LANDSCAPING AND METHODS BRIEF – DRAFT FOR PDVAC

Partnering with regions and countries to identify priority pathogens for vaccines

Immunization Agenda 2030 Monitoring and Evaluation

Abbreviations

AFRO	WHO Regional Office for Africa
AMR	Antimicrobial Resistance
AMRO	WHO Regional Office for the Americas
CDC	Centers for Disease Control
CEPI	Coalition for Epidemic Preparedness Innovations
DALYs	Disability-adjusted Life Years
DCVMN	Developing Country Vaccine Manufacturers Network
EID	Emerging Infectious Disease
eJRF	Electronic Joint Reporting Form
EMRO	WHO Regional Office for the Eastern Mediterranean
ETEC	Enterotoxigenic *Escherichia coli*
EURO	WHO Regional Office for Europe
GVAP	Global Vaccine Action Plan
IA2030	Immunization Agenda 2030
IVIR-AC	WHO's Immunization and Vaccines Related Implementation Research Advisory Committee
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
iNTS	Invasive Non-typhoidal *Salmonella*
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
M&E	Monitoring and Evaluation
MCDA	Multi-criteria Decision Analysis
PAPRIKA	Potentially All Pairwise Rankings of All Possible Alternatives
PDVAC	Product Development for Vaccines Advisory Committee
R&D	Research and Development
RITAG	Regional Immunization Technical Advisory Group
RO	Regional Office
RSV	Respiratory Syncytial Virus
SAGE	WHO's Strategic Advisory Group of Experts on Immunization
SEAR-ITAG	South-east Asian Regional Immunization Technical Advisory Group
SEARO	WHO Regional Office for South-east Asia
SP7	Strategic Priority 7 of IA2030, "Research and Innovation"
TB	Tuberculosis
VIMS	Gavi Vaccine Investment Strategy
VIPS	Gavi Vaccine Innovation Prioritisation Strategy
VVP	Vaccine Value Profile
WHO	World Health Organization
WPRO	WHO Regional Office for the Western Pacific

I. Executive Summary

Context

Immunization Agenda 2030: A Global Strategy to Leave No One Behind (IA2030) is the global strategy for immunization, aimed toward maximizing the impact of vaccines. Within IA2030, "Research and Innovation" comprises the seventh and final strategic priority area, referred to as "SP7". In the IA2030 Monitoring and Evaluation (M&E) Plan, Indicator 7.2 monitors progress relating to a "short list" of global R&D targets. According to this plan, "WHO headquarters and regional offices together with key partners/stakeholders are to mutually define targets and evaluate progress at the global and regional levels. This process will require a prioritization framework to align on priorities, targets, and a mechanism for monitoring and evaluation."[1] The Product Development for Vaccines Advisory Committee (PDVAC) has been charged with proposing the short list of pathogen targets for new vaccines (where vaccines do not yet currently exist, or where a new indication is needed), for endorsement by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) in April 2023.

This call for mutually defined pathogen targets is in keeping with the IA2030 core principles of "people-centered, country-owned, partnership-based, and data-guided." IA2030 hypothesizes that a robust priority-setting process at country and regional levels will build awareness of disease burden, risks, and threats, and increase capacity for evidence-based decision making. Aligning priorities across global, regional, and country levels can focus funding and other resources, and enable greater coordination. Ultimately, products that are responsive to country priorities will be implemented more rapidly and achieve greater impact.

Currently, global vaccine development stakeholders and funders do not have a robust, established mechanism to engage with regional or country stakeholders on pathogen or product priorities, so this initiative will require designing and implementing a new mechanism. While this mechanism is initially focused on identifying pathogen priorities for new vaccines, it will also be needed to collaboratively develop and align on other important aspects of research and innovation strategies, such as priorities for implementation and operational research.

To ensure that this mechanism is informed by what has gone before and uses existing processes and structures to the greatest extent feasible, an initial landscape review was conducted. This report gives the results of that review and highlights key considerations for creating this new mechanism.

Existing priorities for research and innovation

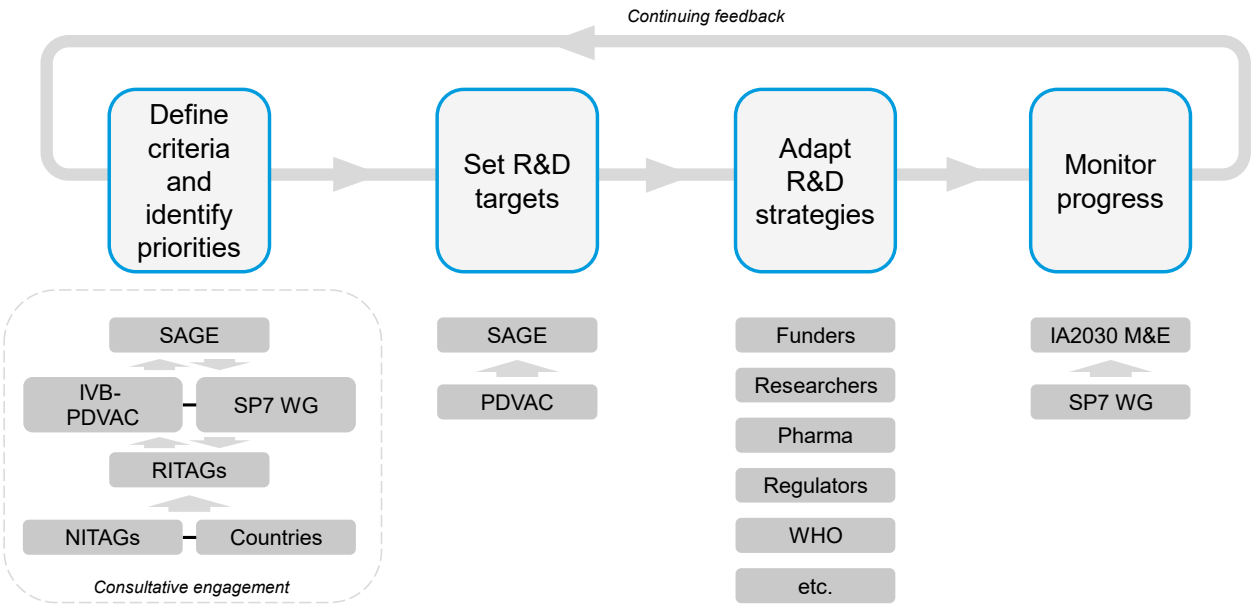
The landscape review showed that regional priorities for research and innovation, as stated in IA2030 or GVAP-related strategic plans, most commonly focus on implementation and operational research for existing vaccines and are intended to support decision-making and maximize the benefits of vaccines or efficiency of vaccination programs. Priorities for new vaccine R&D are not commonly stated at a regional level, but some regional organizations and many countries and funding bodies have stated specific vaccine R&D objectives. Vaccine R&D is often discussed more generally in the context of preparedness for emerging infectious diseases (EIDs) or to address antimicrobial resistance (AMR). In low- and middle-income countries, these objectives often focus on building clinical trial or manufacturing capacity, including manufacturing capacity for COVID-19 vaccines.

Systematic priority setting methods include expert surveys and consultations; quantitative methods such as single-criterion analysis and multi-criteria decision analysis (MCDA); and combinations of quantitative methods and stakeholder consultations.

Key considerations for a priority-setting mechanism

Stakeholder engagement across all levels, global, regional, and country, will be important to ensure the legitimacy of the results. Figure 1 shows a proposed engagement model for the prioritization mechanism.

Figure 1 Proposed Engagement Model for IA2030 R&D Priorities



WHO regional offices (ROs) and their associated Regional Immunization Technical Advisory Groups (RITAGs) have been invited to co-develop the prioritization mechanism and to serve as liaisons to regional and country decision makers and experts. Their engagement will be invaluable in the design and implementation of the prioritization process and in the surveys and consultations that will establish regional priorities. Exploratory discussions with WHO RO staff and RITAG chairs have found keen interest in some regions, but very limited ability in any region to engage substantively in this effort, to date. As a result, it may be necessary to develop this engagement and prioritization mechanism in partnership with 2 or 3 regions initially, and then expand it to additional regions after it has matured.

Because MCDA can support decision making in the context of multiple trade-offs and diverse stakeholder perspectives, SAGE has agreed to use it for this prioritization. SAGE has also agreed to limit this prioritization exercise to priority pathogens for new vaccines (where vaccines do not yet currently exist, or where a new indication is needed), rather than a wider range of needs and opportunities in research, development, and systems innovation because no single prioritization exercise can address such divergent topics, and because the objective is to elicit the priorities of regional and country stakeholders, rather than R&D experts. If successful, the mechanism and methodology could be expanded to address other aspects of the Research and Innovation strategy.

The landscape review identified over 150 pathogens that could potentially be included in the scope of this prioritization. Eliminating animal pathogens, pathogens with licensed vaccines, and pathogens without vaccines in clinical development reduces the list to 65 pathogens. Of these, 35 pathogens have been prioritized for vaccine R&D through global mechanisms such as the WHO R&D Blueprint, by PDVAC, or by global disease control strategies. An additional 30 pathogens have vaccines in clinical development and could be included in this scope. **The decision on which pathogens to include in this prioritization exercise must consider data availability, and should be made in consultation with regional partners in order to achieve both feasibility and legitimacy**.

Broad stakeholder engagement will also be crucial to establishing the criteria for prioritization. The MCDA criteria should capture all the factors relevant to regional and country priorities without overlap or interdependency. Based on precedents found in the landscape review, **9 criteria and 3 descriptive attributes are proposed for this prioritization. Finalizing these criteria will require input from regional and country stakeholders, to ensure that they are sufficiently representative.** It will require advice from MCDA experts, to ensure that they are clearly defined. It will also require advice from disease experts to capture the data that are available for each pathogen and to address data gaps.

II. Report

A. Context: Need for a Short List of R&D Priorities

Immunization Agenda 2030 (IA2030) is the global strategy for immunization, aimed towards maximizing the impact of vaccines.[2] Within IA2030, "Research and Innovation" is the seventh strategic priority area, referred to as "SP7". Identifying the diverse needs and opportunities for research and innovation, be it in the development of new or improved vaccines, or in vaccine delivery systems or immunization implementation, is a key initial step in advancing this strategic priority and IA2030 as a whole.

