). Report of the meeting of the OIE Ad Hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals. Paris; 2015.

¹² World Organisation for Animal Health (OIE). Report of the meeting of the OIE Ad Hoc group on prioritisation of diseases for which vaccines could reduce antimicrobial use in cattle, sheep, and goats [Internet]. 2018. Available from: https://www.oie.int/fileadmin/SST/adhocreports/Diseases%20for%20which%20Vaccines%20could%20reduce%20Antimicrobial%20Use/AN/AHG_AMUR_Vaccines_ruminants_May2018.pdf

¹³ World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.

¹⁴ Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. 2019.

¹⁵ World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) Report Early implementation. 2017.

BOX 2

Wellcome's assessment of vaccine priorities for targeting 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 to facilitate global coordination of antibiotic R&D strategies against AMR.^a Following an extensive consultation and review process, using a systematic methodology taking into account 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 antibiotic-resistant bacteria, and did not consider the value of vaccines against viral pathogens.

Priority 1: CRITICAL

A. baumannii, *Pseudomonas aeruginosa*, *Enterobacteriaceae* (*K. pneumoniae*, *E. 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.*, *N. gonorrhoeae*.

Priority 3: MEDIUM

S. pneumoniae, Hib, *Shigella spp*

Subsequently, a prioritization exercise on the role of vaccines targeting these pathogens was undertaken.^b Prioritization was based on potential for health impact, probability of R&D success and probability of uptake. Pathogen clusters for which different interventions are required were identified.

The **"increase uptake"** cluster is composed of pathogens with effective licensed vaccines. Hib vaccines and pneumococcal conjugate vaccine (PCV) population uptake are globally at ~70% and 45%, respectively. A new, conjugated *S. Typhi* vaccine has recently been prequalified by 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 *E. coli* (enteric) is a challenge for vaccine development, but inclusion of heat-labile toxoid and fimbrial antigens may help increase vaccine strain cover. Vaccines

against non-typhoidal *Salmonella* and against *Shigella* appear technically feasible and potentially impactful against high disease burdens in Africa and other LMICs. *M. 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 justify 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 *N. gonorrhoeae* is strong due to high incidence, high morbidity, and current circulation of resistant strains. Evidence of *N. meningitidis* B vaccine to cross-protect against *N. gonorrhoeae* has fostered optimism. The incidence of extraintestinal *E. coli* infections is high and constitutes an important target for vaccination, but antigen selection remains a challenge. Vaccine development for *P. aeruginosa* is particularly needed for high-risk groups such as cystic fibrosis patients and other immunocompromised patients, but clinical testing in such patients is complex. Morbidity and mortality from *S. aureus* in high-income countries means the market for a vaccine is attractive, but significant gaps remain 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 gaps remain, or alternative control strategies may be preferable. *S. Paratyphi* has low incidence and low associated mortality and morbidity. Uptake of a standalone vaccine is unlikely and combination vaccines with *S. Typhi* should be contemplated. More data are 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 *H. pylori* and gastric cancer, and of how AMR is likely to evolve due to relative current treatability of the pathogen, is necessary. *K. 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*, *A. baumannii* and *E. 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.

^a Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18(3).

^b Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities. 2018.

2. 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.



3. 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:



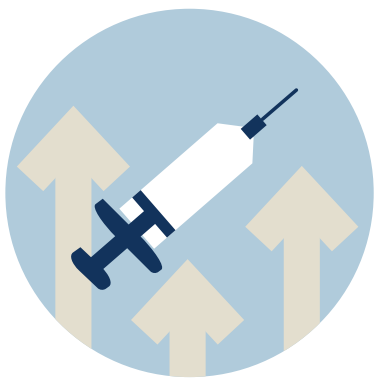
1. Expanding use of licensed vaccines to maximize impact on AMR



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



3. Expanding and sharing knowledge of vaccine impact on AMR



Goal 1.

Expand use of licensed vaccines to maximize impact on AMR

Expanding the use of licensed vaccines will require reaching current uptake targets, 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).¹⁶ 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 (Table 2). Recent data from WHO and the United Nations Children's Fund (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 have not yet met vaccine uptake targets included in the Decade of Vaccine's Global Vaccine Action Plan 2011–2020. The Immunization Agenda 2030¹⁷ 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 on AMR. Priority should be given to completion of the full basic series of PCV, Hib vaccine, rotavirus vaccine, measles-containing vaccines as well as increasing coverage for influenza and TCV.
- 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. 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 AMR sectors to include the role of vaccines to control AMR

In addition to the objectives and indicators set out in the Global Action Plan on AMR 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

¹⁶ World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.

