Full value vaccine assessment

Improved influenza vaccines

World Health Organization

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A health worker administers a vaccine, the Lao People's Democratic Republic © The Partnership for International Vaccine Initiatives/ Emily Cramer

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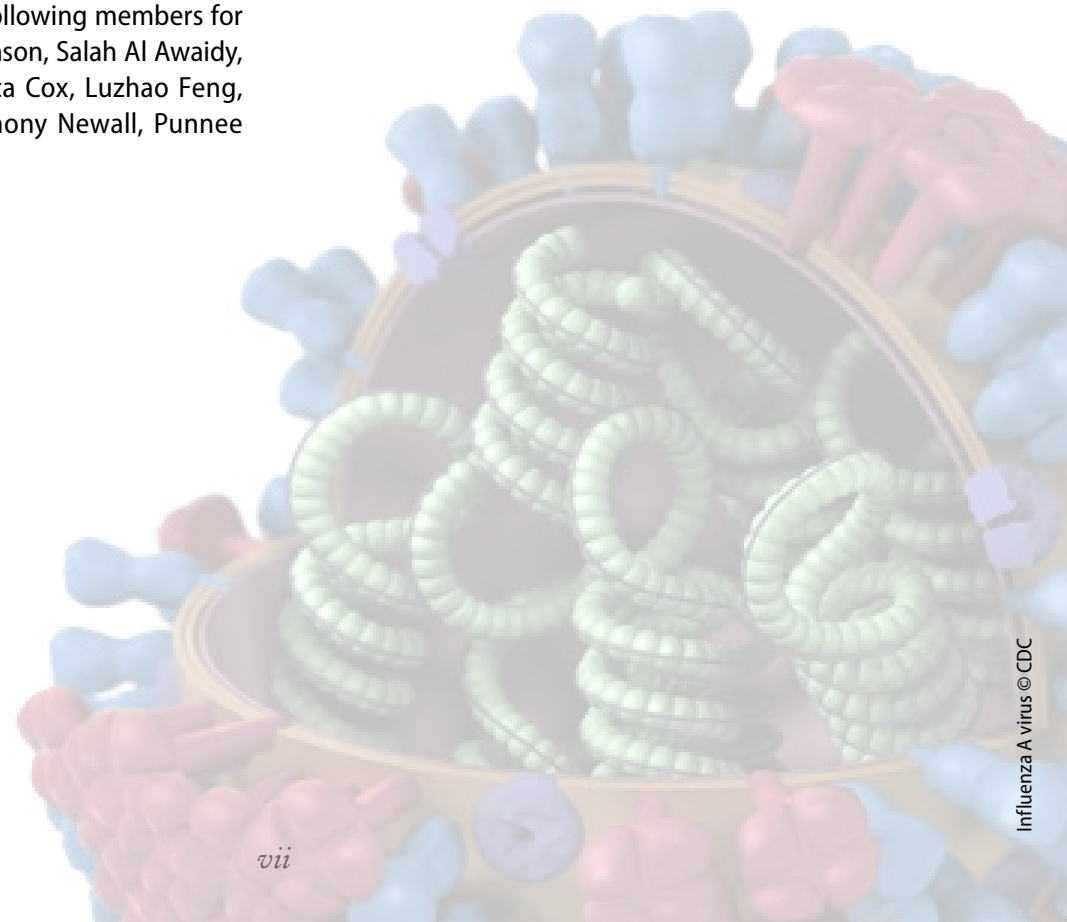


Influenza A virus © CDC

Abbreviations

ASC	Available supply for commercialization
CIDRAP	Center for Infectious Disease Research and Policy
FVIVA	Full value of improved influenza vaccine assessment
FVVA	Full value of vaccine assessment
GIS	WHO Global Influenza Strategy
GISRS	Global Influenza Surveillance and Response System
HA	Haemagglutinin
HIC	High-income country
IIV	Inactivated influenza vaccine
IVIR-AC	WHO Immunization and vaccines related implementation research advisory committee
IVR	Influenza Vaccines Research and Development Roadmap
LAIV	Live attenuated influenza vaccine
LIC	Low-income country
LMIC	Lower-middle-income country
L&MIC	Low- and middle-income country
LRTI	Lower respiratory tract infection
M1, M2	Matrix protein
MCDA	Multiple criteria decision analysis
NA	Neuraminidase
NITAG	National immunization technical advisory group
NPV	Net Present Value
PAHO	Pan American Health Organization
PPCs	WHO Preferred Product Characteristics
R&D	Research and development
RIV	Recombinant influenza vaccine
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse transcription polymerase chain reaction
TAG	Technical Advisory Group
TFGH	Task Force for Global Health
UMIC	Upper-middle-income country
UNICEF	United Nations Children's Fund
VLP	Virus-like particle vaccine
WHO	World Health Organization

Executive summary

Seasonal influenza remains a significant global public health challenge, causing substantial morbidity and mortality each year. The World Health Organization's Global Influenza Strategy 2019–2030 and the recommendations of the Strategic Advisory Group of Experts on Immunization both emphasize the need for more effective and durable influenza vaccines.

The Full Value of Improved Seasonal Influenza Vaccines Assessment (FVIVA) report outlines key considerations for advancing seasonal influenza vaccine development and describes the potential impact that improved vaccines can have on global public health. The report assesses the need for, and articulates the value of, more effective and durable seasonal influenza vaccines to address the significant global burden of seasonal influenza. Its findings can help to inform efforts to accelerate the development and availability of improved seasonal and pandemic influenza vaccines.

VACCINE DEVELOPERS

The FVIVA highlights the potential of current platforms and technologies – such as mRNA vaccines, recombinant proteins and virus-like particles – to improve vaccine effectiveness and programmatic suitability. It confirms that the market size for these vaccines will remain significant in the future, ensuring their commercial viability. The report also outlines the pathways to address key challenges in clinical development for regulatory approval and widespread adoption.

FUNDERS AND TECHNICAL PARTNERS

The FVIVA highlights areas where financial and technical support is critical for developing, producing and delivering improved seasonal influenza vaccines. For development, support is needed for the definition of more efficient (i.e. time and resources required) clinical pathways and creation of a distributed manufacturing ecosystem. For implementation, support is crucial to overcoming existing barriers, especially in low- and middle-income countries, to ensure access to influenza vaccines and to achieve high coverage.

GLOBAL, REGIONAL AND COUNTRY POLICY-MAKERS

The FVIVA confirms that improved influenza vaccination can significantly reduce the global, regional and national burden of influenza, including infections, hospitalizations and deaths. Economic analysis shows that influenza vaccines could be cost-saving or cost-effective in many countries, especially if priced appropriately. The research identifies the key criteria – including vaccine efficacy, duration of protection, breadth of protection, safety, temperature stability and shelf-life – related to the performance of improved influenza vaccines that will influence adoption decisions in low- and middle-income countries.

NATIONAL PROGRAMMES

The FVIVA identifies barriers to current seasonal influenza vaccine uptake in low-resource settings, such as inadequate surveillance infrastructure, public scepticism, limited financial resources and logistic challenges. It also describes enablers to vaccine access, including strong sentinel surveillance systems, supportive vaccination policies and robust institutional frameworks. The research identifies well-structured immunization programmes and integration within a life-course immunization approach as critical for successful uptake of the improved seasonal influenza vaccines. There will also be an important need to identify the most efficient strategies for using improved vaccines among the populations at highest risk in order to ensure cost-effectiveness, particularly in low-income settings.

The FVIVA report underscores the critical importance of developing and implementing improved influenza vaccines to enhance global public health outcomes. By addressing key challenges in vaccine development, decision-making, market demand, health and economic impact, financial viability, and implementation, these vaccines have the potential to reduce the global burden of influenza significantly and to improve health outcomes, particularly in low- and middle-income countries.

This report is organized in sections that address specific elements related to the value of improved influenza vaccines – such as the current disease burden and unmet public health need, the current state of the development pipeline, health and economic impact, anticipated market dynamics, and policy and implementation considerations. Readers are encouraged to focus on the sections most relevant to their interests while using the conclusions and recommendations as a guide for understanding the broader implications of the findings.

1. WHO's full value of improved seasonal influenza vaccines

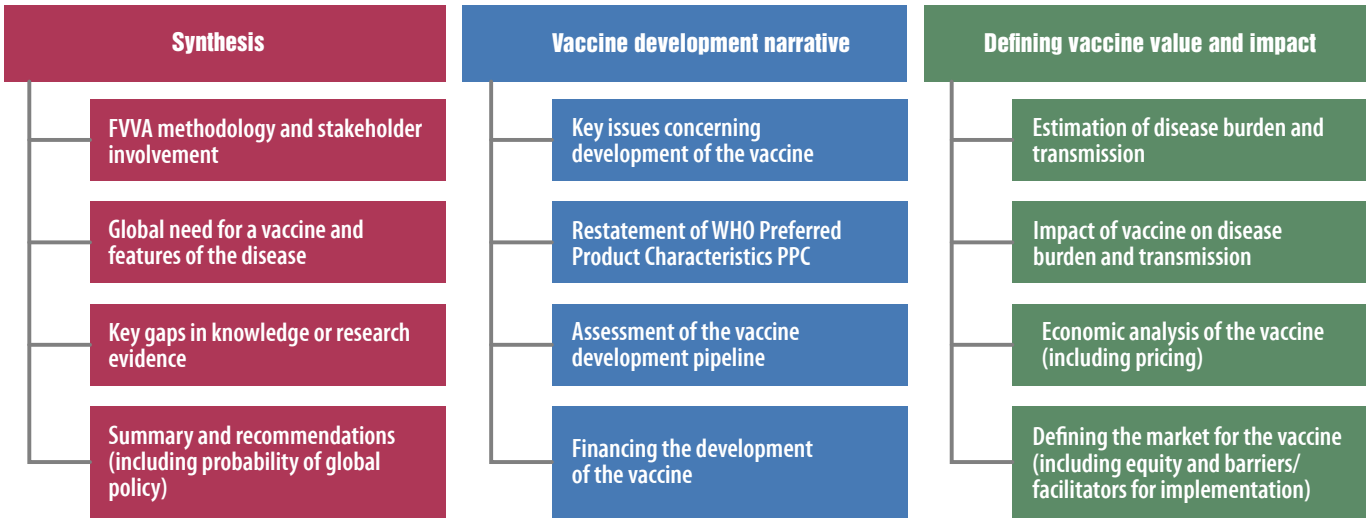
1.1 WHO's call for improved seasonal influenza vaccines

The Global Influenza Strategy 2019–2030 (GIS) is WHO's current strategy for influenza control, prevention and preparedness *(1)*. The GIS outlines strategic objectives for influenza prevention and control broadly, but with substantial focus on expanding vaccination programmes and developing improved influenza vaccines. Specifically, the GIS calls for the development of improved, novel and universal influenza vaccines that provide broader, longer-lasting protection, greater effectiveness against severe disease and reduced production times *(1)*. The Strategic Advisory Group of Experts on Immunization has guided WHO's position and recommendations on influenza vaccines, which also emphasize the need for enhanced vaccine effectiveness and access, particularly in low- and middle-income countries (LMICs), and recommend research to support technology transfer of next-generation vaccine technologies that facilitate use and access in LMICs *(2)*. Additionally, the Immunization Agenda 2030 highlights the importance of life-course vaccination for all age groups, with influenza as a key example *(3)*. Complementing these efforts, WHO is currently updating the Public Health Research Agenda for Influenza, which prioritizes the need for research dedicated to enhancing immunogenicity, availability and delivery of influenza vaccines *(4)*.

1.2 Definition and purpose of a full value of vaccine assessment

The full value of vaccine assessment (FVVA) framework offers a holistic approach to assessment of the benefits of vaccines, describing their health, economic and societal value. The development of an FVVA supports alignment among different stakeholders and improved decision-making with regard to investments in new vaccine development, policy guidance, procurement strategies and vaccine introduction *(5)*. FVVAs are evidence-based and consolidate a broad set of information and perspectives gathered through literature reviews, stakeholder consultations, and commissioned research and analysis (**Fig. 1**).

FIG. 1. Key elements of full value of vaccine assessments



The purpose of this Full Value of Improved Influenza Vaccine Assessment (FVIVA) report is to describe the full value of developing improved vaccines against disease caused by seasonal influenza, to inform decision-making and create a common understanding across the continuum from vaccine development to uptake with a view to sustainable public health impact (Fig. 2). Its objectives are:

- to describe the rationale for developing improved vaccines against disease caused by influenza in the context of global health;
- to provide data to the primary stakeholders involved in vaccine development and implementation to optimize influenza vaccination programmes worldwide;
- to create an understanding of the return on investment for both countries and manufacturers.

The findings of the FVIVA can also be used to inform key elements of a WHO Evidence Considerations for Vaccine Policy framework for improved influenza vaccines, if developed, to accelerate the adoption of improved influenza vaccines once available *(6)*.

FIG. 2. Vaccine development and introduction continuum

1.3 WHO preferred product characteristics for next-generation influenza vaccines

To set out a strategic vision to guide the development of improved influenza vaccines that better meet global public health needs, WHO published a second edition of its preferred product characteristics (PPCs) for next-generation influenza vaccines in 2017 *(7)* and 2025 *(8)* The primary objective of the PPCs are to outline the desired attributes for new influenza vaccines, thus serving as a roadmap for researchers, manufacturers and policy makers to encourage the development of innovative, next-generation vaccines that align with global health priorities. The PPCs emphasize the need for vaccines with broader and longer-lasting protection, enhanced efficacy against severe illness, and greater programmatic suitability for high-risk populations, including those in LMICs. This FVVA defines next-generation vaccines as those with enhanced efficacy and/or broader and longer-lasting protection. The PPCs also encourage the development of vaccines that can be produced more rapidly and at lower costs, with simpler delivery systems that facilitate widespread access, especially in low-resource settings.