IA2030 is informed by the lessons of its predecessor, the Global Vaccine Action Plan (GVAP) 2011-2020.[3] GVAP was widely seen as an important and influential strategy, but one with insufficient traction at country and regional levels. In contrast, IA2030 was developed collaboratively with countries to ensure that its vision, strategic priorities, and goals serve country needs. While GVAP focused on research and development (R&D) for new products, SP7 focuses on building capacity for innovation in immunization products, services, and practices.[4]

These differences between GVAP and IA2030 are reflected in the indicators for monitoring and evaluation (M&E) of research and innovation. (Figure 2) GVAP indicators, which focus on progress in R&D, were defined at the global level. The GVAP approach to setting priorities was consistent with historical approaches to prioritizing investment in R&D, in which funders and the pharmaceutical industry have defined their own priorities. But because priorities differ by context, such global priorities may not align with the priorities of regions or countries. And while global experts and advocates have influenced priority setting to some degree, countries and regions have previously had little voice in the process.

In contrast, IA2030 hypothesizes that increasing country input into global priorities will yield many benefits. A robust priority-setting process at country and regional levels will build awareness of disease burden, risks, and threats, and increase capacity for evidence-based decision making. Aligning priorities across global, regional, and country levels can focus funding and other resources, and enable greater coordination. Ultimately, products that are responsive to country priorities will be implemented more rapidly and achieve greater impact.

Accordingly, IA2030 Indicator 7.1 monitors the proportion of countries with a national agenda for research on immunization. This indicator will reflect country engagement in evidence generation and product development. Indicator 7.2 monitors progress relating to a "short list" of global R&D targets. Consistent with the IA2030 core principles of "people-centered, country-owned, partnership-based, and

data-guided", this short list should be based on country and regional priorities and established through a collective approach.

Figure 2 GVAP and IA2030 Monitoring and Evaluation for Research and Innovation

GVAP	**Goal 4. Develop and introduce new and improved vaccines and technologies** • Indicator 4.1. Licensure and launch of vaccine or vaccines against one or more major currently non-vaccine preventable diseases • Indicator 4.2. Licensure and launch of at least one platform delivery technology • Indicator 4.3. Number of low-income and middle-income countries that have introduced one or more new or underutilized vaccines **Strategic Objective 6. Country, regional, and global research and development innovations maximize the benefits of immunization** • Indicator 6.1. Progress towards development of HIV, tuberculosis (TB), and malaria vaccines • Indicator 6.2. Progress towards a universal influenza vaccine (protecting against drift and shift variants) • Indicator 6.3. Progress towards institutional and technical capacity to carry out vaccine clinical trials • Indicator 6.4. Number of vaccines that have either been re-licensed or licensed for use in controlled-temperature chain at temperatures above the traditional 2 – 8 ˚C range • Indicator 6.5. Number of vaccine delivery technologies (devices and equipment) that have received WHO prequalification against the 2010 baseline
IA2030	**SP7 Goal. Innovations to increase the reach and impact of immunization programs are rapidly made available to all countries and communities** **SP7 Objectives** 1. Establish and strengthen capacity at all levels to identify priorities for innovation, and to create and manage innovation 2. Develop new vaccines and technologies, and improve existing products and services for immunization programs 3. Evaluate promising innovations and scale up innovations, as appropriate, based on the best available evidence **SP7 Indicators** • Indicator 7.1. Proportion of countries with national agenda for research on immunization. To be monitored through annual Joint Reporting Form process • Indicator 7.2. Progress toward global research and development targets. To be monitored based on a "short list" of global targets to be developed by WHO and endorsed by SAGE

B. Approach and Scope

This report describes the proposed first steps toward developing a collective approach to defining a short list of global pathogen targets for vaccine R&D. As shown in Figure 3, this process is being conducted in four phases, in accordance with WHO guidelines for priority-setting exercises.[5] This report describes the results of the "Prepare" phase as of June 2022 and highlights follow-up activities to incorporate regional and country perspectives on the prioritization method. It is intended to support review by the WHO Product Development for Vaccines Advisory Committee (PDVAC) and Strategic Advisory Group of Experts on Immunization (SAGE), and to serve as the basis for collaboration moving forward.

Figure 3 Proposed Process for Prioritization of Pathogen Targets

Prepare	Implement	Synthesize	Monitor
• Initial stakeholder advice on overall approach • Landscape review of existing R&D and pathogen priorities and prioritization methods • Propose prioritization scope, method, and criteria to identify proposed priority pathogens • Agree with regional stakeholders on method and criteria • Prepare and test survey tool	• Conduct survey of pathogen priorities • Hold consultations to refine pathogen priority lists	• Aggregate regional priorities into a global "short list" for SP7 M&E • PDVAC and SAGE review and refine the short list	• Ongoing IA2030 M&E tracks progress against the short list of priorities • As warranted, the prioritization exercise can be repeated in response to new data or changes in context

Shaded elements are described in this report.

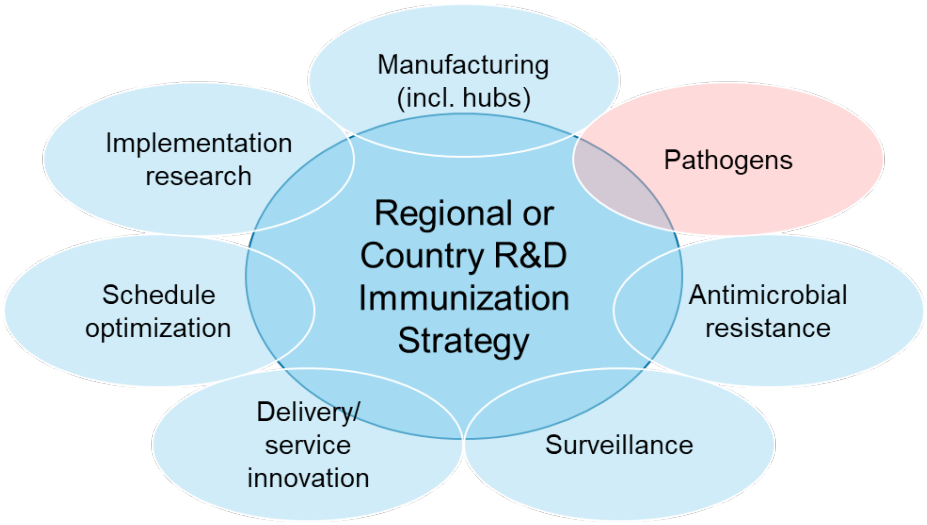
SAGE agreed with this approach in April 2022 and will review the outputs in April 2023. As there is no established WHO mechanism to engage with regional or country stakeholders on pathogen or product priorities, and in view of the extraordinary strain that COVID-19 has placed on these stakeholders, we

aim to design a light-touch and pragmatic approach and test it in partnership with selected WHO regions initially, with the intent to in future apply the lessons learned to additional regions.

SAGE has also agreed to limit this prioritization exercise to pathogens, rather than a wider range of needs and opportunities in research, development, and systems innovation. (Figure 4) The full range of needs is very diverse: opportunities in vaccine R&D include developing new vaccines against potentially vaccine-preventable diseases, including emerging infectious diseases and zoonotic diseases; improving existing vaccines to expand benefits to other target populations, optimize schedules, or reach the under- and under-immunized; creating next-generation vaccines with greater breadth of protection or ease of delivery; and advancing enabling innovations in vaccine platforms, correlates of protection, or disease models; and more. Beyond product R&D, research and innovation are needed to understand more fully the value and impact of vaccines, and to deliver vaccines more efficiently and effectively in different contexts.

Figure 4 **Initial Scope: Priority Pathogens for New Vaccines**

Potential Elements of a Research and Innovation Strategy for Immunization (non-exhaustive)



Because no single, feasible prioritization exercise can address such divergent topics, and because our objective is to elicit the priorities of regional and country stakeholders (rather than R&D experts), PDVAC and SAGE have agreed to focus this prioritization exercise on identifying a "short global list of ***pathogen targets*** for IA2030." This does not mean that other aspects of vaccine R&D are being overlooked. Existing mechanisms such as the Gavi Alliance's Vaccine Innovation Prioritisation Strategy (VIPS)[6] have

identified priority vaccine product innovations, and the Gavi Vaccine Investment Strategy (VIS) may identify licensed vaccines/next-generation vaccines for financing. Going forward, this prioritization platform can also be applied to other aspects of immunization research.

C. Initial Stakeholder Engagement and Interest

Stakeholders representing regional and global bodies were consulted on the overall approach. (Figure 5) For efficiency, these conversations targeted Regional Immunization Technical Advisory Group (RITAG) chairs and global bodies involved in SP7.

Figure 5 Initial Input

African Region	Kwaku Poku Asante, Director, Kintampo Health Research Centre Moredreck Chibi, Regional Advisor for Science and Innovation, WHO Regional Office for Africa (AFRO) Nicaise Ndembi, Senior Science Advisor for the Africa Centers for Disease Control Helen Rees, Executive Director of the Wits Reproductive Health and HIV Institute, University of Witwatersrand, and RITAG Chair, WHO African Region (AFR)
Americas	Peter Figueroa, Professor of Public Health, Epidemiology and HIV/AIDS at the University of the West Indies, Kingston (Jamaica) and RITAG Chair, WHO Region of the Americas (AMR)
South-east Asia	Gagandeep Kang, Professor in the Department of Gastrointestinal Sciences at the Christian Medical College in Vellore, India and RITAG Chair, WHO Region of South-east Asia (SEAR)
Western Pacific	Chris Morgan, RITAG Chair, WHO Region of the Western Pacific (WPR)
Global	SAGE Members in attendance at the April 2023 SAGE breakfast meeting Mark Jit, Professor and Head of Department, London School of Hygiene and Tropical Medicine David Kaslow, Chief Scientific Officer, PATH, and Co-chair of the IA2030 SP7 Working Group

These stakeholders agreed with the need for a stronger regional partnership for prioritization, shared resources, and gave advice. Key observations included:

- A regional approach could help to focus research and investments to address unmet needs, ultimately enhancing equity and health security in a way that is tailored to the needs of each region.