¹⁷ World Health Organization (WHO). Immunisation Agenda 2030: A Global Strategy to Leave No One Behind. 2020.

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 *S. 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 who are at increased risk of exposure to drug-resistant microbes, such as health-care workers.

Priority actions

2a. Where justified, normative guidance, regulatory indications, policy recommendations and health regulations for vaccine use should be adapted to account specifically for the use of vaccines to impact AMR.

Table 2. Recommended use of selected licensed vaccines and potential impact on AMR

Vaccine	WHO recommendation	Global coverage in 2018 ^a	WHO coverage target ^b	Vaccine impact on AMR
PCV	All children, through routine immunization.	47%	90% nationally, 80% at district level.	Reduces resistant and non-resistant pneumococcal disease; reduces antibiotic use in children. ^c
TCV	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.	NA	Access to be prioritized in settings with high endemicity and high levels of AMR.	Modelling suggests vaccine use will proportionally reduce incidence of resistant and non-resistant typhoid, including number of chronic typhoid carriers. ^d
Hib vaccine	All children, through routine immunization.	72%	90% nationally, 80% at district level.	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 <5 years. ^c
Influenza vaccines	All pregnant women, children 6-59 months, adults >65 years, people with chronic medical conditions and health-care workers.	NA	Varies according to risk group.	Good evidence that influenza vaccine reduces antibiotic use by reducing misuse of antibiotics and treatment of secondary bacterial infections. ^e
Rotavirus vaccine	All children, through routine immunization.	35%	90% nationally, 80% at district level.	Expected to reduce antibiotic use but no confirmatory data available.
Measles vaccine	All children, through routine immunization.	69%	90% nationally, 80% at district level	Expected to reduce antibiotic use against secondary bacterial complications, but no confirmatory data available.

NA: not available; PCV: pneumococcal conjugate vaccine; TCV: typhoid conjugate vaccine; WHO: World Health Organization.

^a World Health Organization (WHO). Global and regional immunization profile. 2019.

^b WHO. Global Vaccine Action Plan 2011-2020 [Internet]. Available from: https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

^c Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. Proceedings of the National Academy of Sciences of the United States of America. 2018;115(51).

^d Bilcke J, Antillón M, Pieters Z, Kuylen E, Abboud L, Neuzil KM, et al. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. Lancet Infect Dis. 2019;19(7).

^e Buckley BS, Henschke N, Bergman H, Skidmore B, Klemm EJ, Villanueva G, et al. Impact of vaccination on antibiotic usage: a systematic review and meta-analysis. Clinical Microbiology and Infection. 2019;25(10).

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, 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 preventing disease at the individual and population levels is not completely

understood in parts of 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 contribute to the overarching goal of building confidence in immunization programs (Fig. 5).

Priority actions

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

3b. Institutions involved in the vaccine and AMR sectors 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.

Fig. 5. Visuals from the International Vaccine Institute’s advocacy campaign about the contribution of vaccines in the fight against AMR^a



^a International Vaccine Institute. IVI: World antibiotic awareness week 2019 [Internet]. 2019 [cited 2020 Feb 26]. Available from: <https://www.ivi.int/world-antibiotic-awareness-week-2019/>



Goal 2.

Develop new vaccines that contribute to prevention and control of AMR

New vaccine R&D is an integral part of the Global Action Plan on AMR.¹⁸ Addressing AMR will require new tools and technologies to complement currently available strategies and interventions.¹⁹ Few new antimicrobials have been developed recently or are anticipated to be available soon, and all are threatened by the emergence of resistance.²⁰ In contrast, vaccines have traditionally had sustainable impact, and there has been little or no evidence of escape from immunity.

The pipeline of vaccines with potential impact on AMR includes many early-stage candidates, and some in clinical evaluation. 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 becoming difficult to treat or 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 (Table 3).

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 preclinical and clinical testing to licensure, adoption and implementation.

¹⁸ World Health Organization. Global action plan on antimicrobial resistance. WHO Press. 2015.

¹⁹ World Health Organization (WHO). Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A WHO practical toolkit. 2019.

²⁰ Årdal C, Balasegaram M, Laxminarayan R, McAdams D, Outtersson K, Rex JH, et al. Antibiotic development — economic, regulatory and societal challenges. *Nat Rev Microbiol*. 2019;18(5).