The influenza vaccine PPCs, published in December 2025, reflects on an evolved research and development (R&D) landscape, updated WHO influenza guidance and strategy since their original publication, and perspectives gained from the COVID-19 pandemic. Like the 2017 version, the revised PPCs have the prevention of severe influenza through routine immunization of high-risk groups as the primary objective. The strategic goal of these PPCs is to promote the development of next-generation influenza vaccines that give at least one year of protection with subtype-specific immunity and with decreased manufacturing times to reduce the global influenza burden, accelerate vaccine introduction and uptake in LMICs, and enhance global pandemic influenza preparedness. Notably, the PPCs set currently available influenza vaccines, which include traditional and enhanced vaccines (adjuvanted, high-dose, and recombinant vaccines) as the baseline for improvement. The 2017 PPCs used unadjuvanted, standard dose inactivated influenza vaccines (IIV) or live attenuated influenza vaccines (LAIV) as the baseline for improvement. While enhanced vaccines have demonstrated superior protection in some high-risk groups, more substantial improvements in effectiveness and breadth and duration of protection would lead to greater public health impact and next-generation influenza vaccines could be developed to address these goals.

The 2025 PPCs establishes the desired characteristics and attributes for next-generation influenza vaccines (Table 1).

TABLE 1. Preferred product characteristics for next-generation influenza vaccines

Indication
Prevention of severe influenza illness

Target population
All groups at particular risk of severe influenza or complications

Safety
Mild reactogenicity acceptable; severe reactogenicity and adverse events at a rate comparable to currently approved seasonal influenza vaccines

Co-administration
Demonstration of favourable safety and immunological non-interference upon co-administration or co-formulation with other vaccines recommended for use

Efficacy
Vaccine efficacy should be better than that of currently approved seasonal influenza vaccines *(8)* and the improved efficacy should be demonstrated in terms of one of the following attributes, either:

Duration of protection: Minimum of 1 year (preference for 3 years)

and/or

Breadth of protection: Protection against circulating subtypes (ideally also including subtypes of pandemic potential)

Formulation/presentation
Vaccines seeking WHO prequalification should meet WHO-defined criteria for programmatic suitability in terms of formulation, presentation, packaging, thermostability and disposal

Route of administration
Injectable, inhaled, or oral administration are acceptable

Manufacturing time
Less than 5 months from vaccine strain selection to finished product

Product stability and storage
Vaccines stable under refrigerated conditions (2–8°C) for at least 12 months

Access and affordability
Favourable cost-effectiveness and safety profile should be established, and price should not be a barrier to access and within-country distribution, including in LMICs

1.4 Relationship between the FVIVA and the PPCs

To encourage innovation and the development of improved influenza vaccines for use in settings most relevant to global unmet public health need and to ensure alignment with WHO guidance available, the FVIVA builds on the PPCs for improved influenza vaccines (established in 2017, updated in 2025 *(8)*) available at the time of the project *(7, 8)*. Using the categorization of the vaccine profiles in these PPCs, the FVIVA evaluates the full value of the following influenza vaccine profiles described in Table 2.

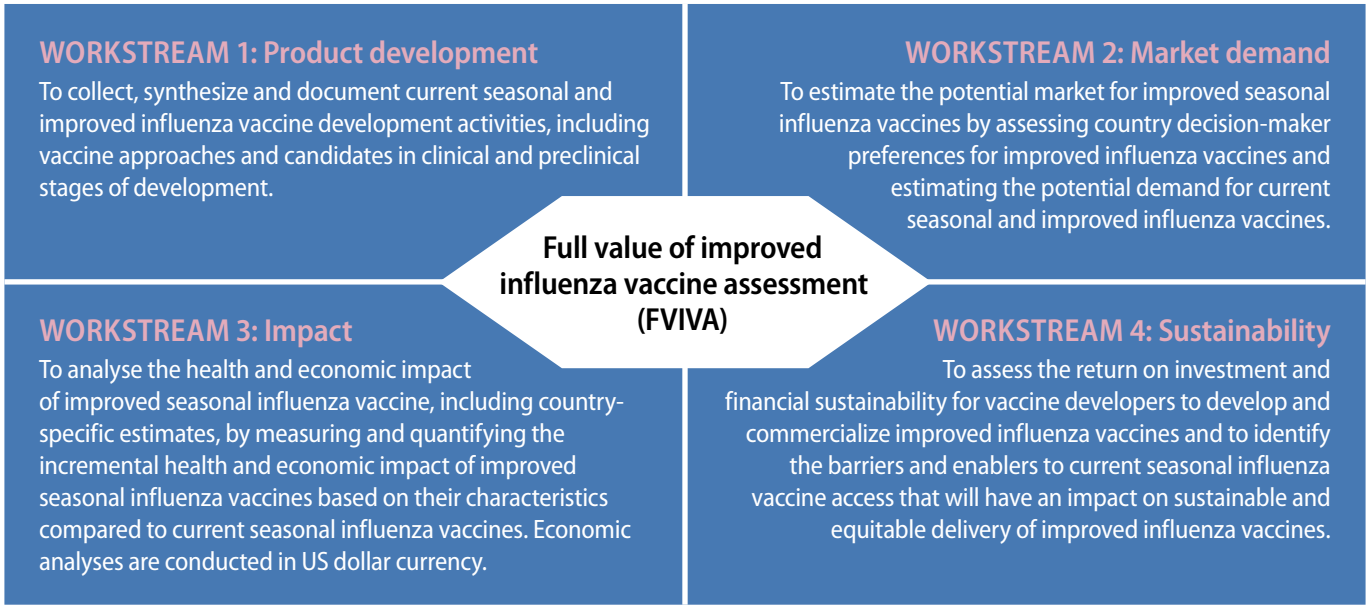
TABLE 2. Vaccine profiles evaluated in FVIVA

Improved influenza vaccine profile		Assumed vaccine efficacy[1] (strain match/mismatch)	Assumed vaccine duration of protection
Profile number	Profile description		
0	Current seasonal vaccine	70%/40%	6 months
A.1	Minimally improved (duration)	70%/40%	1 year
A.2	Minimally improved (efficacy)	90%/40%	6 months
B.1	Significantly improved (efficacy, breadth, duration)	90%/70%	2 years
B.2	Significantly improved (breadth, duration)	70%/70%	3 years
C	Game changer (efficacy, breadth, duration)	90%/90%	5 years

1.5 Methodology development for the FVIVA

The project was designed to fill key data gaps and was structured into four complementary workstreams (Fig. 3). WHO commissioned the London School of Hygiene & Tropical Medicine and MMGH Consulting to synthesize relevant evidence and perform the necessary analyses to inform each of the workstreams.

FIG. 3. Four workstreams addressing key data gaps in the FVIVA



[1] For the FVIVA vaccine profiles, vaccine efficacy is defined as protection against severe laboratory-confirmed influenza illness.

The following manuscripts have been prepared for publication in peer-reviewed journals in order to summarize the analyses conducted to inform the FVIVA *(9)*:

OVERALL

- The need and ongoing efforts to understand the full value of improved influenza vaccines.
- Evaluating the broader impact of next-generation influenza vaccines: a full value of vaccine assessment approach.

WORKSTREAM 1

- Advancing influenza vaccines: a review of next-generation candidates and their potential for global health impact.
- Global production capacity of seasonal and pandemic influenza vaccines in 2023.

WORKSTREAM 2

- Identification and sizing of the current use cases for seasonal influenza vaccines.
- Priority-setting for improved influenza vaccines: a multi-criteria decision analysis.

WORKSTREAM 3

- Modelling the potential global net monetary benefit of improved influenza vaccines (working title, in preparation).
- Costs of influenza associated health care: an umbrella review and meta-regression (working title, in preparation).
- A systematized review of seasonal influenza case-fatality risk (ready for submission).

WORKSTREAM 4

- Findings related to financial sustainability for vaccine developers to develop and commercialize improved influenza vaccines and the identification of barriers and enablers to current seasonal influenza vaccine access will be included in the overall manuscript.

Details are available at the following link: https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/vaccine-impact-value/full-value-of-improved-influenza-vaccine-assessment-(fviva).

2. The global public health need for improved seasonal influenza vaccines

2.1 Disease description

2.1.1 Virology and epidemiology

Influenza is an acute respiratory disease caused by infection with seasonal influenza viruses in humans. Influenza viruses circulate globally, resulting in seasonal epidemics. In temperate climates, seasonal influenza epidemics are typically experienced during the winter, while year-round circulation with irregular outbreaks or prolonged influenza seasons can occur in tropical/subtropical regions.

Influenza viruses are transmitted primarily through droplets and aerosols from respiratory secretions of infected individuals, and infection can range from asymptomatic to severe illness and death. The viruses are classified into four types: A, B, C and D. Influenza A and B viruses are the most relevant to humans. Both Influenza A and Influenza B can cause outbreaks and epidemics. Influenza A and B viruses co-circulate during each seasonal peak, usually with influenza A viruses predominating *(10)*.

Influenza A viruses in animals and humans are classified into subtypes based on the virus surface proteins haemagglutinin (HA) and neuraminidase (NA). Influenza A viruses can infect many avian and mammalian species; among influenza A viruses, 18 different HA and 11 different NA subtypes have been identified. A/H1N1 and A/H3N2 virus subtypes currently circulate in humans, though from 1957 to 1968 an A/H2N2 virus was also circulating. A range of other avian influenza virus subtypes, notably H5 (especially H5N1), H7 and H9 subtypes and swine viruses have caused sporadic cases in humans in the past 25 years.

For influenza B viruses, the primary host is humans. Two antigenic lineages of influenza B viruses – B/Yamagata and B/Victoria – have cocirculated since the 1980s. However, B/Yamagata viruses have not been detected since 2020.

A key feature of influenza viruses is their ability to evolve continuously and rapidly. The ongoing accumulation of genetic mutations (known as "antigenic drift") leads to antigenic changes in the HA and NA surface proteins. Drift variants may evade existing immunity. For this reason, influenza vaccine antigen composition is revised and updated twice a year (February for the northern hemisphere and September for the southern hemisphere) to match circulating influenza viruses.

Influenza A viruses can also undergo abrupt and major change that results in a novel influenza A virus that infects humans. This antigenic shift is likely to occur through reassortment between two or more influenza A viruses co-infecting the same host (e.g. birds or swine or possibly humans) or direct infection by an animal influenza virus. Pandemic influenza results from antigenic shift if the novel virus causes clinical illness, if there is very limited or no population immunity to the novel virus, and if there is sustained person-to-person virus transmission.

2.1.2 Burden of disease

An estimated 1 billion cases of influenza occur annually, of which 3–5 million are severe, resulting in between 290 000 and 650 000 influenza-related respiratory deaths (0.1– 0.2% case-fatality rate) *(10, 11)*. Recent evidence also shows substantial health loss and long-term effects in individuals hospitalized with influenza after the acute phase of illness *(12)*.

Modelled data from the 2017 Global Burden of Disease study estimated that influenza-attributed lower respiratory tract infections (LRTIs) accounted for 9.5 million hospitalizations in 2017, with the highest incidence of influenza LRTIs, non-hospitalized and hospitalized, in children and older adults. Children under 10 years of age account for the greatest number of influenza LRTI episodes and hospitalizations, with an estimated 2.2 million hospitalizations in children under 5 years of age. The highest mortality rate occurred in adults older than 70 years of age (16.4 deaths per 100 000), as did the greatest number of deaths *(13)*.

Rates of illness and death from influenza are estimated to be highest in low-income countries, including countries in sub-Saharan Africa and South-east Asia, particularly in older adults and children under 5 years. High-risk groups for severe influenza or complications include older adults, pregnant women and women up to 2 weeks postpartum, children under 59 months, and individuals with underlying health issues *(14)*. Health workers are an additional risk group due to their increased risk of workplace exposure to or transmission of influenza viruses.

2.2 Current methods of surveillance, diagnosis, prevention and treatment

2.2.1 Surveillance

Influenza surveillance is conducted primarily through sentinel surveillance networks with systematic testing of people meeting case definitions for influenza-like illness and/or severe acute respiratory infection. Global influenza surveillance is based on the Global Influenza Surveillance and Response System (GISRS) which acts as the global mechanism of surveillance, preparedness and response for seasonal, pandemic and zoonotic influenza; the global platform for monitoring influenza epidemiology and disease; and the global alert system for novel influenza viruses and other respiratory pathogens. This global influenza surveillance network also helps to inform biannual vaccine strain recommendations and monitor the potential emergence of epidemic/pandemic strains *(15)*.

FluNet is a global web-based tool for influenza virological surveillance. The virological data entered into FluNet (e.g. number of influenza viruses detected by subtype) are critical for tracking the movement of viruses globally and interpreting the epidemiological data. The data at country level are publicly available and updated weekly. The results are presented in various formats, including tables, maps and graphs. FluID is a global platform for data-sharing that links regional influenza epidemiological data into a single global database. The platform accommodates both qualitative and quantitative data, facilitating the tracking of global trends, spread, intensity and impact of influenza. These data are made freely available to health policy makers to assist them in making informed decisions on the management of influenza. It complements the FluNet virological data.