- Regional priorities can inform efforts to build regional research institutes and vaccine manufacturing capacity.
- Health impact and social/economic impact are among the most important factors for prioritization.
- Pair-wise ranking is a good approach to identifying priorities, and it would be good to involve disease experts as well as experts in particular pathogens.
- Priority setting efforts have not sufficiently addressed animal-specific pathogens (relating to the One Health approach[7]) or the effects of climate change.
- Regional and country stakeholders have their hands full restoring vaccine coverage in the wake of COVID-19 but will support this effort as best as they can.

These exploratory discussions have found keen interest in some regions, but very limited ability in any region to engage substantively in this effort, as yet. As a result, it may be necessary to develop this mechanism in partnership with 2 or 3 regions, and then expand it to additional regions after it has matured.

D. Landscape Review

A landscape review was conducted to address these questions:

- **Existing priorities**. Which countries and regional organizations have described their vaccine R&D priorities? What global priorities have been highlighted?
- **Prioritization Methods.** What approaches to priority-setting have been used by others? What should we use?
- **Pathogens.** Which pathogens could be included in the prioritization exercise?
- **Stakeholders.** Who should be involved? How?

1. Landscape of R&D Priorities

The review of existing priorities was conducted through searches of PubMed, the WHO Institutional Repository for Information Sharing, the NITAG Resource Center, and the internet. Internet searches included keyword searches using terms such as “national health research strategy”, as well as site-specific searches on websites for national agencies for health research. Funder priorities focused on major funders of R&D for neglected diseases in 2021.[8] Their priorities were identified through targeted internet searches on donor websites. Searches were conducted in English. While this was a limitation in researching country priorities, it was not a barrier for regional priorities.

This review was supplemented with national immunization strategies submitted in the annual electronic Joint Reporting Form (eJRF) process. Starting in 2022, the eJRF has included a question relating to IA2030 Indicator 7.1 that asked countries for their national agendas for research on immunization. In addition, resources shared by stakeholders were included in the review.

The landscape review showed that regional priorities for research and innovation, as stated in IA2030 or GVAP-related strategic plans, most commonly focus on implementation and operational research, and other research to support decision-making and maximize the benefits of vaccines or efficiency of vaccination programs. Specific vaccine R&D priorities are less commonly stated at a regional level, but some regional organizations and many countries and funding bodies have stated specific vaccine R&D objectives. Vaccine R&D is often discussed more generally in the context of preparedness for emerging infectious diseases (EIDs) or to address antimicrobial resistance (AMR). In low- and middle-income countries, these objectives often focus on building clinical trial or manufacturing capacity, including manufacturing capacity for COVID-19 vaccines.

Figure 6 summarizes the results of the review. Details, including links to key documents, are given in Annex III.A. Priority diseases and pathogens identified through this review were incorporated in the pathogen list described in Section I.A.1 and criteria used for prioritization were incorporated as discussed in Section E.4.

Figure 6 Overview of Existing Priority Setting by Region/Stakeholder

Global bodies	➢ Priority setting has been used to increase attention to specific health topics, including emerging infectious diseases, neglected tropical diseases, sexually transmitted infections, and antimicrobial resistance. ➢ Prioritization methods typically include expert consultations and may be informed by stakeholder surveys.
Funding bodies	➢ Few funders in this area are transparent about how they set priorities. ➢ When priorities are not stated, they can be inferred to some degree from investment portfolios.
African Region	➢ Strong support for evidence-based priority setting and capacity building for research and vaccine manufacture, including by the Partnership for African Vaccine Manufacturing. ➢ Systematic priority setting has focused on vaccine introductions or on research questions. A few countries prioritize aspects of vaccine R&D (such as clinical trials), but generally do not give specific pathogen targets other than HIV, TB, and malaria.

Americas	➢ Priorities for vaccine R&D have not been established regionally, instead emphasis is on evidence for decision-making and improving delivery of existing vaccines ➢ Some countries have set clear priorities for vaccine R&D.
Eastern Mediterranean	➢ Research priorities focus on ways to improve delivery of existing vaccines, including in emergency contexts, not on R&D needs or capacity ➢ While some countries have defined health research priorities, R&D priorities were not found. ➢ Strong emphasis on systematic prioritization of health issues and on capacity building for evidence-informed policy making.
Europe	➢ Research and innovation priorities include evaluating vaccines and/or innovative technologies, as well as operational, implementation, and formative research. ➢ Strong support for national and regional priority setting.
South-east Asia	➢ Although clinical development is very active in South-east Asia, regional research priorities focus on evidence for implementation. ➢ While priorities have not been established systematically at a regional level, some agencies and organizations at the country level have described their priorities for vaccine R&D.
Western Pacific	➢ *Regional Strategic Framework for Vaccine-preventable Diseases and Immunization* highlights many vaccine research priorities, including R&D on new vaccines, improvements to existing vaccines, and delivery innovations ➢ Strong regional emphasis on emerging infectious and zoonotic diseases and the need to address antimicrobial resistance.

2. Landscape of Prioritization Methods

Methods used to set R&D priorities in health have included expert consultations,[9] expert surveys,[10] single-criterion analysis,[11] and multi-criteria decision analysis (MCDA).[12,13]

MCDA has been used in many ways.[14] The most relevant examples include the Institute of Medicine's Strategic Multi-attribute Ranking Tool (SMART) for Vaccines MCDA tool,[15] which ranks vaccines for development based on user-entered data. The R&D Blueprint has used MCDA as part of a consultative process to prioritize emerging infectious diseases.[12] The Coalition for Epidemic Preparedness Innovations (CEPI) has used MCDA to compare vaccine development proposals.[16] CEPI chose MCDA in order to support decision making in the context of multiple trade-offs and diverse stakeholder perspectives. The WHO Pathogens Priority List Working Group used the "PAPRIKA", or "Potentially All Pairwise Rankings of All Possible Alternatives"[17] MCDA tool to prioritize antibiotic-resistant bacteria for

R&D.[13] PAPRIKA been endorsed by WHO's Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) for use in this prioritization.

Looking beyond priority setting for R&D, there is substantial literature on prioritizing among research questions, rather than R&D investments. This literature includes guidance on best practices[5,18] and abundant case studies in priority setting. Many of the best practices from research prioritization are applicable to R&D priorities. These include the importance of understanding the political context, inclusiveness in deciding who needs to be involved, designing a method that matches the context, and planning for implementation.

In particular, *A Systematic Approach for Undertaking a Research Priority-setting Exercise: Guidance for WHO Staff* notes, "Fair involvement of stakeholders is important. Priority-setting exercises should strive for appropriate representation of different areas of expertise and for balanced gender, ethnic and regional participation. In prioritization exercises for country-level research, stakeholders' involvement in the process ensures legitimacy and fosters the integration of research priorities into the current health system planning cycle and infrastructure in countries."[5]

3. Pathogen Landscape

The initial list of pathogens emerged from the landscape of existing priorities identified in the published and gray literature. These included pathogens prioritized for vaccine R&D, or for research or surveillance. To give a comprehensive picture, pathogens that have already been identified as global priorities through other processes, such as the R&D Blueprint,[19] were not excluded from the list. Additional pathogens were identified by searching for vaccine trials on ClinicalTrials.gov[a] and the International Clinical Trials Registry Platform,[b] and from Health Topics on the WHO website,[20] an analysis of investments in global health research,[21] and Wikipedia.[22]

This search resulted in a list of over 150 pathogens, as shown in Annex III.B. In this list, antibiotic resistance was not considered separately: for example, *Neisseria gonorrhoeae* would include cephalosporin and fluoroquinolone-resistant strains as well as susceptible strains. When divergent

[a] Search conducted on June 6, 2022 using the keyword "vaccine", and limited to phase 1, 2, and 3 trials. 7343 trials found.

[b] Search conducted on June 8, 2022 using the keyword "vaccine", and limited to phase 1, 2, and 3 trials. 6718 trials found.

product profiles apply to a single pathogen, such as seasonal and broadly protective influenza vaccines, or TB vaccines for adults and adolescents, rather than infants, they were captured separately.

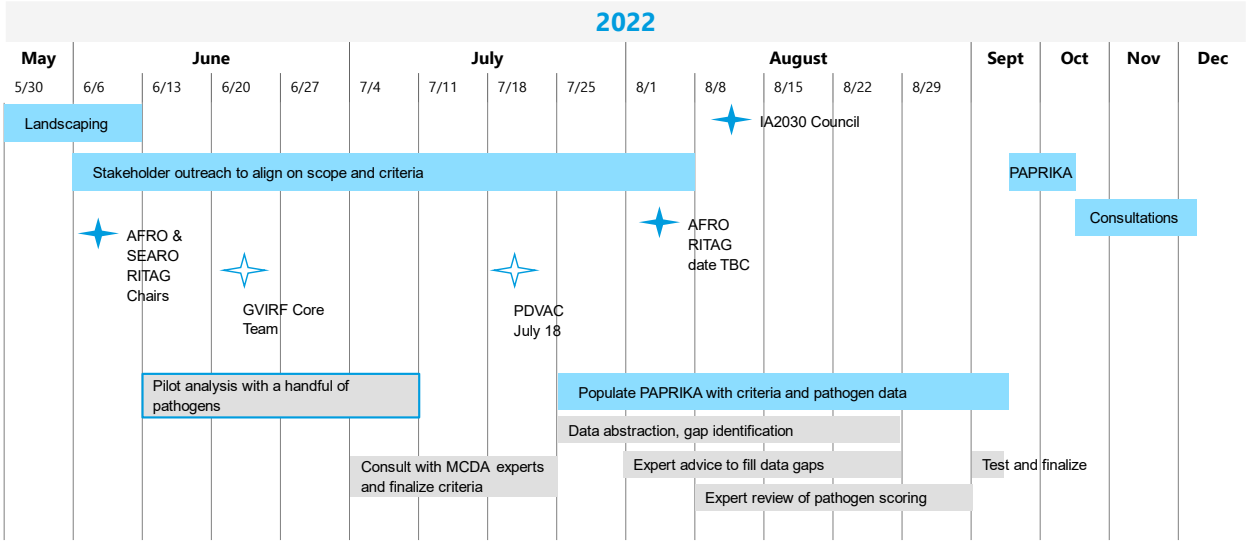
Because it is not feasible to include all potential pathogen targets in the prioritization exercise, this list was filtered to focus on a more manageable number of the most relevant targets as discussed in Section E.2.