Table 3. 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

Target pathogen and disease	Burden	AMR-related impact	Vaccine outlook
<i>M. tuberculosis</i>, tuberculosis (TB)	A quarter of global population latently infected; ^a in 2019, 10 million people fell ill with TB and 1.4 million died. ^b	Resistant TB rising sharply. There were 465,00 rifampicin-resistant diagnoses in 2019, 78% of which were resistant to more than one drug; 182 000 people died from drug-resistant TB infections. ^b	A highly effective vaccine is 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. ^c
<i>N. gonorrhoeae</i>, pelvic inflammatory disease, infertility	78 million new cases per year among people aged 15-49 years; ^d can cause infertility and other severe sequelae.	Once universally susceptible to antibiotics, strains resistant to every current class of antibiotic have emerged; complete treatment failure has been reported. ^e	<i>N. gonorrhoeae</i> shares 80-90% of its genetic sequence with <i>N. meningitidis</i> , a common cause of meningitis. There is some evidence that type B <i>N. meningitidis</i> vaccine partially protects against some <i>N. gonorrhoeae</i> , suggesting a vaccine is feasible. ^f
<i>Plasmodium falciparum</i>, malaria	228 million cases worldwide in 2018, 405 000 deaths. ^g Important driver of antibiotic use for non-specific febrile illness in high endemicity areas.	Artemisinin resistance emerged in South-East Asia in early 2000s; several artemisinin combination therapies now failing. ^g Potential to reduce malaria-driven antibiotic use.	RTS,S/AS01 vaccine provides partial protection in young children, showing that a vaccine is feasible. ^h RTS,S/AS01 is in pilot implementation through routine immunization programmes in Ghana, Kenya and Malawi. Other candidates continue to be developed.
RSV, respiratory disease	A very common respiratory tract infection that affects all ages; most severe in early childhood. Important driver of antibiotic use for undocumented respiratory illness globally.	Potential to reduce RSV-driven antibiotic use.	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.
<i>Enterotoxigenic Escherichia coli (ETEC) and Shigella</i> Gastroenteritis	ETEC caused 51 186 deaths globally including 18 669 deaths in children under 5 years old in 2016. ⁱ <i>Shigella</i> caused 212 438 deaths globally including 63 713 in children under 5 years old in 2016. ⁱ Contributors to long-term morbidity such as malnutrition and stunting.	High and growing rates of multidrug resistance.	Several candidate vaccines are in development. Controlled human infection models may be able to accelerate clinical development.

BCG: bacille Calmette-Guérin (vaccine); RSV: Respiratory Syncytial Virus.

^a Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med.* 2016;13(10).

^b World Health Organization (WHO). Global Tuberculosis Report 2020. 2020.

^c Tait DR, Hatherill M, Der Meeren O Van, Ginsberg AM, Van Brakel E, Salaun B, et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med.* 2019;381(25).

^d Newman L, Rowley J, Hoorn S Vander, Wijesooriya NS, Unemo M, Low N, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. *PLoS ONE.* 2015;10(12).

^e Eyre DW, Sanderson ND, Lord E, Regisford-Reimmer N, Chau K, Barker L, et al. Gonorrhoea treatment failure caused by a *Neisseria gonorrhoeae* strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018. *Eurosurveillance.* 2018;23(27).

^f Azze RFO. A meningococcal B vaccine induces cross-protection against gonorrhoea. *Clin Exp Vaccine Res.* 2019;8(2)

^g World Health Organization (WHO). World Malaria Report 2019. 2019.

^h Olotu A, Fegan G, Wambua J, Nyangweso G, Leach A, Lievens M, et al. Seven-year efficacy of RTS, S/AS01 malaria vaccine among young african children. *N Engl J Med.* 2016;374(26).

ⁱ Khalil IA, Troeger C, Blacker BF, Rao PC, Brown A, Atherly DE, et al. Morbidity and mortality due to *shigella* and enterotoxigenic *Escherichia coli* diarrhoea: the Global Burden of Disease Study 1990-2016. *Lancet Infect Dis.* 2018;18(11).

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

Priority actions

4a. Funders, industry, governments, nongovernmental and supranational organizations, academic institutions and researchers should increase

investments in vaccine candidates with anticipated benefits for AMR.

4b. Funders, including governments and nongovernmental 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 to ensure sufficient manufacturing capacity to meet global needs for vaccines expected to reduce AMR.