The data are reported by the National Influenza Centres of the GISRS and other national influenza reference laboratories collaborating actively with GISRS, or are uploaded from WHO regional databases.

2.2.2 Diagnosis

The clinical diagnosis of influenza is challenging because the signs and symptoms can be nonspecific and vary depending on virus type and patient host characteristics. Reverse transcription polymerase chain reaction (RT-PCR) is the gold standard for influenza diagnosis because of its high sensitivity and high specificity for the detection of influenza viruses in respiratory specimens. However, because RT-PCR often requires testing at specialized public health laboratories, the turnaround times for results may not be sufficiently rapid to inform clinical management decisions and the availability of RT-PCR may be limited in lower resource settings. Rapid diagnostic tests for respiratory specimens – such as rapid influenza diagnostic tests that detect influenza virus antigens, digital immunoassays (which are rapid influenza diagnostic tests with analyser devices), and rapid nucleic acid amplification tests (molecular assays) – are available in clinical and pharmacy settings and can provide results within 30 minutes, although they have limited sensitivity and their availability remains limited in lower resource settings *(14, 16)*.

2.2.3 Prevention

WHO recommends that all countries consider implementing seasonal influenza vaccination programmes *(2)*. The recommendations specify that:

> *"For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that the following target groups should be considered for vaccination (not in order of priority): health workers, individuals with comorbidities and underlying conditions, older adults and pregnant women. Depending on national disease goals, capacity and resources, epidemiology, national policies and priorities, and disease burden, countries may consider additional (sub)populations for vaccination, such as children."*

Influenza vaccines are considered the most effective prevention against severe influenza disease and strong influenza programmes are beneficial for pandemic preparedness and response. Registered influenza virus vaccines are currently produced using either egg-, cell- or recombinant-based methods, with inactivated vaccines produced in eggs being the most commonly used *(2)*. Nucleic acid-based vaccines, including mRNA-based combination vaccines, are anticipated to become available in the next two years. Live attenuated, adjuvanted and high-dose formulations are also available for certain populations (e.g. older adults). Influenza vaccines have been found to be safe and effective and inactivated vaccines are approved for use in people aged 6 months and older. There is considerable variability in the effectiveness of influenza vaccines, depending on both the season and the population group. The limitations

of current seasonal influenza vaccines are described in further detail in Chapter 1 and play a part in the insufficient allocation of public health resources to reduce influenza's health and economic impact. WHO has therefore called for the development of improved influenza vaccines with increased breadth and longer duration of protection, and greater effectiveness against severe influenza disease *(16)*.

Importantly, public health and social measures (which were previously called non-pharmaceutical interventions) also play an important role in the prevention of seasonal epidemic and pandemic influenza *(17)*.

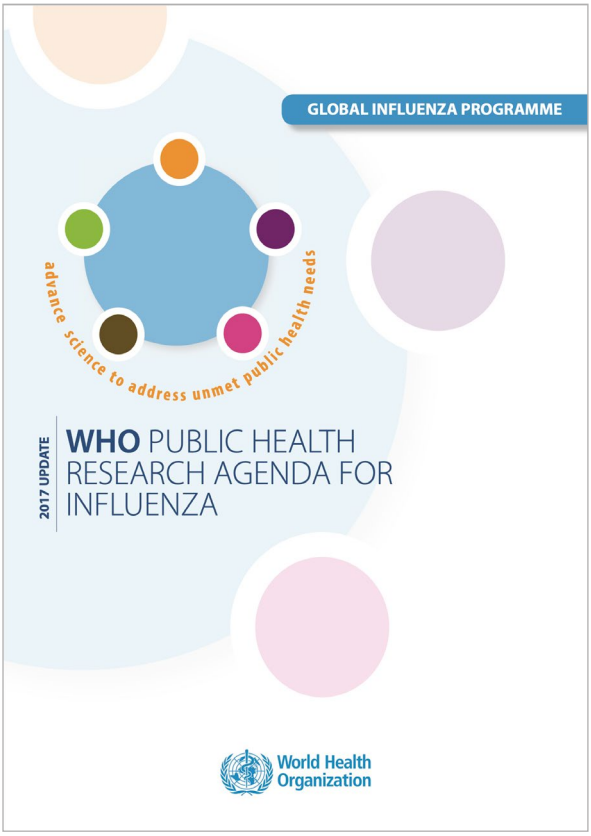
2.2.4 Treatment

The aim of clinical management of patients with, or at risk for, severe influenza virus infection is to provide optimal intensive supportive care for severe clinical syndromes and administration of efficacious, influenza-specific antivirals. Four NA inhibitors are widely available and active against all currently circulating seasonal influenza A and B viruses and zoonotic influenza A viruses. Newer antivirals are being developed that use a different mechanism of action (selective inhibitor of influenza cap-dependent endonuclease) compared to neuraminidase inhibitors. One of these newer antivirals has been approved for early treatment of adolescent and adult patients with uncomplicated influenza. Clinical management guidelines for influenza were updated by WHO in 2024 *(18)*.

2.3 Key gaps in knowledge or research evidence

The key gaps in knowledge and research evidence are detailed in WHO's Public health research agenda for influenza. With specific regard to minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza and making improvements over current seasonal influenza vaccines, the research agenda identified the following research as high priority *(19)*:

- Conduct studies to enhance the clinical applications of existing vaccines, including improvements in production, duration and breadth of protection; safety and immunogenicity profiles; and dose-sparing formulations, especially for high-risk groups.
- Develop new vaccines, vaccine platforms and formulations that are safe and have enhanced immunogenicity, as well as vaccine delivery systems with improved ease of storage and administration, especially for use in under-resourced settings.
- Systematically evaluate the steps in vaccine production to reduce bottlenecks in the production of vaccines, and improve the processes of rapid response, surge capacity, rapid deployment and tracking of vaccine usage.
- Develop innovative clinical trial methodologies to study the effectiveness and safety of novel vaccines for pre-licensure and post-licensure evaluation and vaccine effectiveness studies, with an emphasis on pharmacovigilance and the reduction of disease burden for post-licensure vaccine evaluation in a wider range of settings (including children) and examine and develop ways to harmonize the regulatory processes.



The public health research agenda has been updated in 2024 *(20)*.

3. Target audiences and stakeholder engagement

3.1 Target audiences for the FVIVA

The process of developing the FVIVA brings together relevant national, regional and global experts in a working group, establishing lines of communication and alignment among these experts to gather, evaluate and synthesize evidence on the value of vaccines from a range of perspectives. The experts typically include stakeholders from the vaccine R&D community; funders of research and vaccine implementation; vaccine market experts; global policy makers; regulatory authorities, national policy makers and programme managers; immunization partner organizations; and civil society organizations *(5)*.

The FVIVA aims to inform and encourage action among the following key stakeholders:

- vaccine research and development entities (biotech and manufacturers);
- funders of vaccine development research, procurement, and implementation; and
- global, regional and national policy-making bodies and health planners.

Different sections of the document may be of greater relevance to different stakeholders but it is recommended that the document is used in its entirety. The document may be useful to other audiences with an interest in influenza and/or immunization.

3.2 Overview of the influenza stakeholder ecosystem

A broad set of stakeholders is involved in supporting the research and development of improved influenza vaccines, their implementation and ongoing disease surveillance (**Fig. 4**).

With regard to the development of and access to influenza vaccines, several key stakeholders are of particular relevance to the development of the FVIVA. Through the Global Influenza Strategy (GIS) for 2019–2030, WHO is leading efforts to coordinate the improved development and manufacture of influenza vaccines as well as to support country-level implementation of vaccination programmes. The GIS aims to provide global policy direction, set the global research agenda, and support Member States to develop and implement evidence-based influenza vaccination programmes for both seasonal and pandemic preparedness. WHO also manages the Pandemic Influenza Preparedness Framework aimed at improving global preparedness and response to pandemic influenza by ensuring equitable access to vaccines and antiviral medicines *(21, 22)*. WHO's Immunization Agenda 2030 includes a strong focus on life-course immunization which is particularly relevant for influenza vaccines *(23)*.

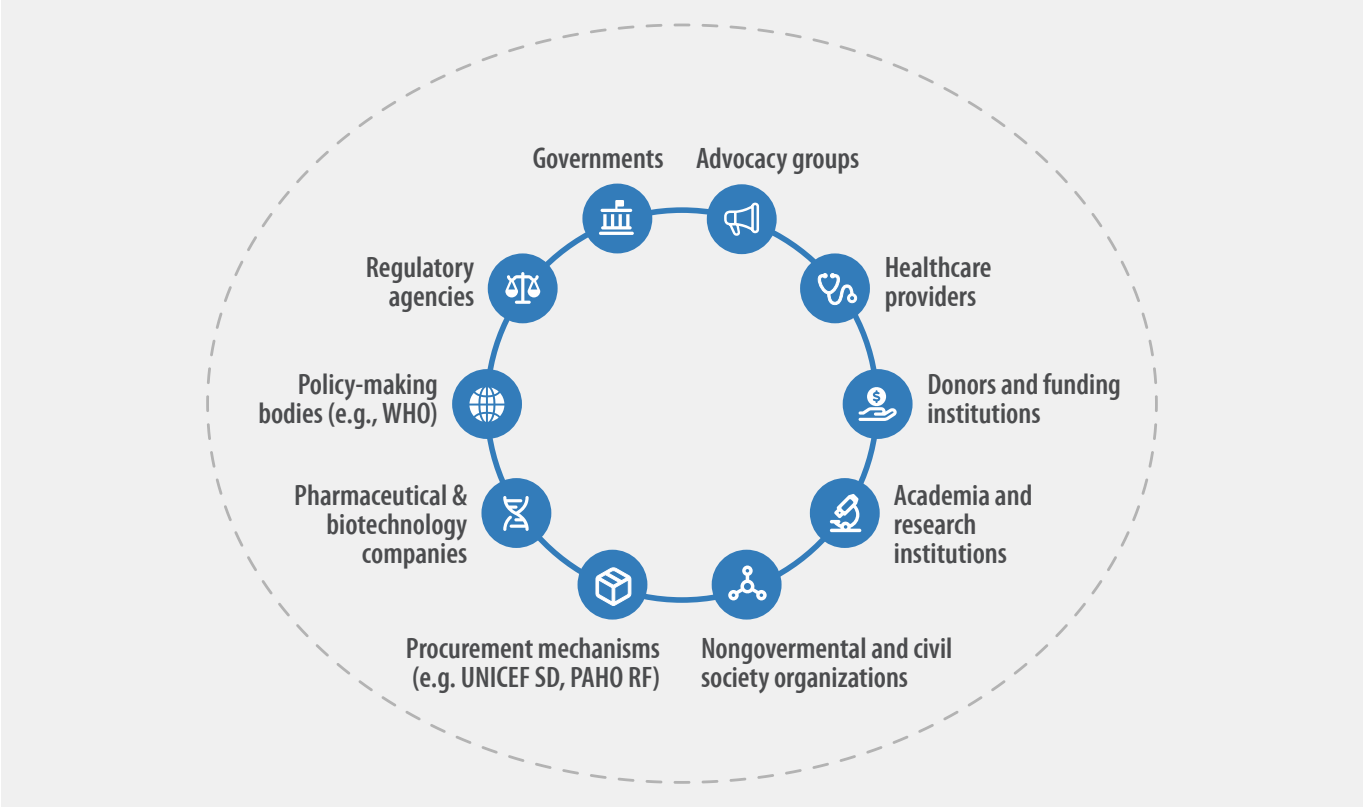
The Center for Infectious Disease Research and Policy (CIDRAP) recently coordinated the development of the Influenza Vaccines Research and Development Road-map (IVR) *(24)*. The IVR was developed to provide a unified strategic planning tool for influenza across global stakeholders and provide opportunities for research and funding alignment. The IVR is aligned with WHO's Global Influenza Strategy 2019–2030.

Other key global coordination and engagement activities include Gavi's Influenza vaccine Learning Agenda (which was approved by Gavi's board in 2019 and conducted by WHO between January 2021 and January 2023), the Task Force for Global Health (which houses the Partnership for International Vaccine Initiatives and the Global Funders Consortium for Universal Influenza Vaccine Development), and the Sabin-Aspen Scientific Policy Group *(25)*.

Various initiatives have been established at regional level in recent years, including: the European Influenza Surveillance Network managed by the European Centre for Disease Prevention and Control; the European Scientific Working Group on Influenza and Other Respiratory Viruses (ESWI);

the Pan American Health Organization (PAHO) Severe Acute Respiratory Infections Network (SARInet plus) and the Network for the Evaluation of Vaccine Effectiveness in Latin America and the Caribbean – Influenza (REVELAC-i); the Asia-Pacific Alliance for the Control of Influenza; the African Influenza Surveillance Network, the Middle East and North Africa (MENA) Influenza Stakeholder Network; the Eastern Mediterranean Acute Respiratory Infection Surveillance, managed by the WHO Regional Office for the Eastern Mediterranean; and the International Society for Influenza and other Respiratory Virus Diseases (ISRV).