E. Proposal for a Priority-setting Mechanism

As discussed with SAGE, priorities will be defined through a consensus-building process with regional and country stakeholders using the PAPRIKA tool to support discussions. Figure 7 gives a detailed view of the next steps in implementing the PAPRIKA tool and engaging with stakeholders to build awareness, ensure buy-in, and set the stage for implementation.

The PAPRIKA tool will be developed in two stages. An initial pilot will be conducted with a small number of pathogens. The pilot tool will be used in stakeholder meetings to build awareness and refine the approach. Based on stakeholder feedback and advice from experts in MCDA, a final tool will be developed and used for the prioritization exercise. See Section 5 for a description of the PAPRIKA pilot.

Figure 7 Detailed Timeline



1. Stakeholder Engagement

Appropriate stakeholder engagement will be essential to ensure the relevance and legitimacy of the prioritization exercise.[18] Proposed roles are shown in Figure 8, and will be refined through consultation with regional and global policy makers.

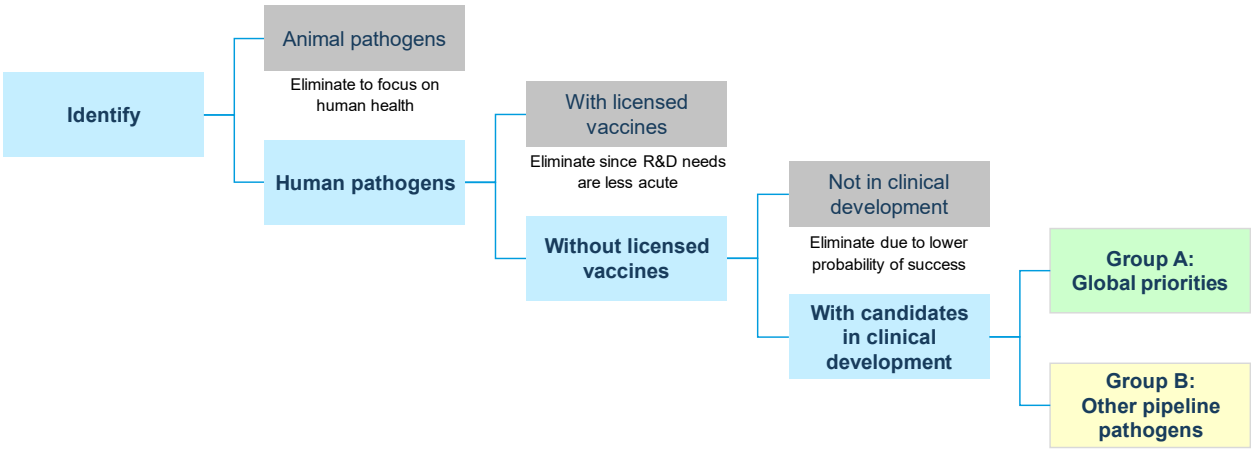
RITAGs are proposed as the principal mechanism for engaging with regional and country stakeholders. In this model, RITAG members will be asked to give feedback on the prioritization methods and to advise on how to incorporate perspectives of country-level stakeholders. They will also help to organize regional consultations on final priority lists. Discussion is underway with the Chairs of the AFRO and SEARO RITAGs, and additional RITAGs will be included progressively as they have availability.

Figure 8 Proposed Stakeholder Roles

2. Pathogens to Include in Prioritization

A series of filters were applied to the pathogen list to reduce it to a more manageable number, as shown in Figure 9.

Figure 9 Pathogen Filtering Scheme



1. **Focus on humans**. In order to focus on human health, 18 exclusively non-human pathogens without significant zoonotic outbreak potential, such as brucellosis, were excluded. (Zoonotic pathogens were retained on the list.)
2. **Omit pathogens with licensed vaccines**. To focus on new vaccine R&D, 40 pathogens for which vaccines have been licensed were omitted. In many cases, next-generation vaccines are already in development for these pathogens. Licensure was defined as approval by a national regulatory authority operating at maturity level 3 (ML3) or maturity level 4 (ML4) for vaccines,[23] or by a national regulatory authority on the list of transitional WHO-listed Authorities where vaccines are included in the scope of products.[24] For adenovirus and leptospirosis, the licensed vaccines are available only to the military or high-risk individuals. These pathogens were retained on the list. Pathogens for which currently licensed vaccines do not fulfill critical target product attributes were retained on the list. These included as dengue, influenza, malaria, and tuberculosis.
3. **Omit pathogens without candidates in clinical development**. To limit the scope to pathogens where prioritization would have the greatest potential influence, 27 pathogens for which no vaccine candidates were identified in clinical development were excluded. In some instances, vaccines are not needed for these pathogens due to the availability of effective alternatives for prevention and treatment, or it may be that development of a vaccine is not considered to be

technically feasible. One pathogen without products in clinical development, *Haemophilus influenzae* type A, was retained because it is a priority for vaccine development under the *Defeating Meningitis Roadmap*.[25]

The resulting filtered list consists of 65 pathogens. (Figure 10) Of these, **35 pathogens have been identified as priorities through global mechanisms such as the WHO R&D Blueprint, PDVAC, or global disease control strategies.** (These are referred to as Group A.) The remaining 30 have vaccines in clinical development but have not been identified as global priorities (Group B).

Based on this analysis, we propose to:

- **Include Group A pathogens in the initial scope of the prioritization**, since these pathogens will be most feasible in terms of data availability.
- **Give regional and country stakeholders an opportunity to add more pathogens**, in case this list omits pathogens of more local importance
- **Drop pathogens that are found to have insufficient data for prioritization**

Alternatively, we could:

- **Include pathogens with VVP in the initial scope of the prioritization**, since these pathogens will be most feasible in terms of data availability. The list of pathogens for VVP development was identified in discussions between WHO, Gavi, and other stakeholders.
- **Add selected pathogens based on advice from PDVAC.** For example, broadly protective SARS-CoV-2 could be added to the list.
- **Give regional and country stakeholders an opportunity to add more pathogens**, in case this list omits pathogens of more local importance

Figure 10 **Proposed Pathogen Scope – to be finalised in Regional Consultations**

Group A – Focus of Prioritization			Group B – Potential Additional Pathogens (Other pipeline pathogens)		
Vaccine Value Profiles	**CEPI / Blueprint Priorities**	**Other roadmaps**			
• Chikungunya • Cytomegalovirus • ***Enterotoxigenic E. coli*** • ***Neisseria gonorrhoeae**** • Group A streptococcus* • Group B streptococcus* • **HIV-1** • **Hookworm** • HSV 1 and 2 • **Influenza** (cross-protective) • **Leishmania** • **Norovirus** • ***Mycobacterium tuberculosis**** (beyond infancy) • **Respiratory syncytial virus** • ***Salmonella*, non-typhoidal*** • ***Salmonella paratyphi**** • **Schistosomiasis** • ***Shigella****	• Crimean-Congo hemorrhagic fever virus • Lassa fever virus • Marburg virus • MERS-CoV • Nipah virus • Rift Valley fever virus • SARS-CoV-1 • SARS-CoV-2 (broadly protective) • **Zika virus**	• **Dengue** (for naïve individuals) • *Haemophilus influenzae* type A • *Klebsiella pneumoniae** • Leprosy • *Neisseria meningitidis* serogroup X • *Pseudomonas aeruginosa** • *Staphylococcus aureus** • Uropathogenic and other extra-intestinal pathogenic *E. coli* (UPEC and ExPEC)	• *Borrelia burgdorferi* (Lyme disease) • Campylobacter • *Candida* spp • *Chlamydia trachomatitis* (chlamydia and trachoma) • *Clostridium botulinum* • Clostridium difficile • Coccidioides (Valley fever/ coccidioidomycosis) • Coxsackievirus Group B • Epstein-Barr virus	• Equine Encephalitis (includes Eastern, Venezuelan, and Western) • *Francisella tularensis* (tularemia) • *Haemophilus influenzae* non-typeable • Hanta viruses (including Hantaan and Puumala) • Helicobacter pylori • Henipavirus • Hepatitis C • Hepatitis E • Human metapneumovirus • Human parainfluenza virus type 1 • Human parainfluenza virus type 2 • Human parainfluenza virus type 3	• Leptospirosis (broad protection) • *Listeria monocytogenes* • Monkeypox virus • *Mycobacterium avium* subspecies paratuberculosis • Parvovirus (Fifth's disease) • *Plasmodium vivax* • Ross River Virus • West Nile Virus • Yersinia pestis (plague)

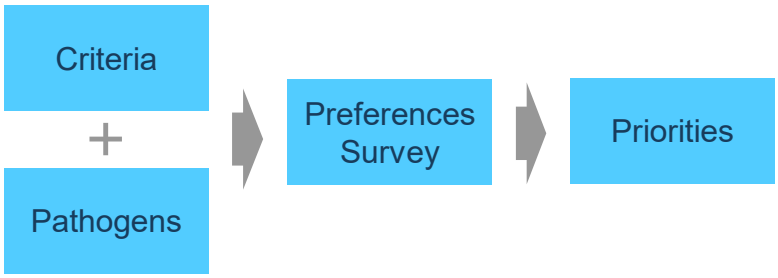
Bold = IHME burden data available
***** = IHME AMR data available

3. Multi-criteria Decision Analysis (MCDA)

Figure 11 gives an overview of MCDA. Rather than ranking alternatives directly, decision-makers define their criteria for prioritization and then decide on the relative importance, or "weight", of each criterion. Finally, those weights are used to rank the alternatives.

The PAPRIKA MCDA tool simplifies and streamlines the weighting process by asking decision-makers to choose between pairs of hypothetical pathogens. An example question might be, "Which is more important, a pathogen with low mortality and very high contribution to inequity, or a pathogen with moderate mortality and low contribution to inequity?" Based on their choices, the method ranks criteria in order of importance. Because the PAPRIKA Preferences Survey asks users to choose between pairs of alternatives, it can be used by non-experts.