BOX 3

A sample of organizations investing in vaccine candidates to control AMR

CARB-X is a public-private partnership to support R&D to tackle AMR in bacteria. Founded in 2016, it supports early development of antibiotics, diagnostics, vaccines and alternative therapies to combat the most serious drug-resistant bacteria. CARB-X has supported several vaccine projects, including work on candidate vaccines for *K. pneumoniae*, group A *Streptococcus*, and *S. aureus*. CARB-X does not require a monetary return on its investment. Recipients of funding must have intellectual property rights to a promising product that will help prevent or control AMR, and need to be able to cost-share the funding required to move that product through preclinical development or phase 1 clinical trials. The funding agreements with awardees contain specific stewardship and access provisions. For every dollar CARB-X has invested in its projects, private capital has subsequently invested eight more. For more information see <https://carb-x.org>.

Wellcome and the EDCTP Partnership calls for proposals. Calls for proposals for vaccine development and/or evaluation of the impact of vaccines on AMR were issued by both Wellcome and the EDCTP in 2019. For more information see <https://wellcome.ac.uk/funding/schemes/impact-vaccines-anti-microbial-resistance> and <http://www.edctp.org/call/new-drugs-and-vaccines-for-priority-pathogens-in-antimicrobial-resistance-2019/>.

Bill & Melinda Gates Medical Research Institute (Gates MRI). The development of effective vaccines against drug-sensitive and -resistant malaria, TB and diarrhoeal diseases constitute research priorities for product development activities.

IAVI and Serum Institute of India have recently announced a product development partnership to develop and manufacture globally affordable and accessible antibody products, including monoclonal antibodies targeting AMR pathogens.

BOX 4

Gavi adds AMR impact to its Vaccine investment strategy criteria

Gavi, the Vaccine Alliance, brings together public and private sectors with the mission to increase equitable use of vaccines in lower-income countries. Gavi formally redevelops its guiding Vaccine Investment Strategy every five years, and is currently working on its strategy for 2021-2025. The strategy identifies and prioritizes opportunities for investment in vaccines and immunization products for Gavi-supported countries in terms of impact, cost, value and programme feasibility. In 2018, Gavi decided to include impact on AMR

as one of the indicators of a vaccine's value. In its assessments, most weight is given to a vaccine's potential to reduce AMR-related mortality and morbidity and to reduce antibiotic use. PCV, TCV and malaria vaccines were given higher scores for AMR impact. Gavi plans to enhance its assessment methodology using quantitative data as they become available.

For further information see <https://www.gavi.org/about/strategy/vaccine-investment-strategy/>

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 benefit-risk 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 policy-makers 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 policy-making 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 knowledge of investigational product risk-benefit balance.
- 5b. Regulators and policy-makers 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.
- 5c. WHO, through its PDVAC and SAGE, 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 policy-makers, during the approval process, when and how to include evaluation of a vaccine's potential to reduce antimicrobial use and AMR in these studies.

BOX 5 Regulatory pathways

Accelerated approval pathways similar to those being developed for some epidemic vaccines may be appropriate for AMR-reducing vaccines. This includes vaccines involving controlled human infectious challenge models and using 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 are as follows.

FDA 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.



Goal 3.

Expand and share 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 policy-making 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 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 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. Since few data are currently available, there is an urgent need to increase data collection and analysis.²¹ This is particularly relevant to settings where issues of both access to, 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 link vaccination data with antimicrobial use and resistance data, with the greatest practicable level of geographic and demographic granularity to enable interventions that focus 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 on:
 - 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;
 - socioeconomic and ethical aspects of vaccine impact on AMR.

²¹ Buckley BS, Henschke N, Bergman H, Skidmore B, Klemm EJ, Villanueva G, et al. Impact of vaccination on antibiotic usage: a systematic review and meta-analysis. *Clinical Microbiology and Infection*. 2019;25(10).