FIG. 4. High-level influenza stakeholder landscape



PAHO RF: PAHO Revolving Fund; UNICEF SD: UNICEF Supply Division

The Collaborative Influenza Vaccine Innovation Centers, an initiative launched in 2019 by the United States National Institute of Allergy and Infectious Diseases, is functioning as a network designed to encourage collaborative research, vaccine manufacturing and clinical trials, with specific focus on the United States but with output that can have global relevance.

Academic institutions, biotechnology companies and vaccine manufacturers are also actively working to develop new and improved influenza vaccines, as evidenced by the broad pipeline of candidates detailed in Chapter 4.

3.3 Stakeholder involvement in FVIVA

In developing this FVVA, WHO facilitated engagement with a broad and diverse group of stakeholders in the influenza ecosystem at national, regional and global levels. A Technical Advisory Group (TAG) was convened, with members providing scientific, policy and implementation expertise in relation to influenza and representing different regions. This TAG provided:

1. advice on the methodology and process of the planned project;
2. technical advice to specific technical issues arising during the project *(9)*; and
3. advice and review of resulting products of the project *(26)*.

WORKSTREAM 1

Development of activities supporting Workstream 1 (improved influenza vaccine landscape review, update of next-generation influenza vaccine PPCs, assessment of challenges and opportunities in next-generation influenza vaccine R&D) was supported through the guidance and feedback of the FVIVA TAG and Working Group for the update of the PPCs. The review of current influenza vaccines, including improved vaccines, included input from WHO technical experts and those from private industry. The invitation to comment on the updated PPCs was posted publicly on the WHO website and feedback was received from government and industry stakeholders. The PPCs were reviewed by the Product Development for Vaccines Advisory Committee and was endorsed in 2025 *(8)*. The process to identify key issues in next-generation influenza vaccine R&D included a survey completed by 17 next-generation influenza vaccine developers, and interviews with 4 developers.

WORKSTREAM 2

The development of the influenza vaccine supply and demand forecasts were informed by 15 interviews with WHO regional offices, key regional influenza experts, vaccine industry associations and individual vaccine manufacturers. WHO's Technical Advisory Group on Market Access for Vaccines also validated the methodology and results. Extensive stakeholder surveys (139 respondents), interviews (30 interviews), and virtual and in-person workshops (97 participants across 12 countries) – with representatives from ministries of health, government agencies, pharmaceutical companies, nongovernmental and civil society organizations, and academia – were conducted to inform the development of the use cases for influenza vaccines and the multiple criteria decision analysis (MCDA) which assessed the attributes of improved influenza vaccines most important to decision-makers when considering their inclusion in national immunization programmes.

WORKSTREAM 3

Development of the analyses for Workstream 3 (health and economic impact of improved influenza vaccines) was supported through the guidance and feedback of the FVIVA TAG.

WORKSTREAM 4

Focus groups with vaccine market and commercial experts were convened to validate the assumptions and results of the vaccine price benchmarking and financial sustainability analyses, and the analysis of seasonal influenza vaccine access barriers and enablers was reviewed by the FVIVA TAG. Additional validation was performed of selected coverage and uptake assumption for improved vaccines with 7 expert representatives of different stakeholder groups and regions.

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To ensure overall robustness of methods and review of results of the project, WHO's Immunization and vaccines related implementation research advisory committee (IVIR-AC) was consulted to provide advice to the project, which the advisory committee did in March 2021, September 2022, February 2024 and February 2025 *(9, 27–29)*. IVIR-AC's input to the FVIVA was focused on the planned application of the FVVA methodology to improve influenza vaccines, the development of use cases for seasonal influenza vaccines, the proposed methods to support supply and demand forecasts for seasonal and improved influenza vaccines, and the methodologies to model health and economic impact of improved influenza vaccines and the implications of these results, including additional areas for future research.

4. Development of improved seasonal influenza vaccines and assessment of the pipeline

4.1 Biology of the influenza vaccine

The influenza vaccine is designed to protect against the human influenza virus. It works by stimulating the immune system to recognize and combat the virus effectively if exposed in the future. However, the ability of influenza viruses to undergo antigenic drift allows the virus to evade previously acquired immunity, either through natural infection or vaccination, leading to the possibility of reinfections. While prior exposure to or vaccination against influenza may not completely prevent future infections, they often mitigate the severity of disease, reducing hospitalizations and deaths *(30)*.

Immunity against influenza is complex and involves both humoral and cell-mediated responses. Humoral immunity is primarily mediated by antibodies targeting the HA protein, which neutralizes the virus by preventing it from entering host cells, while antibodies against the NA protein help limit viral spread. This antibody-driven response is crucial in reducing viral load and severity of infection *(31–33)*. Additionally, cell-mediated immunity, involving T cells, plays a critical role in clearing infected cells, and may offer broader protection by targeting more conserved internal viral proteins, such as nucleoprotein and matrix proteins (M1, M2), which are less prone to variation across strains. While natural infection tends to elicit robust responses from both arms of the immune system, protection from traditional inactivated influenza virus vaccines comes largely from humoral immunity, with vaccines designed to target HA. Some vaccines also include NA, which may enhance immunogenicity and provide greater breadth of protection. While inactivated influenza vaccines (IIV) and recombinant influenza vaccines (RIV) elicit little cell-mediated immunity, which has a role in protection and recovery, live attenuated influenza vaccines (LAIV) were developed to better mimic natural infections with influenza viruses, resulting in a humoral and cell-medicated response *(34–36)*.

Most influenza vaccines that are currently licensed are administered intramuscularly, thus stimulating systemic immune responses, primarily through the production of circulating antibodies. However, intranasal vaccines, such as LAIV, offer the potential to induce mucosal immunity at the site of infection in the respiratory tract. Mucosal immunity, particularly through the production of secretory immunoglobulin A, plays a key role in neutralizing virus at the primary site of infection, potentially providing enhanced protection against transmission.

New vaccine design strategies are being developed to target more conserved regions of the HA protein stem or less variable antigens (e.g. NA, M2, and nucleoprotein) which provide a more stable target for immune responses, and vaccines targeting them may achieve broader, longer-lasting protection across different strains and subtypes.

4.2 Existing platforms for seasonal influenza vaccines

Seasonal influenza vaccines that are licensed currently are designed for strain-specific protection, primarily eliciting neutralizing antibodies against the HA glycoprotein, and are available in trivalent or quadrivalent formulations. These include three or four WHO-recommended strains – typically two influenza A strains (H1N1 and H3N2) and one or two influenza B lineages. As of September 2023, WHO recommends trivalent seasonal influenza vaccines which include the B/Victoria lineage and exclude the B/Yamagata lineage as B/Yamagata viruses have not been detected in global surveillance since 2020. Vaccine formulations are regularly updated to match circulating strains, and therefore annual re-vaccination is recommended.

The level of antibodies against HA is correlated with protection from clinical disease. The level of vaccine-induced antibodies can be related to the dose of vaccine as well as to host factors such as age and underlying health conditions. As a result, vaccines have been developed to increase vaccine-induced humoral responses by increasing the HA antigen content per dose or by adding adjuvants to the vaccines.

The WHO position paper on Vaccines against influenza (2022) recommends that, where resources are limited, countries should aim to achieve maximum population impact of seasonal influenza vaccines; this may be most equitably achieved using traditional, less expensive influenza vaccines (e.g. trivalent inactivated influenza vaccines) that are more widely available. Other vaccines (e.g. high-dose or adjuvanted influenza vaccines) have shown some benefit in certain groups, but their use may result in fewer available vaccines for other groups *(37)*. Currently available influenza vaccines include several types – IIVs, LAIVs and RIVs – which have recently been reviewed. Their characteristics are summarized in **Table 3**. Standard-dose, unadjuvanted IIVs and LAIVs are considered traditional influenza vaccines, in comparison to enhanced vaccines, which include adjuvanted and high-dose vaccines that use traditional IIV technology and manufacturing with higher antigen dose or oil-in-water adjuvants to improve vaccine performance (**Table 3**). RIVs are also considered enhanced vaccines, using technology to produce recombinant HA protein or virus-like particle (VLP) vaccines. IIVs are the most widely used, typically given through intramuscular injection, and have a long history of safe and effective use. Current LAIVs, delivered intranasally, offer the advantage of ease of use, particularly in children, although they are not recommended for several key target groups (e.g. pregnant women, health workers, immunocompromised individuals, children under 2 years of age, older adults) *(37)*. Current RIVs are also delivered intramuscularly and are recommended for older adults, although their use is largely limited to high-income countries *(38–39)*.

While IIVs are the most widely used, their effectiveness varies from season to season, by population group and by type and subtype. IIVs can be produced through egg or cell-based methods, though the majority (over 80%) of influenza vaccines (IIV and LAIV) that are currently manufactured use eggs *(40)*. Licensed RIVs are produced in cells and do not require physical virus as starting material. Future RIVs, such as those in development using nucleic acid platforms, may utilize an entirely synthetic manufacturing process.

While egg-based production of seasonal IIVs is widely used and established, the production period is lengthy (approximately 6–8 months) and mutations to the vaccine virus during the growth process in eggs or mutations to circulating strains through antigenic drift can result in a vaccine with reduced effectiveness. Cell-based approaches are an alternative to egg-based vaccine production, offering the advantage of eliminating egg-adapted mutations in IIV. Cell-based production in combination with recombinant technology may potentially enable faster manufacturing of RIV. However, cell-based vaccines face challenges related to intellectual property, higher costs, and the need for access to approved cell lines *(41)*. This may limit the ability to expand the supply of cell-based vaccines.

Currently available influenza vaccines are safe and efficacious, including when co-administered, although their effectiveness varies from season to season, by population group, and by type and subtype. Enhanced vaccines have demonstrated stronger performance than traditional vaccines in older adults.

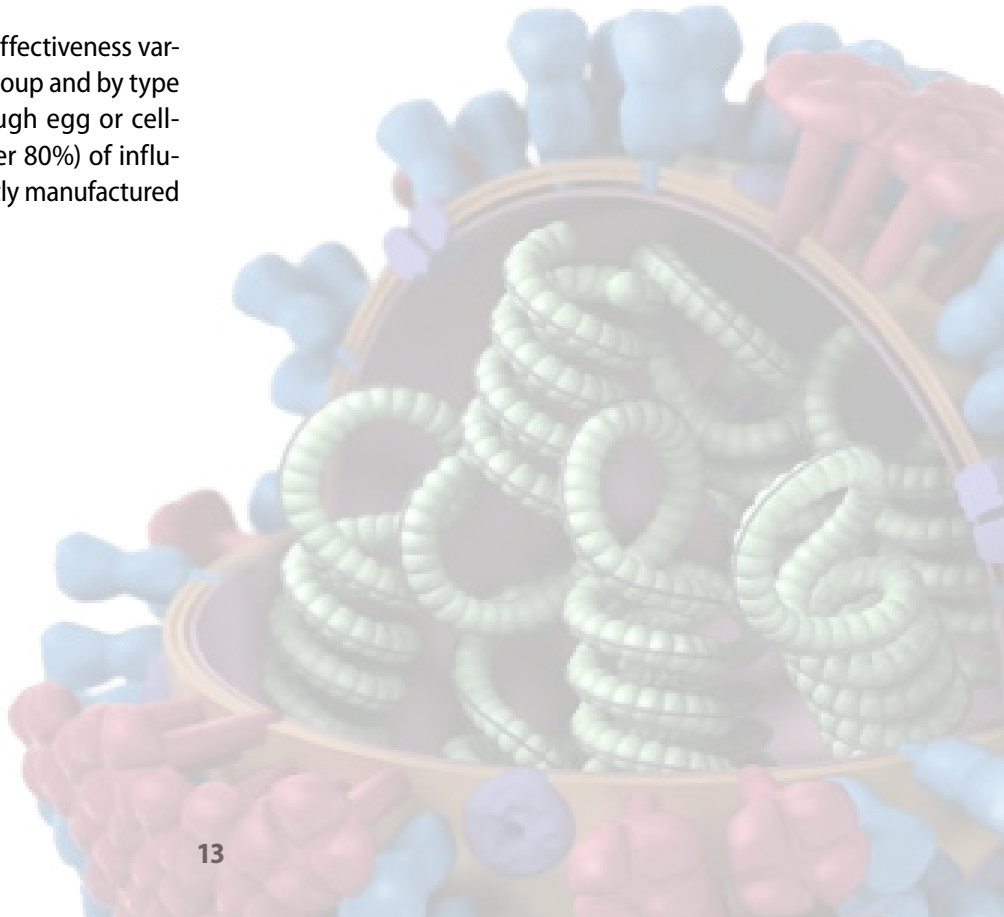


TABLE 3. Summary characteristics of current influenza vaccines *(42)*

		Traditional influenza vaccines		Enhanced influenza vaccines		
		IIV	**LAIV**	**Recombinant HA**	**Adjuvanted IIV**	**High-dose IIV**
Manufacturing	Starting material	Physical virus[a]	Physical virus[a]	Viral genetic sequence	Physical virus[a]	Physical virus[a]
	Substrate	Eggs or mammalian cells	Eggs	Insect cells	Eggs	Eggs
	Production speed	6–8 months (seasonal) *(43)*[b] 23–24 weeks (pandemic) *(44)*	6–8 months (seasonal) *(43)* [b] 21 weeks (pandemic) *(44)*	5 months (seasonal) *(43)* [b] 38 days for production of purified antigen *(45)*	Similar to traditional inactivated vaccines	Similar to traditional inactivated vaccines
Immunogenicity	Antibody response	Moderate	Moderate	Moderate to strong	Moderate to strong	Moderate to strong
	Cell-mediated response	Low (moderate for whole virion)	Moderate	Low	Low	Low
Effectiveness[c]	Infants and children	Good	Infants: N/A[d] Children: good	N/A	Good	N/A
	Healthy adults	Good	N/A[d]	Good	N/A	N/A
	Older adults (≥ 65 years)	Moderate	N/A[d]	Good	Good	Good
	Pregnant women	Good	N/A[d]	Good	N/A	N/A
Safety and tolerability	Serious events	No evidence of safety concerns	No evidence of safety concerns	No evidence of safety concerns	No evidence of safety concerns	No evidence of safety concerns
	Local and systemic reactions	Low (low to moderate for whole virion)	Low	Low	Low	Low
Market	Usage and demand[e]	Very high (approx. 98%)[f]	Low (approx. 2%) *(15)*	Estimates unavailable	Estimates unavailable	Estimates unavailable
	Vaccine price	Moderate	Moderate to high	High	High	High
Other considerations	Advantages	**Egg-based**: widely used and available **Cell-based**: no mutations from egg-based adaptation; easier ramp-up	Ease of administration; possible herd immunity, some mucosal immunity	Rapid production; not reliant on eggs; no mutations from egg-based adaptation;	Stronger effectiveness and immunity in older adults	Stronger effectiveness and immunity in older adults
	Disadvantages	**Egg-based**: occasional decreased effectiveness from egg-based adaptation mutations; production could be affected by global supply **Cell-based**: more costly	Poorly and/or inconsistently effective in adults; cannot use in children under 2 years old[g]	Three times amount of HA protein required	Added cost	Four times amount of HA protein required

Abbreviations: HA =haemagglutinin; IIV =inactivated influenza virus; LAIV =live-attenuated influenza virus vaccine; N/A =not applicable; SAGE =Strategic Advisory Group of Experts.