Figure 11 **Multi-criteria Decision Analysis**



Criteria, Levels, and **Thresholds**	Criteria: Qualitative or quantitative attributes by which the pathogens are evaluated and compared. For example, criteria could include mortality burden or contribution to inequity. Criteria definitions include Levels and Thresholds. Levels: To simplify decision-making, decision-makers will compare pathogens in terms of *Levels*, rather than numeric values. For example, a pathogen may be described as having Very low, Low, Medium, High, or Very high mortality burden. Thresholds: Qualitative or quantitative definitions used to distinguish between the different levels. For example, a pathogen with less than a certain number of global deaths per year may be deemed to have very low mortality burden.
Pathogens	The alternatives that are to be prioritized—in this case, pathogens for vaccine development
Preferences Survey	A tool that enables Decision-makers to assign Weights to each criterion.
Decision-makers	The stakeholders whose preferences are to be captured using the PAPRIKA prioritization tool.
Weights	Numeric results that reflect the relative importance of each criterion to a decision-maker or group of decision-makers.

4. Criteria for Prioritization

Criteria for prioritization were developed in 5 steps:

1. A broad list of potential criteria was compiled through the literature search.
2. Criteria that are not consistent with best practices were eliminated.
3. Criteria for prioritization were proposed. Additional vaccine-related attributes were identified to be used descriptively.
4. For all criteria, initial definitions of levels and thresholds (as explained in Figure 13) were developed.
5. Invalid combinations of levels were excluded.

a) Compiling a list of potential criteria

Criteria were compiled from the literature review as discussed above, and included criteria used to set research priorities as well as R&D priorities by other stakeholders. In addition, criteria used to set priorities for vaccine introduction were included, since they are relevant to the adoption of new vaccines.[26] Attributes described in VVPs were also included, since they have been identified by PDVAC as relevant to vaccine R&D decision making.

b) Eliminating criteria not consistent with best practices

According to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommendations,[27] criteria used for MCDA should be:

- **Complete**. The criteria should capture all factors relevant to the decision.
- **Non-redundant**. Criteria that do not help discriminate between alternatives should be removed.
- **Non-overlapping**. Criteria should measure separate attributes. Ones that overlap other criteria should be removed to avoid double-counting.
- **Preference-independent**. Criteria should be independent of one another. Criteria that interact can be combined into a composite criterion.

Several criteria were eliminated based on these recommendations, as shown in Annex III.C.

c) Proposing pathogen-related criteria

Nine criteria are proposed, as shown in Figure 12. These criteria take into consideration the data likely to be available for the pathogens within the scope of the prioritization exercise.

Figure 12 Proposed Criteria – to be finalised before survey launch

Proposed Criteria	Type and Definition
1. Annual deaths in children under 5	Quantitative Deaths attributable to the pathogen in both sexes, < 5 years old Data will be stratified by region
2. Annual deaths in people older than 5	Quantitative Deaths attributable to the pathogen in both sexes, ≥ 5 years old Data will be stratified by region
3. Annual DALYs	Quantitative Disability-adjusted life years (DALYs) lost due to ill-health, disability or premature mortality, in all ages. Data will be stratified by region
4. Morbidity	Qualitative Reflects individual impact other than deaths.
5. Economic burden	Qualitative Reflects costs of prevention, health care, and lost productivity. Data will be stratified by region to the extent possible.
6. Contribution to inequity	Qualitative Reflects disproportionate impact on socially and economically disadvantaged groups, including women Data will be stratified by region to the extent possible.
7. Contribution to antimicrobial resistance	Qualitative Reflects the threat of resistance, based on current levels of resistance, contribution to antibiotic use, and designation as an AMR priority
8. Health security threat	Qualitative Reflects threat of causing emergencies or outbreaks, or designation as a priority pathogen by the R&D Blueprint Criteria were adapted from those used by the R&D Blueprint[28]
9. Current alternatives for prevention and treatment	Qualitative Reflects the effectiveness of and access to prevention and treatment

Vaccine-related attributes, such as "Probability of technical and regulatory success," are highly dependent on specific technology choices and the R&D and implementation context, so it is not feasible to include them as criteria for prioritization. That said, they are important considerations for R&D investments. Therefore, vaccine-related information will be used descriptively in displaying the results of the prioritization exercise and to inform next steps.

Figure 13 Vaccine-related Attributes

Vaccine Attribute	Type and Definition
Probability of technical and regulatory success	Qualitative Reflects key factors relating to biological and product development feasibility. Definition is based on framework developed for VVPs.
Access and implementation feasibility	Qualitative Reflects availability of licensure and policy pathways and of financing mechanisms, compatibility with existing delivery systems, and public perceptions Definition is based on framework developed for VVPs.
Public health priority	Qualitative Reflects the availability of strategic and technical guidance for product development, funding for research, existence of partnerships to coordinate R&D, and awareness in the public health community

d) Initial definitions of levels and thresholds

According to ISPOR recommendations, criteria should be unambiguous, comprehensive (covering the full range of possible consequences), direct (relating to fundamental objectives rather than proxy outcomes), operational (the information required are available and it is possible to make value trade-offs), and understandable.[27] Proposed levels and thresholds developed according to these recommendations are shown in Figure 14 and Figure 15.

- **Quantitative criteria**: Thresholds will be defined based on the distribution of actual data for all pathogens.
- **Qualitative criteria**: Threshold definitions were informed by the literature search. These are intended as a guide for distinguishing between levels. Because qualitative levels are inherently subjective, the levels assigned to each of the pathogens should be reviewed by disease experts to ensure they are consistent across pathogens and reflect the best available data.

These levels and thresholds will be refined through advice from experts in MCDA and based on feedback on the PAPRIKA pilot. Two key issues need to be addressed:

- **Stratification by region**. While decision makers are likely to prefer data specific to their own region, global data provide important context. Moreover, for many criteria, stratification by WHO region may be difficult because data are sparse in some settings or analyzed using other country groupings, such as income classification. The initial approach, to be refined with expert advice and stakeholder feedback, will be to use region-specific data and thresholds to the extent possible within existing data.
- **Subjectivity of qualitative criteria**. The qualitative criteria could be defined more consistently through use of specific definitions and a scoring system in place of subjective terms such as "mild", "severe", "sometimes", or "frequently." Such scoring systems, which are commonly used to create composite indicators, could increase the transparency and consistency of the prioritization method but would require additional effort to establish.

Quality of evidence was not included in these definitions to be unambiguous and because including both level of evidence and the magnitude of the effect in a definition has been found to create methodological challenges.[29] However, evidence is insufficient for many pathogens in the scope of this exercise, contributing to uncertainties in priority setting. Instead of including uncertainty in the definitions of the criteria, we propose to document the data gaps, supplement available data with expert opinion, transparently report how expert opinions was incorporated, and conduct a sensitivity analysis to understand the impact of these uncertainties.

Figure 14 Proposed Criteria Levels and Threshold Definitions – to be finalised before survey launch

Proposed Criteria	Level	Threshold Definitions
1. Annual deaths in children under 5	Very high	Regionally specific thresholds will be set based on pathogen data.
	High	
	Medium	
	Low	
	Very low	
2. Annual deaths in people older than 5	Very high	Regionally specific thresholds will be set based on pathogen data.
	High	
	Medium	
	Low	
	Very low	

Proposed Criteria	Level	Threshold Definitions
3. Annual DALYs in people of all ages	Very high	Regionally specific thresholds will be set based on pathogen data.
	High	
	Medium	
	Low	
	Very low	
4. Morbidity	Very high	Infection ***frequently*** causes ***serious*** negative impacts on the lives of survivors.
	High	Infection ***sometimes*** causes ***serious*** negative impacts on the lives of survivors.
	Medium	Infection ***sometimes*** causes ***moderate*** negative impacts on the lives of survivors.
	Low	Infection ***sometimes*** causes ***mild*** negative impacts on survivors.
	Very low	Infection ***rarely*** causes ***any*** negative impact on survivors.
5. Economic burden	Very high	The pathogen causes a ***very high*** economic burden, including through the costs of prevention, health care, and lost productivity.
	High	The pathogen causes a ***high*** economic burden, including through the costs of prevention, health care, and lost productivity.
	Medium	The pathogen causes a ***medium*** economic burden, including through the costs of prevention, health care, and lost productivity.
	Low	The pathogen causes a ***low*** economic burden, including through the costs of prevention, health care, and lost productivity.
	Very low	The pathogen causes a ***very low*** economic burden, including through the costs of prevention, health care, and lost productivity.
6. Contribution to inequity	Very high	The pathogen affects socially and economically ***disadvantaged*** groups, including women, ***all or most*** of the time.
	High	The pathogen affects socially and economically ***disadvantaged*** groups, including women, ***much more often*** than other groups.

Proposed Criteria	Level	Threshold Definitions
	Medium	The pathogen affects socially and economically ***disadvantaged*** groups, including women, ***somewhat more often*** than other groups.
	Low	The pathogen affects all communities equally.
	Very low	The pathogen affects socially and economically ***privileged*** groups, including men, ***all or most*** of the time.
7. Contribution to antimicrobial resistance	Very high	The pathogen has been highlighted as a ***global*** priority for AMR,[30] or A high proportion of ***global*** isolates is resistant to first-line antimicrobial drugs
	High	The pathogen has been highlighted as a ***regional*** priority for AMR, or A high proportion of ***regional*** isolates is resistant to first-line antimicrobial drugs
	Medium	The pathogen has been highlighted as a ***country*** priority for AMR, or A ***moderate*** proportion of regional isolates is resistant to first-line antimicrobial drugs, or ***High*** antibiotic use is associated with infection by the pathogen
	Low	The pathogen has ***not*** been highlighted as a priority for AMR, and A ***low*** proportion of regional isolates is resistant to first-line antimicrobial drugs, and ***Moderate or low*** antibiotic use is associated with infection by the pathogen
	Very low	The pathogen has ***not*** been highlighted as a priority for AMR, and Very few global isolates are resistant to first-line antimicrobial drugs, and ***Low*** antibiotic use is associated with infection by the pathogen
8. Health security threat	Very high	The pathogen has been highlighted as a priority by the *WHO R&D Blueprint*

Proposed Criteria	Level	Threshold Definitions
	High	The pathogen poses a ***high*** threat of causing emergencies or outbreaks due to patterns of transmission, severity, societal impact, need for specialist surveillance or intervention.
	Medium	The pathogen poses a ***medium*** threat of causing emergencies or outbreaks due to patterns of transmission, severity, societal impact, need for specialist surveillance or intervention.
	Low	The pathogen poses a ***low*** threat of causing emergencies or outbreaks due to patterns of transmission, severity, societal impact, need for specialist surveillance or intervention.
	Very low	The pathogen poses a ***very low*** threat of causing emergencies or outbreaks due to patterns of transmission, severity, societal impact, need for specialist surveillance or intervention.
9. Current alternatives for prevention and treatment	Very high	Preventive or treatment interventions are ***highly effective*** in controlling a pathogen and are ***accessible*** to those in need.
	High	Preventive or treatment interventions are ***highly effective*** in controlling a pathogen, but are ***not always accessible*** to those in need.
	Medium	Preventive or treatment interventions are ***moderately effective*** in controlling a pathogen ***OR*** they are ***not always accessible*** to those in need.
	Low	Preventive or treatment interventions are ***moderately effective*** in controlling a pathogen ***OR*** they are ***seldom*** accessible to those in need.
	Very low	Effective preventive or treatment interventions do not exist.