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

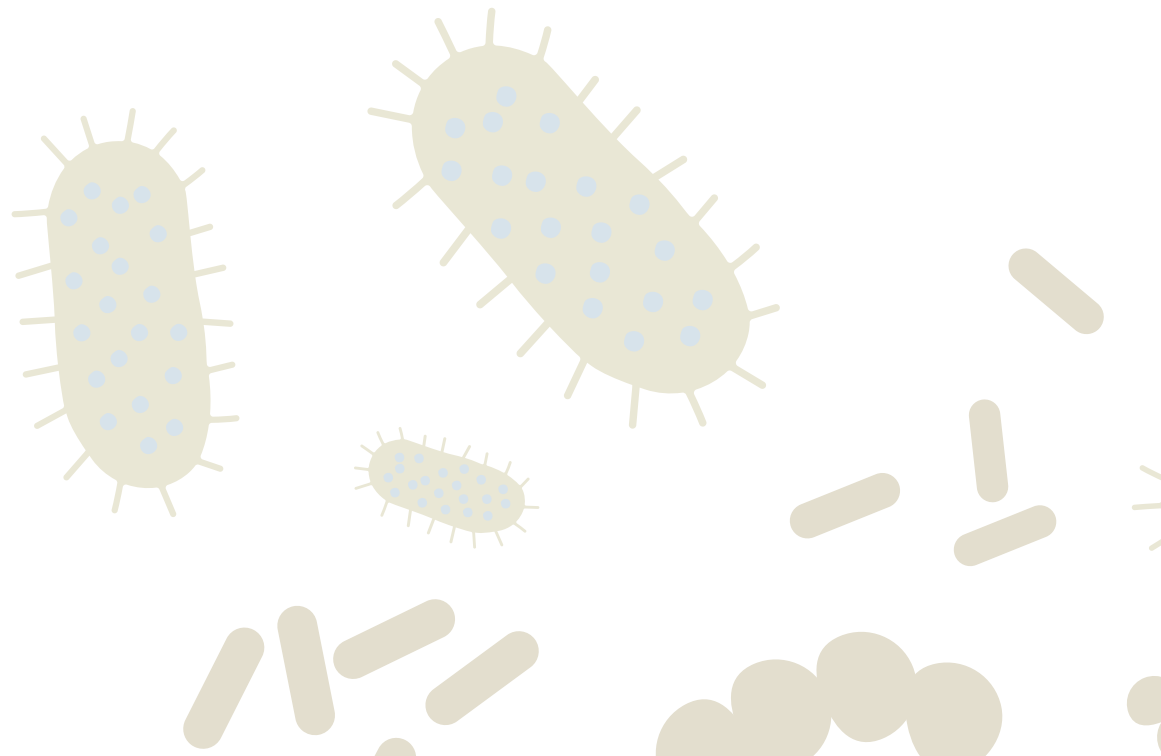
In a context of resource constraints, prioritization of investments should be informed by estimates of the value of existing and future vaccines in their ability to prevent and control AMR. Mathematical modelling, multi-criteria decision analysis and other methodologies including empirical approaches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

Beyond cost-effectiveness analyses, the full scope of investments needed and societal impact should be considered (impact on antibiotic use, direct medical costs, social care costs, loss in productivity, impact on social justice and equity, 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 policy-makers, ministries 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 standardized 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.



4. Conclusions

Vaccines are already contributing to the battle against AMR through prevention of infections and an associated decrease in antibiotic use. The priority activities outlined in this document provide the opportunity for vaccines to contribute fully, sustainably and equitably to the prevention and control of AMR, as a complementary approach to other AMR-reduction efforts.

Increased investments from the private, philanthropic and public sectors are needed for existing vaccines to reach higher coverage, as well as to develop 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, TCV, and influenza vaccines should be prioritized for impact on antibiotic use and AMR. Among disease areas for which vaccines are not available, but proof-of-concept evidence suggests that vaccine development is technically feasible, TB constitutes a major public health emergency and priority for investment. Vaccines against gonococcal infections and enteric diseases due to *Shigella*, *E. coli* and non-typhoidal *Salmonella* also constitute priority R&D opportunities.

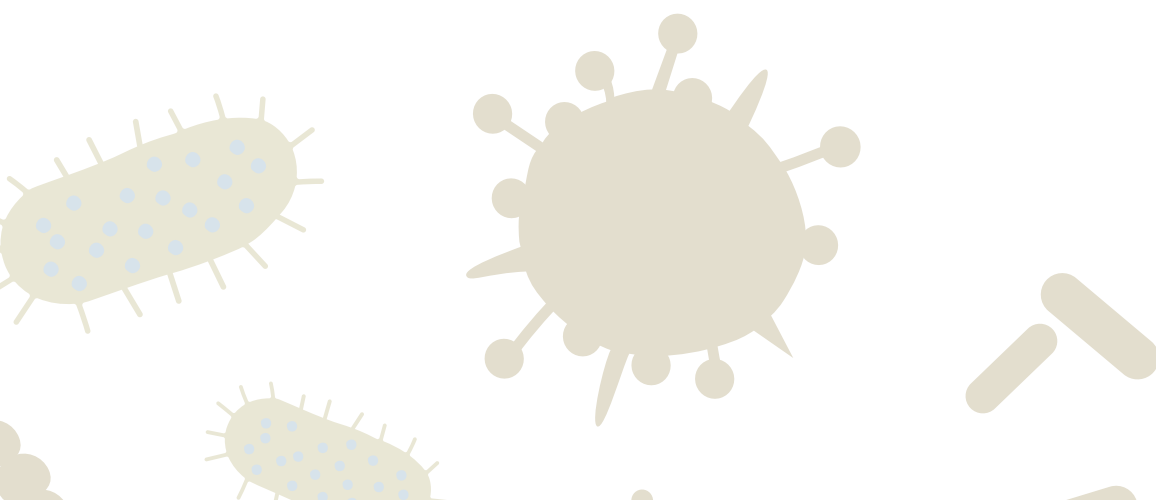
Development should be accelerated of next-generation vaccines providing expanded strain