[a] A physical virus or parts of it can be generated from genetic information, but currently approved vaccines are largely produced from candidate vaccine viruses (CVVs) prepared for that purpose.

[b] From strain selection to availability of vaccines.

[c] Effectiveness in protecting against laboratory confirmed infection; scale is a subjective and comparative assessment based on wide ranges reported across studies in existing literature.

[d] Not recommended in this population, as per SAGE recommendations *(37)*

[e] Estimated share of globally procured influenza vaccine supply.

[f] Adjuvanted and high-dose IIV included in this estimate, representing a very small share.

[g] Based on available evidence and recommendations from WHO *(37, 46, 47)*.

4.3 New technical platforms under consideration

New approaches to influenza vaccines are numerous and diverse and are designed to address one or more of the various challenges of influenza immunization, including candidates that hope to provide broader protection than current vaccines, a longer duration of protection, and higher and more predictable levels of effectiveness.

Use of influenza virus-based, recombinant proteins, virus-like particle (VLP), virus-vectored, non-VLP, and nucleic acid-based vaccine platforms in the development of next-generation influenza vaccines (described in detail in **section 4.8**) has been documented in a recent review and by CIDRAP's Universal Influenza Vaccine Technology landscape *(42, 48)*. This includes numerous vaccine candidates undergoing clinical trials and an extensive list in preclinical development. Recombinant technology can be, and often is, used in the production of novel influenza vaccines using these platforms.

The development of combination vaccines that include multiple respiratory viruses, including influenza, SARS-CoV-2 and/or respiratory syncytial virus (RSV), is a growing trend in vaccine R&D *(42)*. These vaccines promise advantages of broader protection across pathogens from one product, streamlining immunization schedules, and optimizing health system resources by reducing the need for multiple separate vaccines that need to be stored in a cold chain and given in separate injections. This approach has shown feasibility in clinical trials without compromising safety or effectiveness. However, challenges include potential vaccine hesitancy, where reluctance to receive one component (e.g. a COVID-19 antigen) could affect overall vaccine uptake. Additional complications include the frequency of re-vaccination as target groups need a single RSV vaccination but will need to be re-vaccinated against influenza and COVID-19 vaccination each year. Additionally, differences in antigen composition update timelines and recommendations between the targeted viruses could complicate manufacturing and deployment of these combination vaccines.

While most current influenza vaccines are produced using viruses grown in eggs or cell cultures, future vaccines are expected increasingly to utilize recombinant technology. This approach enables manufacturers to produce antigens directly in cells without the need for large-scale virus growth and purification, offering a significantly faster production process compared to traditional methods. Additionally, recombinant technology can simplify the development of virus-based vaccines by allowing the direct generation of candidate vaccine viruses from genetic sequences, reducing safety risks and eliminating the time required to ship physical virus samples to manufacturers.

Needle-free delivery systems, such as microarray patches, might offer significant benefits for influenza vaccination, especially in low-resource settings. These innovative methods can simplify administration, making it easier to conduct large-scale vaccination campaigns during seasonal outbreaks or pandemics and can offer advantages in the cold chain (cold chain space and logistics during campaigns) due to higher stability profiles. Additionally, alternative delivery methods (e.g. intranasal, as is already used for LAIV, or inhaled vaccines) can further streamline vaccine distribution, offering options that are less invasive and easier to administer, thereby expanding access to influenza vaccination in diverse populations.

4.4 Preclinical development: key issues

The Universal Vaccine Technology Landscape lists more than one-hundred candidate vaccines in late preclinical development, representing the promise of improved vaccine in the future. However, only a subset of these products will move forward into clinical trials after successful product development and demonstrated performance in preclinical studies. Several key issues in the preclinical development space were identified through a survey sent to developers of next-generation influenza vaccines, as described below *(49)*.

Scientific, technical, financial and regulatory factors influence progress through preclinical development. Key enablers include financial and technical support from funders, risk-sharing among partners, and the use of innovative vaccine platforms and adaptable technologies proven successful with other viruses. Access to robust animal models, serological and virological reagents, and iterative testing opportunities, along with expertise in process optimization and adherence to good laboratory practices, are also important to enable preclinical development, although these factors have also been cited as challenges. Additional challenges include the lack of established correlates of protection, evaluating vaccine performance for vaccines whose mechanism is different from that of current influenza vaccines, and the limited predictive value of preclinical data for human responses.

Regulatory and funding constraints further influence preclinical development. High costs associated with manufacturing and testing good manufacturing practices, materials and studies involving large animals, such as non-human primates, place significant financial burdens on developers.

Regulatory issues related to the absence of clear guidance on alternative models for evaluation, such as human challenge studies, or outcome measures for licensure, are considered challenges even in the preclinical stage of development.

4.5 Clinical development and regulatory pathway: key issues

The clinical development of influenza vaccines faces challenges due to the lack of well-defined biomarkers or correlates of protection. In the absence of specific immune markers that can serve as proxies for protection, influenza vaccines often rely on haemagglutination inhibition titres to estimate immunogenicity. While haemagglutination inhibition assays are suitable for vaccines that target the HA protein, they may not adequately reflect the protective potential of novel platforms or vaccine design approaches, such as those targeting different viral components or aiming for cell-mediated and/or broader immunity. This lack of standardized correlates of protection means that large-scale clinical trials with clinical endpoints such as laboratory-confirmed influenza infections are needed to assess efficacy, particularly for severe disease, which can be resource-intensive.

Clinical development, particularly large Phase 3 trials required to demonstrate efficacy, is costly. Unsurprisingly, the cost and funding of clinical development was cited as a key issue by next-generation influenza vaccine developers *(49)*. Many novel vaccines are being developed by academic or small biotech groups that lack large internal funding to support clinical product development. Progression through the development pipeline, even with positive early-stage data, can be delayed while seeking external funding and/or may require partnership with or technology transfer to a large vaccine manufacturer, including those that may have a competing product in development or on the market.

Human challenge studies have emerged as a way to evaluate influenza vaccine efficacy and immune responses in a small and controlled study, offering precise data on how well a vaccine can prevent or reduce disease using specific influenza strains. This model could help to identify correlates of protection for novel vaccines and provide baseline data on vaccine efficacy that de-risks further development and testing in larger clinical trials. However, there are challenges in selecting appropriate challenge viruses that accurately reflect circulating strains, as this selection can significantly influence the outcomes of such studies. These issues and others are discussed in detail in two reports following a meeting on the role of human challenges studies in the development of novel influenza vaccine candidates *(50, 51)*.

The regulatory process may be a significant challenge in licensing new vaccines, particularly for those aiming to provide broader or longer protection. The appropriate immune measures and validated assays to evaluate immunogenicity from novel vaccines must be determined prior to entering a large clinical trial. However, vaccine developers often do not know upfront what will be expected by regulatory agencies, adding uncertainty to their vaccine's ability to meet requirements for licensure. There is no widespread guidance, and developers must engage directly with regulatory agencies to plan their trials appropriately. The process for licensing a vaccine for longer protection (>1 year) may be conservative and lengthy, with initial licensing based on traditional regulatory pathways and timelines used for current influenza vaccines, followed by additional studies that can demonstrate longer protection.

Current clinical development has not included most high-risk populations in testing, with the exception of older adults. Although it is expected that post-licensure studies will eventually include these groups to broaden the vaccine's indication, initial licensure could result in unequal access to new influenza vaccines, especially among those most at risk for severe influenza.

Without established correlates of protection or accepted immunogenicity measures, large scale and costly efficacy trials will be required, at least initially, to evaluate the performance of novel vaccines. Use of immunogenicity measures for vaccine evaluation, as is the case for current influenza vaccines, may be a possibility once mechanisms of protection are elucidated for new vaccines, easing the cost of development for similar vaccines using the same platform or technology. Clear evaluation expectations, prompt communication and feedback on trial design, and some flexibility in licensure pathways from regulatory agencies would facilitate the clinical development of improved influenza vaccines.

4.6 Vaccine effectiveness: key issues

Vaccine effectiveness against influenza tends to vary significantly by season and across age and population groups. According to data from the United States Influenza Vaccine Effectiveness Network, the effectiveness of seasonal influenza vaccines in preventing laboratory-confirmed infections across all age groups has ranged from 19% to 60% over the past 16 seasons since 2009, with variations depending on the specific season *(52)*. Multi-country networks (e.g. REVELAC-i in Latin America and the Caribbean as well as i-MOVE and EuroSAVE in the European Region) are also monitoring influenza vaccine effectiveness and have produced estimates that fall within this range *(53–55)*.

The overall effectiveness of influenza vaccines is influenced by many host and viral factors, which include the following:

- **Circulating strain differences and virus evolution:** WHO updates vaccine formulations twice a year to match the predominant circulating strains in each hemisphere. However, in seasons with significant antigenic drift, especially those dominated by H3N2, lower vaccine effectiveness has been observed *(56–58)*. In particular, H3N2 typically shows the lowest vaccine effectiveness among vaccine influenza strains, and vaccine performance against this subtype can vary even within a single season due to differences in effectiveness against various phylo-genetic subclusters or variants of the H3N2 virus *(56, 59)*.
- **Age and population:** Older adults typically have reduced immune responses to influenza vaccines due to immunosenescence, and possibly the effects of previ-ous influenza exposures, which can alter immune respo-nse to vaccination. In addition, the health status of the person, the presence of comorbidities, and being immunocompromised, may affect the immune response.
- **Local epidemiological factors:** Previous exposure to influenza strains can influence vaccine effectiveness across different regions as some populations may have residual immunity, or limited responses to new variations, which can have an impact on the effectiveness of the current season's vaccine.

Beyond the factors directly affecting vaccine performance, the methodology for measuring vaccine efficacy or effectiveness has a significant impact on what is recorded. Randomized placebo-controlled trials of influenza vaccines are relatively scarce, especially in LMICs, leading to a reliance on observational studies for evaluating vaccine effectiveness. These observational studies provide estimates of vaccine effectiveness but are prone to various biases – such as confounding, selection bias, and information bias – and it is challenging to isolate the specific impact of influenza infection on broad outcomes such as all-cause mortality or pneumonia hospitalizations *(60)*. As a result, estimating how well vaccines reduce such nonspecific outcomes is complex, with potential over- or under-estimation of vaccine effectiveness due to confounders that are unaccounted for. In the absence of randomized controlled trials, the "test-negative design", which tests all patients meeting certain criteria for influenza-like illness using sensitive and specific methods like RT-PCR, has become a preferred method for assessing vaccine effectiveness against laboratory-confirmed influenza cases, especially in outpatient settings. WHO has developed technical guidance to support conducting influenza vaccine effectiveness assessments, including their design and interpretation *(61)*. In addition, WHO is developing a tool to estimate the burden averted by influenza vaccination, which takes into consideration vaccine coverage, effectiveness, and timing of the vaccination campaign to determine how many hospitalizations and deaths were prevented through vaccination.

These methodological challenges may have implications for the development of improved influenza vaccines, given the desire to show improved effectiveness in each population compared to current seasonal influenza vaccines, which will require side-by-side comparison in clinical trials or effectiveness studies in different target populations.