Figure 15 Proposed Levels and Threshold Definitions for Vaccine-related Attributes

Attribute	Level	Typical Characteristics
Probability of technical and regulatory success	Very high	Phase 3 candidate with high likelihood of licensure by a WHO-listed national regulatory authority Well established that natural exposure confers protects against severe disease with durable immunity Strong evidence that a vaccine will protect against all relevant strains Necessary animal models, in vitro assays, and diagnostic tools are fit-for-purpose for decision-making and licensure Efficacy trial is feasible or human challenge models are available and widely accepted
	High	Phase 3 candidate Good evidence of relatively long-lasting immunity Strong evidence that a vaccine would protect against majority of pathogenic strains Necessary animal models, in vitro assays, and diagnostic tools are available but their fit for purpose has not been established Efficacy trial is feasible or human challenge models are developed but their use is limited
	Medium	Phase 2 candidate Some evidence and/or immunity of limited duration Some evidence that a vaccine would protect against majority of pathogenic strains Necessary animal models, in vitro assays, and diagnostic tools are available but their utility has not been established Efficacy trial is feasible with investment in clinical infrastructure, human challenge models are in development

Attribute	Level	Typical Characteristics
	Low	Phase 1 candidate Conflicting or minimum evidence of relatively long-lasting immunity Limited evidence that a vaccine would protect against majority of pathogenic strains Necessary animal models, in vitro assays, and diagnostic tools do not exist Large and/or long efficacy trial required, human challenge models are in early development
	Very low	Preclinical or no candidates in the pipeline No evidence that natural exposure confers immunity Evidence that a vaccine would not protect against majority of pathogenic strains Necessary animal models, in vitro assays, and diagnostic tools do not exist and no progress has been made to develop them Complex trial design or low disease incidence impedes efficacy trial, human challenge models are not in development
Access and implementation feasibility	Very high	A clear, highly precedented, fit-for-purpose licensure and policy pathway currently exists Advanced purchasing commitment from, for example Gavi, PAHO RF, or other pull mechanism(s) in place Vaccine can be delivered within existing delivery systems as-is Well-defined target population with likelihood of high acceptability Lack of other significant barriers to introduce a vaccine Strong national commitment to introduce a vaccine
	High	A clear licensure and policy pathway with minor amendments High level of interest expressed from public financing agencies such as Gavi, PAHO RF, and from national procurement agencies" Vaccine can be delivered within existing delivery systems with amendments

Attribute	Level	Typical Characteristics
		Well defined target population with likelihood of high acceptability, but possible difficulties in infrastructure for vaccination
	Medium	A possibility to leverage an existing licensure and policy pathway with major amendments Potential interest from global funders, depending on public health impact data, interest from national procurement agencies Limited use of existing delivery systems to deliver a vaccine New vaccination touchpoint required
	Low	A need for novel licensure and/or policy pathway Unlikely to be of interest to global funders, requiring commitment from national procurement Some evidence that existing delivery systems could be leveraged to deliver a vaccine Evidence of low uptake for marketed vaccines Cultural barriers, negative patient perceptions
	Very low	A need for novel licensure and/or policy pathway, which is currently unclear No interest from global funders or national procurement agencies, potential for private market No possibility to leverage existing delivery systems due to a complex vaccine immunisation schedule. Extensive challenges with a new vaccination touchpoint required High level of clinician judgement and clinical engagement Additional extensive barriers to uptake including lack of national commitment
Public health priority	Very high	Existence of a ***strategic roadmap*** or technical guidance for vaccine development, AND ***Robust*** funding for R&D, AND Existence of ***partnerships*** to support and coordinate R&D.
	High	Existence of a ***strategic roadmap*** or technical guidance for vaccine development, AND

Attribute	Level	Typical Characteristics
		Adequate funding for R&D, AND Existence of ***partnerships*** to support and coordinate R&D.
	Medium	Existence of a ***strategic roadmap*** or technical guidance for vaccine development, OR ***Moderate*** funding for R&D, OR Existence of ***partnerships*** to support and coordinate R&D.
	Low	***Low*** public awareness in public health community and ***Limited funding*** for research.
	Very low	***Very low*** awareness in public health community and ***Declining or no funding*** for research.

e) Excluding invalid combinations

Some combinations of levels are not plausible. For example, a pathogen could not cause a **Very low** number of DALY's while causing **Very high** number of deaths, since higher deaths would lead to higher DALYs. Figure 16 lists the invalid combinations. To minimize the number of choices and avoid confusion, these combinations will be excluded from the MCDA exercise.

Figure 16 Invalid combinations

These attributes…	cannot coexist with these attributes…	because…
Annual deaths in children under 5: **High or Very high**	Annual DALYs in people of all ages: **Low or Very low**	High deaths would lead to higher DALYs
	Health security threat: **Very high**	High deaths would mean that the threat has materialized
Annual deaths in people older than 5: **High or Very high**	Annual DALYs in people of all ages: **Low or Very low**	High deaths would lead to higher DALYs
	Health security threat: **Very high**	High deaths would mean that the threat has materialized

These attributes…	cannot coexist with these attributes…	because…
Current alternatives for prevention and treatment: **High or Very high**	Contribution to AMR: **High or Very high**	High AMR would undermine alternatives for treatment
	Health security threat: **Very high**	Alternatives for prevention and treatment would mitigate the threat to health security

5. PAPRIKA Pilot

To examine the feasibility of the proposed prioritization approach, the WHO Secretariat has developed a prioritization pilot to be tested and reviewed by immunization stakeholders. Five pathogens were included in the pilot: enterotoxigenic *Escherichia coli* (ETEC), invasive non-typhoidal *Salmonella* (iNTS), norovirus, respiratory syncytial virus (RSV), and *Shigella*.

Data for each pathogen were drawn from the VVPs and supplemented by health burden data from the Global Burden of Disease study.[31,32] Global data were used for the pilot: in the actual prioritization, region-specific burden data will be used as much as feasible. For the quantitative criteria, thresholds from Very low to Very high were developed by analyzing the distribution of global health burden data from the GBD for all pathogens and developing thresholds that group pathogens with similar values for each criterion. For qualitative criteria we used the definitions shown in Figure 14. For each pathogen/criterion combination, pathogen data were assessed against the of thresholds and scored as shown in Figure 17 and Figure 18. Supporting data for the pathogen scoring are available upon request.

The PAPRIKA pilot will be shared with immunization stakeholders, PDVAC, and MCDA experts to elicit their feedback on the criteria and MCDA tool.

Figure 17 Scoring for Pilot Pathogens – Example, indicative scores

Proposed Criteria	ETEC	iNTS	Norovirus	RSV	Shigella
1. Annual deaths in children under 5	Low 12,400	Medium 49,900	Medium 43,500	Very High 123,800	High 93,800
2. Annual deaths in people older than 5	Low 27,400	Low 29,200	Medium 92,300	High 214,700	Medium 54,400
3. Annual DALYs	Low 1,695,400	Medium 6,114,000	Medium 6,879,400	High 14,965,500	High 10,602,900
4. Morbidity	High	High	Low	High	High
5. Economic burden	Low	Low	Very high	High	Low
6. Contribution to inequity	Very high	Very high	Medium	High	Very high
7. Contribution to antimicrobial resistance	Very high	High	Low	Low	Very high
8. Health security threat	Very low	Low	High	Very low	Low
9. Current alternatives for prevention and treatment	Medium	Medium	Very low	Very low	Medium

Figure 18 Vaccine-related Attributes for Pilot Pathogens – Example, indicative scores

Attribute	ETEC	iNTS	Norovirus	RSV	Shigella
Probability of technical and regulatory success	High	High	Medium	Maternal: High Infant mAb: High Infant vaccine: Medium Elderly: Very high	Pediatric: High Adults: Medium
Access and implementation feasibility	Medium	Medium	Pediatric: High Adults: Low	Maternal: Medium Infant mAbs: High	Medium
Public health priority	Medium	Medium	High	Maternal: Very high Infant mAbs: Very high	High

III. Annexes

A. Landscape of Existing Priorities

The review of existing priorities was conducted through searches of PubMed, the WHO Institutional Repository for Information Sharing, the NITAG Resource Center, and the internet. Internet searches included keyword searches using terms such as "national health research strategy", as well as site-specific searches on websites for national agencies for health research. Country-specific searches focused on countries with domestic vaccine manufacturing capacity or known to be investing in vaccine R&D or manufacturing capacity, and on major funders of vaccine R&D.[33] Funder-specific searches focused on major funders of R&D for neglected diseases in 2021.[8] Their priorities were identified through targeted searches on donor websites. Searches were conducted in English. While this was a limitation in researching country priorities, it was not a barrier for regional priorities.

This review was supplemented with national immunization strategies submitted in the annual electronic Joint Reporting Form (eJRF) process. Starting in 2022, the eJRF has included a question relating to IA2030 Indicator 7.1 that asked countries for their national agendas for research on immunization. In addition, resources shared by stakeholders were included in the review.

1. Global Priorities

- Priority-setting has been used to increase attention to specific health topics and to inform R&D
- Prioritization methods typically include expert consultations and may be informed by stakeholder surveys.