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 such as *S. aureus*, *P. aeruginosa*, *E. coli*, *Campylobacter*, *H. pylori*, *K. pneumoniae*, *Enterobacteriaceae*, *A. baumannii*, *E. faecium*, *C. difficile*, *Chlamydia* and *Candida*, but confidence in feasibility needs to be built.

Across disease areas, key activities to maximize impact, including for AMR control, comprise: further development of 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.

Decisions should be based on evidence, and investments based on careful value-based prioritization. More and better collection and analysis of data on the role of vaccines against AMR across a variety of microbiological, health and economic sectors are critical. Modelling provides 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 everyone against infections and curb the threat that AMR poses to individuals, societies and global health.



5. Useful links

The links below have been identified as useful sources of information about vaccines and AMR. WHO does not favour nor prioritise institutions listed below.

AMR Control

<http://resistancecontrol.info/>

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

BMGF

<https://www.gatesfoundation.org/>

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) is 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

<https://www.cdc.gov/drugresistance/intl-activities/amr-challenge.html>

The US Centers for Disease Control and Prevention (CDC) website summarizes 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 well-being 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 is a not-for-profit organization whose mission is to analyse and promote the understanding of major international issues and current affairs. This website summarizes their current work and perspectives in the AMR field.

Coalition against Typhoid

<https://www.coalitionagainststtyphoid.org/>

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.

COMBACTE

<https://www.combacte.com/>

COMBACTE fights antimicrobial resistance by speeding up the development of new antibiotics.

European Commission

https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/antimicrobial-drug-resistance-amr_en

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

European Commission Joint Programming Initiative on Antimicrobial Resistance

<https://www.jpiamr.eu/>

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

FAO

<http://www.fao.org/antimicrobial-resistance/en/>

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

Global AMR R&D Hub

<https://globalamrhub.org/>

The 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.

IACG

<https://www.who.int/antimicrobial-resistance/interagency-coordination-group/en/>

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.

IFPMA

<https://www.ifpma.org/subtopics/antimicrobial-resistance/>

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) represents research-based biopharmaceutical companies to advocate policies and practices that encourage discovery and access to life-saving and life-enhancing medicines and vaccines, for people everywhere. Its website presents 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 Co-operation and Development (OECD) offers a forum for discussion and provides countries with evidence to implement effective and cost-effective policies to tackle AMR, and promote effective use of antimicrobials and R&D in the antibiotic sector.

OIE

<https://www.oie.int/en/for-the-media/amr/>

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

PATH

<https://www.path.org/articles/drug-resistance-vaccines/>

PATH's article 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

<https://www.reactgroup.org/>

Created in 2005, ReAct is one of the first international independent networks to articulate the complex nature of antibiotic resistance and its drivers. ReAct's goal is to serve as a global catalyst, advocating and stimulating global engagement on antibiotic resistance by collaborating with a broad range of organizations, individuals and stakeholders.

REPAIR Impact Fund

<https://www.repair-impact-fund.com/>

Novo Holdings established the REPAIR Impact Fund commissioned by the Novo Nordisk Foundation in February 2018. With a total budget of US\$ 165 million, the Fund invests in companies involved in discovering and 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.

UNICEF

<https://www.unicef.org/documents/time-running-out>

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.

United Kingdom Government

<https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024>

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

Vaccines Europe

<http://www.vaccines europe.eu/>

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/>

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 AMR. It contains fact sheets, the Global action plan on antimicrobial resistance, data collection platforms such as Global Antimicrobial Resistance Surveillance System (GLASS), and WHO resolutions regarding antimicrobial resistance.