4.7 Vaccine safety: key issues

The safety of currently available influenza vaccines is well established, with different types offering varying profiles suitable for diverse population groups. IIVs have a long history of safe use. Adverse reactions are usually mild and transient, and severe adverse events are very rare. Guillain-Barré Syndrome has a vaccine-attributable risk of 1–2 cases of per million persons vaccinated *(37)*. Updated analyses show no excess risk of Guillain-Barré syndrome in adults ≥65 years. Concerns about anaphylaxis in individuals with egg allergies and risk of narcolepsy from ASO3-adjuvanted vaccines have been countered by evidence showing no increased risk of anaphylaxis from vaccination, and the association with narcolepsy limited to only one A(H1N1)pdm09 vaccine administered in several European countries during the H1N1 pandemic *(37)*. Recent data confirm continued safety in pregnancy, with no increased risks and some studies showing reduced risks for outcomes such as miscarriage and preterm birth *(62)*. However, there are some considerations with certain formulations, such as the adjuvanted or high-dose IIVs which tend to show slightly higher reactogenicity due to their enhanced immune-stimulating properties but which are still considered safe. Licensed recombinant protein HA vaccines have a similar reactogenicity profile to traditional IIVs *(38)*.

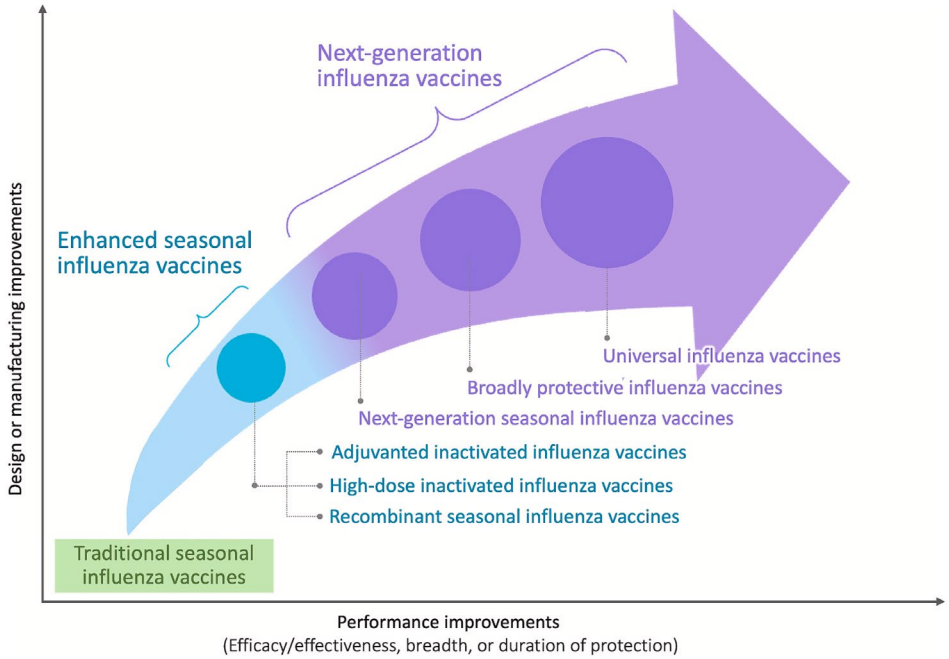
LAIVs, which are administered intranasally, have also demonstrated a strong safety record, particularly among children over 2 years of age and adolescents. LAIVs are associated with mild symptoms such as low-grade fever, a runny nose or sore throat post-vaccination, as the virus in the vaccine is weakened but is still able to replicate at lower levels. Due to their live nature, LAIVs are not recommended for certain groups, such as immunocompromised individuals or pregnant women, where the theoretical risk may be higher. LAIVs are also not recommended for children aged under 2 years due a higher likelihood of wheezing following vaccine administration *(63)*.

New influenza vaccines would be held to safety levels similar to those of existing vaccines, with any increased reactogenicity acceptable only in the context of improved protection against disease. Vaccines in the development pipeline using new platforms have not shown any safety concerns thus far; however, if licensed, ongoing post-licensure surveillance will be critical to monitor and identify any potential adverse events that may arise during wider use. In both pre- and post-licensure studies, the safety of new vaccines must include all target groups for vaccination, including older adults, pregnant women, children and individuals with comorbidities or underlying health issues *(64)*.

4.8 Summary of improved seasonal influenza vaccines development pipeline

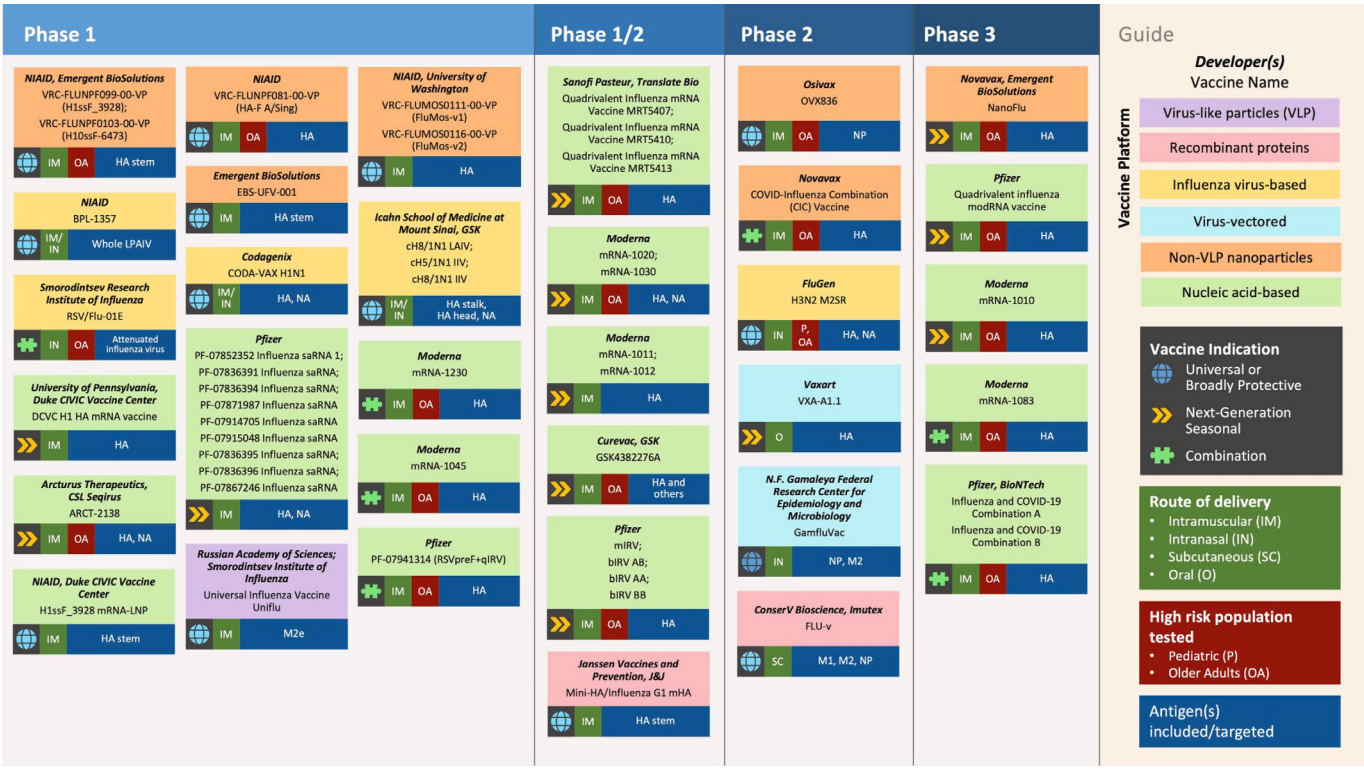
A general framework was used to categorize different improvements to influenza vaccines (**Fig. 5**).

FIG. 5. Framework for improved influenza vaccine categorization *(42)*



A recent analysis of the next-generation influenza vaccine candidates reveals a robust clinical development pipeline with a diversity of candidates and approaches to improve influenza vaccines for public health impact (Fig. 6) *(42)*. This pipeline is supported by an equally diverse and large preclinical landscape *(48)*. As of April 2024, the pipeline featured 56 candidates in clinical development across 24 developers using influenza virus-based, recombinant proteins, virus like particle (VLP), virus-vectored, non-VLP, or nucleic acid-based vaccine platforms. These platforms, combined with novel vaccine design approaches, could offer faster production timelines, enhanced immunogenicity, and broader protection against various influenza strains, including those not currently circulating. All identified vaccine developers are based in Australia, Europe, United Kingdom of Great Britain and Northern Ireland, or the United States. Any new information that may have become available between the time of the analysis and the publication of this report is not included.

FIG. 6. Landscape of next-generation influenza vaccines in clinical development, as of April 2024 *(42)*



Next-generation seasonal influenza vaccines make up the largest portion of the clinical pipeline, with 30 candidates under development as of April 2024. Nearly all of these vaccines ($n = 28$) are based on mRNA platforms, which could enable rapid production and customization against circulating influenza strains. Notable exceptions include two candidates that utilize nanoparticle- and adenovirus-based platforms, respectively, and one orally administered vaccine in the pipeline. While the mRNA vaccines primarily target the HA antigen, some developers are also targeting NA to improve protection. Three candidates from this category have been in Phase 3 trials.

There are 18 broadly protective or universal influenza vaccine candidates under development, representing the most diverse category in terms of vaccine platforms, as all named platforms are represented. These vaccines primarily target conserved influenza antigens, such as nucleoprotein, matrix protein (M1, M2), and neuraminidase, alongside the HA antigen. Notably, no universal or broadly protective vaccine is currently in Phase 3 trials, and two products were discontinued after Phase 3 trials due to failure to meet efficacy endpoints or closure of the company *(65, 66)*. Some candidates are being tested with adjuvants to boost immunogenicity.

The landscape also includes eight combination vaccine candidates, which integrate an influenza component with other respiratory viruses such as SARS-CoV-2 and RSV. Several of these products use similar platforms to their standalone influenza counterparts, and most combination vaccines primarily rely on mRNA technology. Three combination products are in Phase 3 trials.

Many next-generation influenza vaccine candidates in clinical trials are being tested in high-risk populations, particularly older adults (≥65 years), with all Phase 3 candidates focused on this age group. Only one candidate has been tested in children; results are pending. The safety profiles across platforms have been positive, with no serious adverse events reported. Next-generation vaccines are also being tested against current licensed vaccines, with some candidates demonstrating non-inferiority or superiority in immune response and efficacy. Combination vaccines are progressing showing similar effectiveness to standalone influenza vaccines *(42)*. Universal and broadly protective vaccines have shown encouraging results in terms of cross-reactivity and duration of immune responses, with some candidates inducing long-lasting and broad immune protection against both influenza A and B strains *(42)*.

Developers of late-stage next-generation influenza vaccines have a track record of successfully taking products to licensure, as they have all successfully developed and licensed COVID-19 vaccines with the same platforms as their Phase 3 influenza vaccine candidates. Several smaller biotech companies or academic groups have partnered with or been bought out by leading influenza vaccine manufacturers to develop their products, strengthening their capacity to advance their vaccines through clinical development. It is likely that a standalone or combination mRNA influenza vaccine will be licensed first among all candidates in the pipeline. With numerous mRNA influenza vaccines in development, the licensure of one is likely to set a precedent and pave the way for others to follow.

In addition to next-generation influenza vaccine candidates, there are ongoing clinical studies to expand the evidence base on enhanced influenza vaccines, testing these vaccines in paediatric age groups and other populations at high risk for severe disease, such as those who are immunocompromised or living with comorbidities. Other notable development of improved influenza vaccines includes early clinical testing of a seasonal influenza vaccine delivered through a microarray needle patch.

4.9 Pathway and timescale to licensure

Development of a novel vaccine can take 10–15 years after a candidate vaccine has been developed preclinically and has moved into clinical trials *(67)*. Existing infrastructure and regulatory familiarity with influenza vaccines, as well as gains in knowledge and clinical trial infrastructure from the immense amount of research done in developing COVID-19 vaccines with different platforms, may facilitate faster development and licensure of new influenza vaccines *(68)*. For example, new vaccines using existing platforms like inactivated virus vaccines can leverage the data and methodologies already established for current seasonal influenza vaccines, such as by using the response to HA as a primary immunogenicity measure. This immunogenicity measure may also be appropriate for vaccines using different platforms, provided they are designed elicit a response against HA and this response is predictive of protection from disease with that vaccine. For vaccines whose mechanism of protection is not HA antibody-based, it is likely that initial licensure will be based on efficacy against disease, which would require larger costly clinical trials to demonstrate a protective effect and could lengthen the development timelines.

The European Medicines Agency is currently updating its guidelines on evaluation of influenza vaccines to include or revisit guidance on novel platforms such as mRNA, the role of neuraminidase and human challenge studies in vaccine development, seasonal vaccine effectiveness data, paediatric vaccine development requirements, and primary readouts in serological studies.

Several next-generation influenza vaccine candidates are in or have completed Phase 3 development, including mRNA candidates from manufacturers with approved mRNA vaccines for other respiratory pathogens. These vaccines are expected to be used similarly to existing seasonal vaccines (annual administration, composition based on WHO-recommended strains) but may provide superior protection or programmatic suitability and shortened production time resulting in early deployment to countries. It is conceivable that a novel influenza vaccine may be approved in the next few years. The timeline for vaccines that provide broader protection is expected to be longer as these candidates are in earlier stages of development.