- WHO's *R&D Blueprint for Research and Development in **Emergency Contexts*** currently prioritizes 12 diseases, including COVID-19 and "Disease X", a pathogen currently unknown to cause human disease.(link) Blueprint priorities are updated regularly, and this list is currently under review
- The *Road Map for **Neglected Tropical Diseases** 2021-2030* calls for vaccine R&D for dengue, chikungunya, leishmaniasis, leprosy, and schistosomiasis (link)
- The *WHO Priority List of **Antibiotic-resistant Bacteria and Tuberculosis*** prioritizes pathogens based on AMR threat.(link) An evaluation classified these pathogens as critical, high, or medium priority for vaccine R&D. Seven pathogens were classified as "not currently well suited to vaccine development" (link)
- *Draft global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections 2022-2030* calls for continued efforts in **HIV vaccine** R&D (link)

- **Sexually transmitted infections** prioritized for vaccine development include herpes simplex virus, *C. trachomatis*, gonorrhea and syphilis (link) Among these, experts viewed gonorrhea and syphilis as the highest priorities for vaccine development (link)
- *Defeating Meningitis by 2030: a Global Road Map* calls for R&D of new **group B streptococcus** vaccines and additional vaccines against other causes of **meningitis** (link)
- **PDVAC** has prioritized pathogens for development of technical advice such as preferred product profiles (PPPs), target product profiles (TPPs), and vaccine value propositions (VVPs). To date, WHO has defined TPPs or PPCs for 14 pathogens (link) and value propositions are in preparation for 19 vaccines.
- The *WHO Global **Leprosy** Strategy 2021-2030* calls for research on new vaccines (link)
- The Global Integrated Arboviruses Initiative has been launched to tackle **dengue, yellow fever, chikungunya** and **Zika** virus diseases (link)

2. Funders

- Few funders in this area are transparent about how they set priorities.
- When priorities are not stated, they can be inferred to some degree from investment portfolios.

- Public sector funders have invested in vaccine R&D and related research directly and through public-private partnerships (PPPs), innovation funds, and other mechanisms.(link)
- **Funding agencies** such as the US National Institutes of Health, UK Vaccine Network, and European Commission generally state their priorities without describing the prioritization method or criteria that were considered.(US, UK, EC) One exception is the Government of Canada, which set its vaccine R&D priorities through a 3-stage consultative process.(link)
- Disease priorities can be inferred from funding streams for global health R&D.(link)
- **Public-private partnerships** have varied in their approaches to priority setting in vaccine R&D.
    - **CEPI**, the Coalition for Epidemic Preparedness Innovations, used the *WHO Blueprint* as the basis for its priority pathogen list (link) and prioritizes pathogens through its governance mechanisms.(link) It is currently investing in R&D for broadly protective vaccines for COVID-19. (link)
    - **EDCTP**, the European and Developing Countries Clinical Trials Partnership, has described the criteria they use in setting priorities as well as their priority pathogens.(link)
    - **Gavi, the Vaccine Alliance**, through its Vaccine Innovation Prioritization Strategy (VIPS) has prioritized innovations to facilitate the delivery of existing and new vaccines. The VIPS method consisted of expert consultations informed by landscape analysis and stakeholder surveys.(link) Gavi has taken similar approaches to prioritizing investments in emerging vaccines.(link)
- Private philanthropies such as the **Bill & Melinda Gates Foundation** and **Wellcome** describe their strategies in broad terms, without giving detailed rationales or methods for

prioritization.(BMGF, WT) Their priorities can be inferred from their investment portfolios.(BMGF, WT)

3. African Region

- Strong support for evidence-based priority setting and capacity building for research and vaccine manufacture, including by the Partnership for African Vaccine Manufacturing.(link)
- Systematic priority setting has focused on vaccine introductions or on research questions. A few countries prioritize vaccine R&D, but generally do not give specific pathogen targets other than HIV, TB, and malaria.

a) Context

- *Addis Declaration on Immunization Roadmap* recommends to "expand and invest in Africa-based research, development, and production of vaccines".(link)
- African Union *Africa Health Strategy 2016-2030* calls for research capacity building. (link)
- **Kenya**, **Nigeria**, **Senegal**, and **South Africa** are participating in mRNA vaccine technology transfer.

b) Regional R&D priorities

- *Framework for Implementation of IA2030 in the WHO African Region* notes that priorities for innovation should be identified by member states.(link)
- *Strategic Framework for Research on Immunization (SFRI) in the African Region* describes the innovation ecosystem and recommends priority-setting mechanisms.(link)
- Partnership for African Vaccine Manufacturing (PAVM) has identified priority pathogens or vaccines for capacity building.(link)
- RITAG recommendations include R&D and expanded manufacture for SARS-CoV-2 vaccines and novel OPV, and research relating to other vaccines.

c) National R&D priorities

Note: This search focused on countries with known interests in vaccine manufacturing and/or health research capacity

- **Kenya**'s *National Research Priorities 2018-2022* calls for prioritizing vaccine development.(link)
- **Nigeria**'s *National Strategic Health Development Plan 2018-2022* notes efforts to revamp vaccine production in the country but does not specify R&D priorities.(link)
- **South Africa**'s *National Health Research Strategy 2021-2024* systematically prioritizes research topics, including R&D for specific vaccines.(link)
- **Tanzania** has systematically defined health research priorities and included marginalized groups in priority setting.(link) The NHSP calls for strengthening pharmaceutical manufacturing.(link)

- **Zambia**'s *National Health Research Agenda 2018-2021* calls for vaccine trials to test candidate vaccines for HIV, TB, and malaria.(link)
- National health research agendas in Ghana, Ethiopia, Niger, Senegal and Uganda do not mention vaccine R&D.

4. American Region

➢ Regional priorities for vaccine R&D have not been established, but some countries have defined their vaccine R&D priorities

a) Context

- The **US** is the world's leading national donor to global health R&D, ranking 1st in 2019 funding (link)

b) Regional R&D priorities

- *Reinvigorating Immunization as a Public Good for Universal Health* emphasizes the need for evidence-based decision making (link)
- GVAP Action Plan focuses on implementation of existing vaccines, rather than new vaccine R&D (link)
- RITAG recommendations do not highlight unmet needs for new vaccines

c) National R&D priorities

- **Canada** has systematically identified a set of priorities for R&D for human and animal vaccines (link)
- **US** CDC has defined priority pathogens (link). NIAID is supporting an extensive portfolio of disease-specific vaccines (link)

5. Eastern Mediterranean Region

➢ Regional research priorities focus on ways to improve delivery of existing vaccines, including in emergency contexts

➢ Strong emphasis on systematic prioritization of health issues and on capacity building for evidence-informed policy making

➢ While some countries have defined health research priorities, R&D priorities were not found

a) Context

- **Egypt**, **Pakistan** and the **UAE** have manufactured COVID-19 vaccines through technology transfers. **Morocco** is also building COVID-19 vaccine manufacturing capacity.
- **Egypt**, **Pakistan**, and **Tunisia** are participating in mRNA vaccine technology transfer

b) Regional R&D priorities

- EMRO officials recommend research priority setting (link) and the RITAG has recommended that WHO foster regional prioritization exercises and share outcomes for potential use (link)
- Regional Committee resolution EM/RC55/R.5 establishes a framework for action to improve capacity for evidence-informed policy (link)
- RITAG recommendations focus on introduction of existing vaccines, and generally do not highlight unmet needs for new vaccines (2017, 2020)
- WHO's *Strategy for the Eastern Mediterranean Region, 2020-2023*, discusses research in terms of the evidence base needed for informed health policy-making (link) The Eastern Mediterranean Advisory Committee on Health Research (ACHR) emphasizes the importance of prioritizing health needs as a basis for identifying research priorities (link)
- The regional Network of Institutions for Evidence and Data to Policy (NEDtP) recommends that member states and WHO help to identify priority issues at local, national, and regional levels (link)
- Academic groups defined health research priorities in the region in 2010 and 2021

c) National R&D priorities

- In **Iran**, a multidisciplinary group used the CHNRI method to define health research priorities (link)
- **Jordan** has defined health research priorities relating to health systems, health services, and COVID-19 response using a nominal group technique (link)
- **Pakistan** has defined health research priorities relating to TB, Hepatitis B, typhoid using the CHNRI method (link)

6. European Region

- Strong support for national and regional priority setting
- Investments in vaccine R&D are often channeled through PPPs

a) Context

- The UK, European Union, Germany, France, and Norway are major political donors to global health R&D, ranking 2nd to 6th in 2019 funding (link)

b) Regional R&D priorities

- The European Immunization Agenda 2030 established regional priorities through country surveys and consultations. Research and innovation activities include evaluating vaccines and/or innovative technologies, as well as operational, implementation, and formative research (link)
- ETAGE encourages broad consultations to determine national priorities and develop a regional immunization agenda (link)

c) National R&D priorities

- **Germany**'s Global Health Strategy highlights their investments in partnerships for product development, such as CEPI, and prioritizes AMR (link)
- **Norway**'s funding for vaccine R&D has been channeled through GLOBVAC and CEPI (link)
- **Russian Federation** prioritizes improving national capacity for vaccine manufacture and for related activities such as regulatory oversight and surveillance. R&D priorities relate to increasing access to existing vaccines rather than novel vaccine development (link)
- **Sweden** has systematically prioritized pathogens according to public health relevance, to guide resource allocation (link)

7. South-east Asian Region

- Although clinical development is very active in South-east Asia, regional research priorities focus on evidence for implementation.
- While priorities have not been established systematically at a regional level, some agencies and organizations at the country level have described their priorities for vaccine R&D.

a) Context

- In 2017-2019, India ranked second in global vaccine exports, accounting for 25% of doses traded (link)
- Going beyond technology transfer arrangements, vaccine manufacturers in the region are increasingly advancing the development of novel and next-generation vaccines (link)
- Experts, noting that South Asia lags other regions in research capacity, and have called for capacity building (link, link)
- Stakeholders in **Bangladesh** (link), **Indonesia** (link), and **Thailand** (link) have prioritized among existing vaccines for introduction
- **Bangladesh, India,** and **Indonesia** are participating in mRNA vaccine technology transfer
- **Indonesia**'s national health research agency has recently undergone restructuring to form the National Research and Innovation Agency (link)
- The WHO Collaborating Centre on Clinical and Translational Research for Innovation and Access to Medical Products is based in Haryana, **India**. Its Outputs include "Research and development agenda defined and research coordinated in line with public health priorities" (link)

b) Regional R&D priorities

- In the Regional Vaccine Strategic Framework (RSF, link) and draft Implementation Plan (RVIP, link), the key areas of focus for SP7 relate to evidence for implementation
- SEAR-ITAG recommendations, especially in the context of COVID-19, focus on addressing current priorities rather than R&D for new targets (2019, 2020, 2021)

c) National R&D priorities

- **Bangladesh**'s icddr,b has described its targets for vaccine R&D (link)
- **India**'s Department of Biotechnology (link) and Biotechnology Industry Research Assistance Council (link) have invested in diverse vaccine R&D portfolios
- **Thailand** prioritizes domestic research, manufacture, and distribution of vaccines for the sake of vaccine security and self-reliance (link) Thailand hosts multiple vaccine manufacturers, several of which have also developed and/or manufactured COVID-19 vaccines (link)