4.10 Key gaps in knowledge or research evidence

As the number of novel candidates advancing to late-stage clinical trials increases, it will be critical to identify correlates of protection and establish clear clinical evaluation criteria for next-generation influenza vaccines. Robust correlates of protection act as surrogate markers for vaccine efficacy, facilitating the comparative evaluation of vaccine candidates and supporting evidence-based decisions in clinical trial design and analysis. These markers also help to reduce risks for manufacturers during the development of new vaccines *(69)*. Additionally, establishing scientific consensus and regulatory guidelines to define and evaluate the breadth of protection is greatly needed to support regulatory review.

While the evidence base on the safety and performance of enhanced influenza vaccines in different vaccination target groups is growing, next-generation influenza vaccine candidate data are focused on healthy and older adults. Even though testing in other target groups, including children, may be expanded following initial licensure in healthy and older adults, this approach deprioritizes these groups that also are at increased risk for severe disease. It could also delay their access to improved influenza vaccines, which would be especially critical during a pandemic if sufficient evidence on the safety and performance of new vaccines across target groups is lacking.

5. Criteria for country decision-making and attribute preferences for improved influenza vaccines

The extent to which improved influenza vaccines are perceived as valuable and meriting public investment remains poorly understood, particularly in LMICs where seasonal influenza vaccines are in limited use today. Many factors influence those perceptions and can result in different adoption decisions and patterns. Understanding those factors and assessing how the different improved seasonal influenza vaccines profiles score against them is critical to understanding the potential for future adoption and impact of those products.

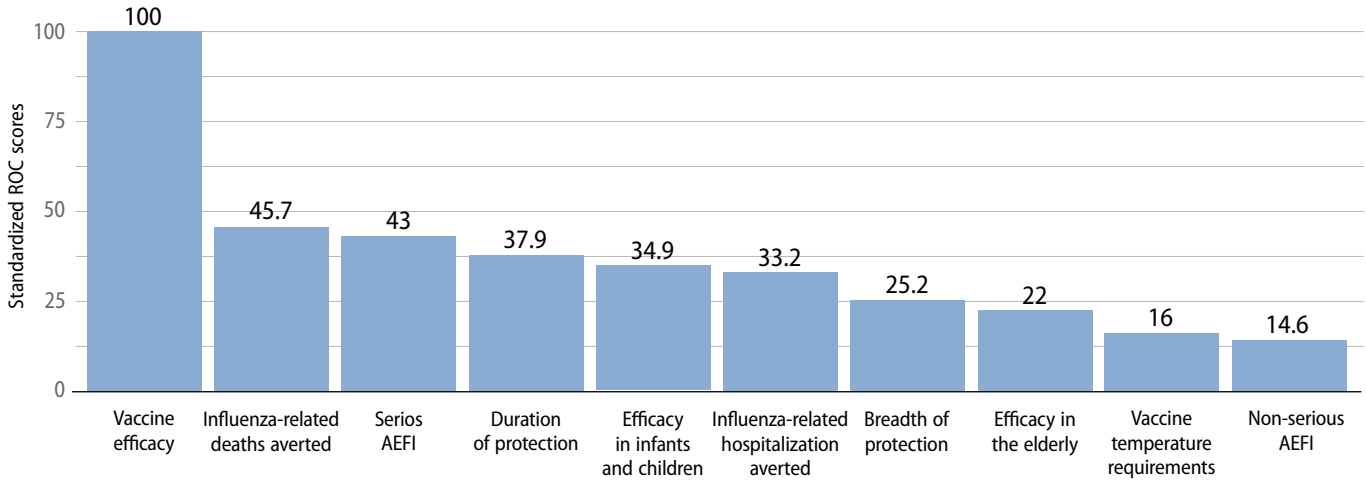
A multiple criteria decision analysis (MCDA) was conducted in Kenya and Thailand to improve the understanding of the factors influencing decision-makers, complemented by an additional assessment in 11 LMICs and UMICs (lower-middle-income and upper-middle-income). These additional countries included: Albania, Armenia, Bhutan, Cote d'Ivoire, Ghana, Mongolia, Morocco, Paraguay, Peru, South Africa and Tunisia. This allowed for the identification of the attributes of improved influenza vaccines that are most important to decision-makers when considering their future inclusion in national immunization programmes.

The MCDA is a structured methodology used to identify which criteria are relevant to decision-makers, the importance attached to each, and how to use this information in a framework for assessing available alternative products or services *(70)*. An MCDA combines qualitative and quantitative elements, incorporating stakeholder perspectives and using models to represent preferences and performance of different alternatives. MCDAs have been previously employed in LMICs to help determine which vaccines to include in national immunization programmes or which other health interventions to prioritize in national healthcare systems *(71–75)*.

In both Kenya and Thailand, stakeholders identified vaccine efficacy, duration of protection, breadth of protection, safety (intended as absence of severe adverse events following immunization), temperature stability, and shelf-life as the key criteria directing future policy decisions on improved influenza vaccines. Other criteria relating to health benefits, such as the number of influenza-related deaths and hospitalizations averted, were also selected.

When considering the responses from the additional 11 countries where criteria preferences were explored, although in less depth compared to the research performed in Kenya and Thailand, the same criteria emerged as the highest priorities except for shelf-life (Fig. 7). The combined results from all respondents highlighted how vaccine efficacy is by far the most important decision criterion in general, and also specifically concerning specific age groups, such as infants, children and the elderly.

FIG. 7. Global standardized rank order centroid criteria ranking of 10 highest ranked criteria (number of respondents = 97)



These results suggest the existence of a core set of criteria relevant to the policy and adoption decisions of future improved influenza vaccines in different upper-middle-income countries (UMICs) and LMICs; among those, vaccine efficacy stands out as the primary area of focus. The criteria identified through the MCDA should guide the development of improved influenza vaccines to meet country priorities, with a specific focus on improving vaccine efficacy to support broader adoption of influenza vaccines globally.

Further details regarding methods and results can be found in the accompanying peer-reviewed article available at: https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/vaccine-impact-value/full-value-of-improved-influenza-vaccine-assessment-(fviva).

6. Defining the market for improved seasonal influenza vaccines

6.1 Market overview

6.1.1 Use cases and potential market segments

Influenza vaccines are used in populations across the life course through different delivery channels. Because of the antigenic drift, vaccines must be administered annually at the beginning of or during the influenza transmission season. These unique aspects of influenza vaccines, combined with an efficacy generally lower than that the other vaccines and a higher lifetime cost of vaccination, lead to lower vaccination coverage than desirable. Expediting improvements in coverage in order to increase the vaccines' health impact and public health value requires sufficient financial resources to procure and deliver influenza vaccines to a larger proportion of the population. Improvements are needed in the performance of the vaccines (e.g. efficacy, duration of protection) and in their delivery and uptake. To this aim, a good understanding of the use cases of influenza vaccines is critical *(76)*.

The improved influenza vaccines under development may deliver higher efficacy but must be developed with a clear understanding of their use (their use cases) to avoid specific product characteristics creating barriers to their implementation (e.g. ultra cold chain requirements). Optimization of the delivery strategies will also be required to achieve high vaccination coverage. This will require an improved understanding of the delivery channels used to deliver current seasonal influenza vaccines to different target populations.[2] In 2024, Member States began reporting to WHO on the delivery strategy and payment approach used to provide seasonal influenza vaccination to recommended populations.

Through the application of a specific methodological framework designed to allow the definition of the use cases, the targeted populations, the health-service providers charged with the administration, and the delivery channels used for the administration were identified as the factors influencing the use of the vaccine across all profiles (i.e. current, minimally improved, significantly improved, game changers) *(77)*.

As a result of the analysis, nine use cases were identified, describing the most relevant uses of existing and, potentially, improved seasonal influenza vaccines (Fig. 8).

Use case 1: A pregnant woman is vaccinated in a health facility with fixed equipment cold chain by a health worker (e.g. during antenatal care visit).

Use case 2: A health worker is vaccinated in their health facility with fixed equipment cold chain by a health worker.

Use case 3: A child, accompanied by a caregiver, is vaccinated in a health facility with fixed equipment cold chain by a health worker.

Use case 4: An individual with underlying conditions is vaccinated in a health facility with fixed equipment cold chain by a health worker (e.g. during a visit to the health facility to monitor and/or treat any underlying condition).

Use case 5: An older adult is vaccinated in a health facility with fixed equipment cold chain by a health worker.

Use case 6: Individuals with underlying conditions and older adults are vaccinated in a pharmacy with fixed equipment cold chain by a health worker or pharmacist.

Use case 7: A pregnant woman is vaccinated in the community without fixed equipment cold chain by a health worker in a mobile session.

Use case 8: A child, accompanied by a caregiver, is vaccinated in the community without fixed equipment cold chain by a health worker in a mobile session.

Use case 9: Individuals with underlying medical conditions and older adults are vaccinated in the community without fixed equipment cold chain by a health worker in a mobile session.

[2] Insert reference for the influenza use case manuscript, once published.

FIG. 8. Seasonal influenza vaccine use cases[3]

Delivery Location	Target Population: Pregnant women	Health workers	Children (6–59 months)	Individuals with underlying conditions	Older adults (>65 years old)
Health facility (hospital, health center, health post) Delivery strategy: fixed site with cold chain	1 Pregnant woman is vaccinated in a health facility with full cold chain by a health worker	2 Health worker is vaccinated in a health facility with full cold chain by a health worker	3 Child, accompanied by caregiver, is vaccinated in a health facility with full cold chain by a health worker	4 Individual with underlying conditions is vaccinated in a health facility with full cold chain by a health worker	5 Older adult is vaccinated in a health facility with full cold chain by a health worker
Pharmacy (public or private accredited) Fixed site or outreach with cold chain				6 Individual with underlying conditions and older adults are vaccinated in a pharmacy with full cold chain by a health worker or pharmacist	
Setting with limited or no health service (e.g. school, workplace, religious institution, nursing home, other locations) Outreach/mobile or fixed site without cold chain	7 Pregnant woman is vaccinated in the community with no cold chain by a health worker in a mobile session		8 Child, accompanied by caregiver, is in the community with no cold chain by a health worker in a mobile session	9 Individual with underlying conditions and older adults are vaccinated in the community with no cold chain by a health worker in a mobile session	

High-level estimates of the respective sizes of the nine use cases were defined to understand their relevance at the global level and differences across geographical regions, as well as to assess the full potential of different implementation strategies.

While acknowledging the limited quality of the data with regard to the frequency at which different vaccine delivery channels are utilized by different populations to access seasonal influenza vaccine, extensive desk reviews and stakeholder consultations were performed to support the development of preliminary estimates. Those reviews focused on collecting available data on the target populations and the use of different delivery channels for seasonal influenza vaccines in different countries.

Health facilities were identified as the delivery channel with the most critical role in the delivery of seasonal influenza vaccines across all populations and geographies, complemented by pharmacies for the elderly and adults with comorbidities in high-income settings and community delivery for children under 5 years of age in lower-income settings. Across all of the use cases, and assuming full (100%) coverage of the targeted populations, more than 3 billion people could be reached with seasonal influenza vaccines, with Use case 4, Use case 5, Use case 3 and Use case 8 in decreasing order of importance, all exceeding the 10% of the total population that can be reached (Fig. 9).

Understanding the use cases for influenza vaccines enables national influenza programmes to optimize delivery of influenza vaccines to maximize their impact. The characteristics of improved influenza vaccines may change the relative importance of some of the identified use cases and may also enable new use cases. To attain high coverage of current and improved influenza vaccines, the use cases should be considered as part of vaccine delivery planning.

Further details on the methodology and results of the definition of the use cases and their sizing can be found in the accompanying peer-reviewed article: https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/vaccine-impact-value/full-value-of-improved-influenza-vaccine-assessment-(fviva).

[3] For the purposes of the use case assessment, older adults were defined as those aged >65 years. The definition of this population for seasonal influenza vaccination recommendations varies (i.e. in some countries it is >60 years).

FIG. 9. Sizing of different seasonal influenza vaccine use cases

Delivery Location	Target Population: Pregnant women	Health workers	Children (6–59 months)	Individuals with underlying conditions	Older adults (>65 years old)
Health facility (hospital, health center, health post) Delivery strategy: fixed site with cold chain	1 180	2 60	3 420	4 1050	5 640
Pharmacy (public or private accredited) Fixed site or outreach with cold chain				6 100	
Setting with limited or no health service (e.g. school, workplace, religious institution, nursing home, other locations) Outreach/mobile or fixed site without cold chain	7 25		8 320	9 250	

Note: Numbers in each box represent millions of people.