8. Western Pacific Region

- Robust and expanding capacity for vaccine R&D and manufacturing, providers of technology transfer for vaccine production in other regions
- *Regional Strategic Framework for Vaccine-preventable Diseases and Immunization* highlights many vaccine research priorities, including R&D on new vaccines, improvements to existing vaccines, and delivery innovations (link)
- Strong regional emphasis on emerging infectious and zoonotic diseases and the need to address antimicrobial resistance.

a) Context

- **Japan**, the **Philippines**, **Singapore, South Korea,** and **Taiwan** are investing in vaccine R&D capacity
- **Vietnam** is participating in mRNA vaccine technology transfer

b) Regional R&D priorities

- RITAG recommendations focus on achieving programmatic goals and new vaccine introductions, and note the importance of expanding R&D for vaccine development and production to strengthen vaccine supply

c) National R&D priorities

- **Japan's** National Plan for AMR includes vaccine R&D, and experts have prioritized research topics to address EIDs
- **Japan** and **South Korea** have laws identifying priority diseases and pathogens for control and prevention
- **Malaysia** has prioritized health research topics
- The **Philippines** uses QALY data to inform priorities in health investments

B. Pathogen Landscape

The initial list of pathogens emerged from the landscape of existing priorities identified in the published and gray literature. These included pathogens prioritized for vaccine R&D, or for research or surveillance. To give a comprehensive picture, pathogens that have already been identified as global

priorities through other processes, such as the R&D Blueprint,[19] were not excluded from the list. Additional pathogens were identified by searching for vaccine trials on ClinicalTrials.gov[a] and the International Clinical Trials Registry Platform,[b] and from Health Topics on the WHO website,[20] an analysis of investments in global health research,[21] and Wikipedia.[22]

In this list, antibiotic resistance was not considered separately: for example, *Neisseria gonorrhoeae* would include cephalosporin and fluoroquinolone-resistant strains as well as susceptible strains. When divergent product profiles apply to a single pathogen, such as seasonal and broadly protective influenza vaccines, or TB vaccines for adults and adolescents, rather than infants, they were captured separately. *Shigella* species were grouped together since current vaccines in development target both *S. flexneri* and *S. sonnei*. Other pathogens were generally considered separately (e.g. *Plasmodium falciparum* and *P. vivax*) except when definitions overlapped (e.g. uropathogenic *E. coli* (UPEC) was grouped with other extra-intestinal pathogenic *E. coli* (ExPEC)) or when data are very sparse (e.g. equine encephalitis viruses were grouped together).

1. Animal pathogens

- Bovine coronavirus
- Bovine respiratory disease
- Brucellosis
- Chronic wasting disease
- Coccidiosis
- Contagious Bovine Pleuropneumonia (CBPP)
- E. coli (cattle)
- Echinococcosis (type not specified)
- Foot-and-mouth disease virus
- Gallid alphaherpesvirus 2 (Marek's disease in chickens)
- Peste des petits ruminants (PPR)
- Porcine epidemic diarrhea virus
- Porcine influenza A
- Staphylococcus aureus (dairy cattle)
- Taenia solium (pork tapeworm)/Cysticercosis
- Theileria parva (East Coast Fever in cattle)
- Tick infestation (animals)
- Toxoplasma gondii

2. Pathogens with licensed vaccines

- Adenovirus
- *Bacillus anthracis*
- *Bordetella pertussis*
- *Clostridium tetani*
- *Corynebacterium diphtheriae* (diphtheria)

[a] Search conducted on June 6, 2022 using the keyword “vaccine”, and limited to phase 1, 2, and 3 trials. 7343 trials found.

[b] Search conducted on June 8, 2022 using the keyword “vaccine”, and limited to phase 1, 2, and 3 trials. 6718 trials found.

- *Coxiella burnetii* (Q fever)
- Dengue virus
- Ebola virus
- Enterovirus 71 (Hand, foot, and mouth disease)
- *Haemophilus influenzae* type B
- Hepatitis A
- Hepatitis B
- Human papillomavirus
- Influenza (avian)
- Influenza (pandemic)
- Influenza (seasonal)
- Japanese encephalitis
- Junin virus
- Measles virus
- Mumps virus
- *Mycobacterium tuberculosis* (BCG for infants)
- *Neisseria meningitidis* serogroup A
- *Neisseria meningitidis* serogroup B
- *Neisseria meningitidis* serogroup C
- *Neisseria meningitidis* serogroup W
- *Neisseria meningitidis* serogroup Y
- *Plasmodium falciparum* (malaria)
- Polio virus (inactivated vaccine)
- Polio virus (oral vaccine)
- Rabies virus
- Rotavirus
- Rubella virus
- *Salmonella Typhi*
- SARS-CoV-2
- Smallpox
- *Streptococcus pneumoniae*
- Tick-borne encephalitis virus
- Varicella zoster virus (chicken pox and shingles)
- *Vibrio cholerae*
- Yellow fever virus

3. Pathogens without vaccines in clinical development

- *Acinetobacter baumannii*
- *Ascaris lumbricoides* (roundworm)
- *Aspergilllus*
- *Burkholderia pseudomallei* (melioidosis)
- *Cryptococcus* spp
- Cryptosporidium
- *Dracunculus medinensis* (Guinea worm)
- *Echinococcus granulosus* (cystic echinococcosis)
- *Echinococcus multilocularis* (alveolar echinococcosis)
- Ehrlichiosis
- *Enterococcus faecium*
- *Enterococcus*, vancomycin-resistant
- Hepatitis D
- Human T-lymphotropic virus type 1
- Lymphatic filariasis
- Mycetoma
- *Mycobacterium ulcerans* (Buruli ulcer)
- *Onchocerca volvulus*
- *Plasmodium falciparum* (malaria)
- *Sarcoptes scabiei* (scabies)
- *Strongyloides stercoralis* (helminth)
- *Treponema pallidum* (syphilis)
- *Treponema pallidum* subspecies pertenue (yaws)
- *Trichomonas vaginalis*
- *Trichuris trichiura* (whipworm)
- *Trypanosoma brucei*
- *Trypanosoma cruzi* (Chagas disease)

4. Global priorities

- Chikungunya virus
- Crimean-Congo haemorrhagic fever
- Cytomegalovirus
- Dengue virus (for dengue-naïve individuals)
- Enterotoxigenic *E. coli* (ETEC)
- *Haemophilus influenzae* type A
- Herpes simplex type 1
- Herpes simplex type 2
- HIV-1
- Hookworm (*Ancylostoma duodenale* and *Necator americanus*)
- Influenza (broadly protective)
- *Klebsiella pneumoniae*
- Lassa fever virus
- *Leishmania* spp
- Marburg virus
- MERS-CoV
- *Mycobacterium leprae*
- *Mycobacterium tuberculosis* (beyond infancy)
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis* serogroup X
- Nipah virus
- Norovirus
- *Pseudomonas aeruginosa*
- Respiratory syncytial virus
- Rift Valley Fever virus
- *Salmonella* (non-typhoidal)
- *Salmonella Paratyphi*
- SARS-CoV-1
- SARS-CoV-2 (broadly protective)
- Schistosomes
- *Shigella* spp
- *Staphylococcus aureus*
- *Streptococcus agalactiae* (group B streptococcus)
- *Streptococcus pyogenes* (group A streptococcus)
- Uropathogenic *E. coli* (UPEC) and other extra-intestinal pathogenic *E. coli* (ExPEC)
- Zika virus

5. Additional pathogens with vaccines in clinical development

- *Borrelia burgdorferi* (Lyme disease)
- Campylobacter
- *Candida* spp
- *Chlamydia trachomatitis* (chlamydia and trachoma)
- *Clostridium botulinum*
- *Clostridium difficile*
- Coccidioides (Valley fever/coccidioidomycosis)
- Coxsackievirus Group B
- Epstein-Barr virus
- Equine Encephalitis (includes Eastern, Venezuelan, and Western)
- *Francisella tularensis* (tularemia)
- *Haemophilus influenzae* non-type B
- Hanta viruses (including Hantaan and Puumala)
- *Helicobacter pylori*
- Henipavirus
- Hepatitis C
- Hepatitis E
- Human metapneumovirus
- Human parainfluenza virus type 1
- Human parainfluenza virus type 2
- Human parainfluenza virus type 3
- Leptospirosis

- *Listeria monocytogenes*
- Monkeypox virus
- *Mycobacterium avium* subspecies paratuberculosis
- Parvovirus (Fifth's disease)
- *Plasmodium vivax*
- Ross River Virus
- West Nile Virus
- *Yersinia pestis* (plague)

C. Criteria not used for prioritization

Figure 19 Redundant or Overlapping Criteria

Excluded Criteria	Rationale
Years of life lost	Non-independent, overlaps with annual deaths and age distribution Not systematically reported across pathogens
Case fatality ratio	Non-independent, overlaps with annual deaths and number of DALYs
Disease incidence	Non-independent, overlaps with annual number of DALYs
Disease incidence rate	Non-independent, overlaps with annual number of DALYs
Annual number of infections	Non-independent, overlaps with annual number of DALYs, not systematically reported
Vaccine-avertable burden	The data varies depending on vaccine attributes and assumptions, difficult to standardise and compare
Cost-effectiveness of the vaccine	The data varies depending on vaccine attributes and assumptions, difficult to standardise and compare
Geographical distribution	Region specific data should will be used to inform criteria, also overlaps with socio-economic status
Gender	Incorporated into “Equity”
Socio-economic status	Incorporated into “Equity”
Alternatives for Prevention	Incorporated into “Prevention and Treatment”
Alternatives for Treatment	Incorporated into “Prevention and Treatment”

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