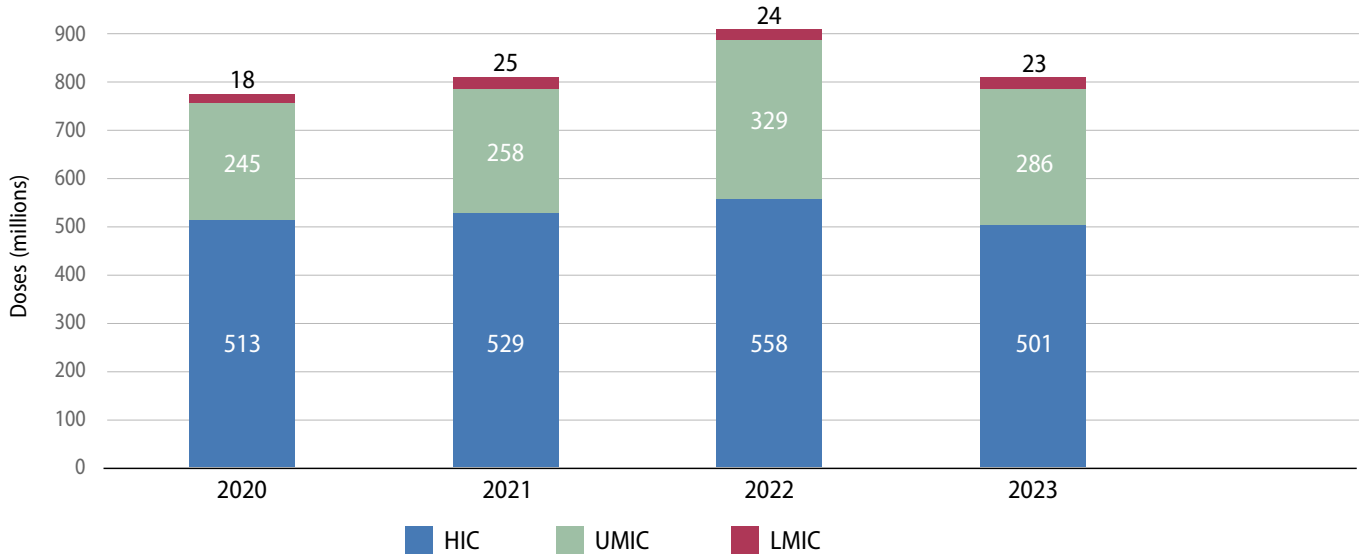
6.1.2 Vaccine demand forecast (current and improved vaccines)

The estimate of potential demand for a new vaccine is a core component of the FVIVA, allowing measurement of utilization of the product as a function of its characteristics (as captured in the PPCs), the alignment with decision-makers' priorities, and the vaccine's use cases. The demand projections provide the basis for estimating the health and economic impact as well as for assessing the vaccine's viability from the perspectives of the country and the producer.

According to WHO's Global vaccine market report, in the past four years the number of seasonal influenza vaccine doses procured globally has ranged in the area of ~600–900 million doses, making it the second largest vaccine market by volumes globally (**Fig. 10**) *(78)*. Procurement of seasonal influenza vaccines is highly concentrated. Since 2019 high-income countries (HICs) and UMICs together have procured ~97% of all seasonal influenza vaccine doses globally, with LMICs and low-income countries comprising 3% and 0%, respectively. As of 2022, 128 WHO Member States had a formal national seasonal influenza vaccination policy, and 143 Member States reported that influenza vaccines were able in the public and/or private sectors *(79)*. In terms of availability of influenza vaccines in the public and private health sectors, according to Member State reporting from WHO/UNICEF's joint reporting form, 19% of low-income countries reported that they have influenza vaccines available in the public and/or private sectors, compared to 43% of Gavi-eligible lower-middle-income countries, 77% of non Gavi eligible lower-middle-income countries, 92% of UMICs, and 95% of HICs *(79)*.

Taking the presented volumes as a starting point, a global demand forecast was developed using a standard population-based forecasting method approved by WHO's IVIR-AC *(80–83)*. The demand forecast for current seasonal influenza vaccines was based on the following key assumptions: implementation of national influenza vaccination policies, targeted populations and vaccination coverage were likely to remain constant at current levels (i.e. no policy expansions or new vaccine introductions). Vaccination coverage for each target population was based on available stratified reports and analyses complemented by assumptions applied to the coverage in the WHO/UNICEF joint reporting form.

FIG. 10. Estimated number of seasonal influenza vaccine doses procured globally



The forecast for the other improved influenza vaccines assumed that all countries would eventually adopt each vaccine (i.e. switch or introduce) and that vaccination coverage was likely to increase in the year of introduction and in subsequent years of implementation, given the greater perceived benefits of these vaccines. The coverage assumptions were varied by target population (Table 4). The frequency of vaccination was assumed to vary on the basis of the characteristics of the improved influenza vaccine profile (i.e. duration of protection). Minimally improved vaccines were assumed to attain marketing authorization in the next two years, while significantly improved influenza vaccines (profiles B.1, B.2, C) were assumed to reach the market in eight years and 12 years, respectively, after which country adoption could begin. Country adoption timelines were determined on the basis of the status of current influenza vaccination policies, the robustness of existing influenza surveillance, vaccine introduction history and fiscal space.

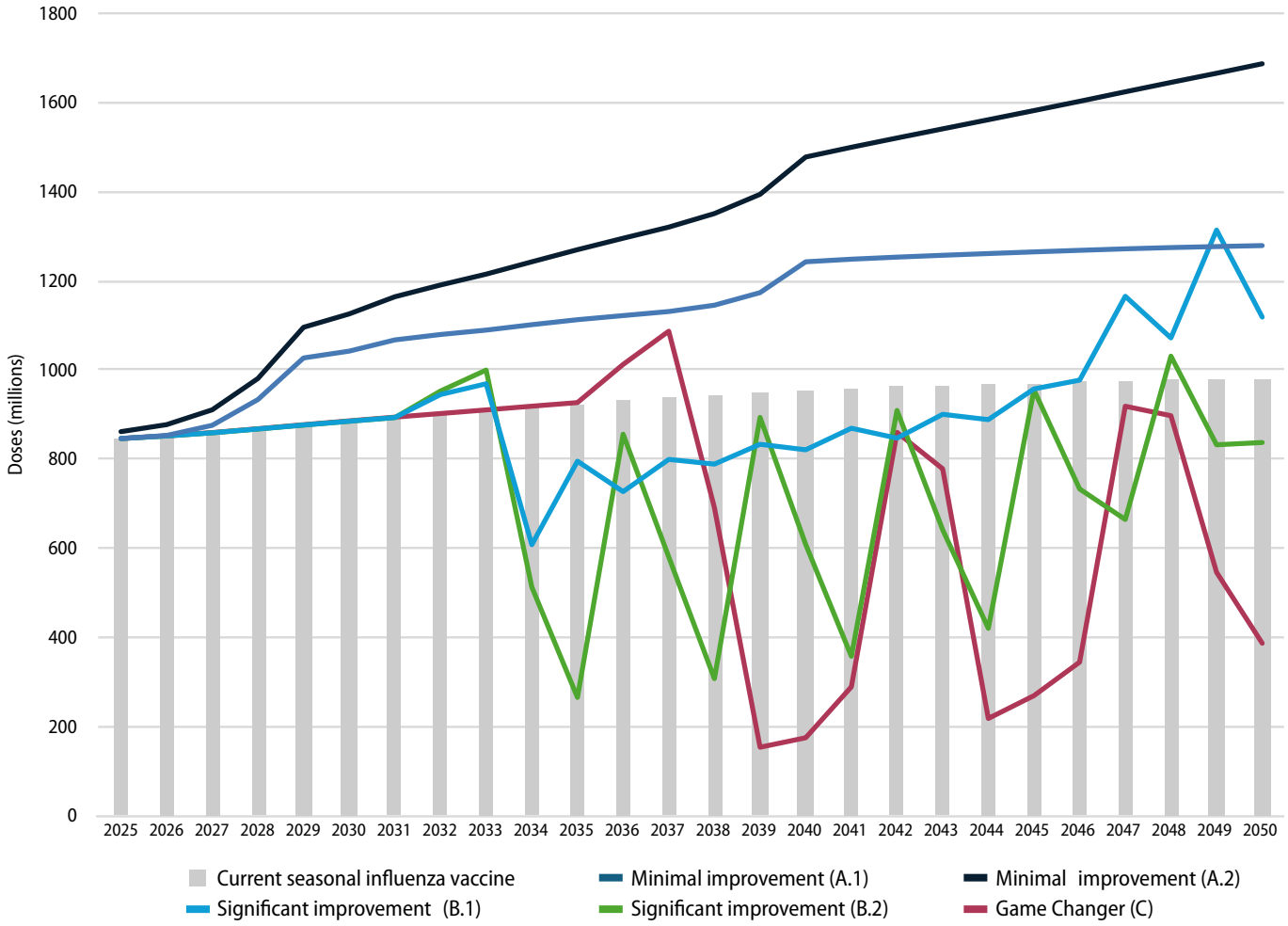
TABLE 4. High-level assumptions for improved influenza vaccine demand forecast

Improved influenza vaccine scenario	Assumed year of introduction or product switch	Absolute coverage increase on year of introduction	Relative annual coverage increase after introduction
Current seasonal influenza vaccine	No new introductions assumed	0%	0%
Minimal improvement (A.1)	HICs: 2027–2029 UMICs: 2028–2032 LMICs: 2029–2043	5%	0%
Minimal improvement (A.2)		0 – 10%	0 – 3%
Significant improvement (B.1)	HICs: 2032–2034 UMICs: 2033–2037 LMICs: 2034–2047	2.5 – 12.5%	2.5 – 5 %
Significant improvement (B.2)		5 – 7.5%	0 – 3%
Game changer (C)	HICs: 2036–2038 UMICs: 2037–2041 LMICs: 2038–2050	7.5 – 15%	2.5 – 5%

The total global demand for current seasonal influenza vaccines is ~850 million doses, and is anticipated to grow ~10% in the next 10 years up to ~920 million doses, driven by demographic changes in the populations currently using seasonal influenza vaccines. Vaccine demand for the improved influenza vaccine profiles was modelled through to 2050 to account for vaccine development and global adoption timelines.

Vaccine demand for minimally improved influenza vaccines (A.1 – duration; A.2 – efficacy) is forecast to exceed demand for current seasonal vaccines by ~30–75%, due to increased coverage in all target populations and the continued annual vaccination requirement (Fig. 11). Demand for an improved influenza vaccine with a profile similar to that of B.1 (efficacy, duration) was estimated to exceed demand for current vaccines by 15% in 2050, driven by higher coverage given its improved perceived benefits but offset by biannual vaccination. For vaccine profiles B.2 and C, which have longer duration of protection, vaccine demand could vary more year over year due to the timing of different populations seeking revaccination. Compared to current vaccines, demand for B.2 and C vaccines is forecast to decline by 5–10% as a result of higher population coverage but with reduced annual demand due to revaccination occurring every 3 or 5 years. For improved influenza vaccines with longer duration of protection, careful coordination of supply and demand between countries and suppliers will be essential to ensure that implementation and supply planning are aligned and to enable a sustainable market. It is important to note that evolution in future demand for current and improved seasonal influenza vaccines is uncertain and is influenced by factors that include the availability of improved influenza vaccines, government fiscal space, and the prioritization of influenza vaccination programmes in lower-resource settings.

FIG. 11. Forecast of influenza vaccine demand, by vaccine profile, 2025–2050



Detailed information on the forecast for current seasonal influenza vaccines can be found in the MI4A market study: https://cdn.who.int/media/docs/default-source/immunization/mi4a/who_mi4a_global_market_study_seasonal_influenza_vaccine.pdf *(84)*.

6.1.3 Global influenza vaccine production capacity

Through the Global Action Plan on Influenza Vaccines (2006–2016), WHO and partners supported low- and middle-income countries (L&MICS) to develop local influenza vaccine production capacity *(85)*. Recognizing that seasonal influenza vaccination production capacity provides insight into the global supply of pandemic influenza vaccines, since 2006 WHO has regularly assessed global influenza vaccine production capacity. Vaccine production monitoring is one of the six high-level actions within the Global Influenza Strategy and is also part of the Pandemic Influenza Preparedness Framework High Level Implementation Plan, which outlines the strategy for strengthening global pandemic influenza preparedness from 2024 to 2030, with a focus on equitable and sustainable supplies of pandemic influenza vaccines and other products *(86)*.

Global vaccine production capacity is estimated through information collected from surveys of established influenza vaccine manufacturers. Vaccine production capacity is estimated as the maximum number of doses that could be produced if manufacturers were operating at full-scale within a 12-month period. This differs from estimates of available supply for commercialization, as estimated in WHO vaccine market studies, which is the number of doses available for sale at global level in one typical year with normal production facility utilization.

Since WHO's initial assessment of influenza vaccine production capacity in 2006 (500 million doses of seasonal influenza vaccines), the global capacity has increased substantially to 1.47 billion seasonal vaccine doses in 2015, which could potentially support a monovalent pandemic vaccine production capacity of 6.37 billion doses *(87)*. In 2019, the best-case scenario for pandemic vaccine production capacity was 8.31 billion doses *(88)*.

Global influenza vaccine production capacity data was last collected in 2023 *(40)*. Overall capacity has been sustained since 2019 at 1.53 billion seasonal vaccine doses and 4.13 and 8.26 billion pandemic vaccine doses at moderate and best-case scenarios, respectively. The moderate case scenario assumes twice as much antigen per dose is needed to elicit a sufficient immune response. The majority (over 80%) of seasonal and pandemic production capacity is from egg-based vaccines, which could be significantly affected if an avian pandemic virus was also circulating in egg-laying poultry. This estimate does not include potential mRNA vaccine production capacity (as no mRNA seasonal influenza vaccines are currently licensed). mRNA vaccine production capacity is likely to be included in the next WHO production capacity assessment (anticipated for 2026–2027).

Vaccine manufacturing capacity exists in all WHO regions except for the African Region, but it is highly concentrated in high-income countries (~80% of global pandemic production capacity), with some in upper-middle- income countries as well (~20% of global pandemic production capacity). WHO is committed to supporting the building of local and regional vaccine production capacity. Between 2007 and 2019, WHO supported developing country manufacturers in establishing or enhancing influenza vaccine production capacity through the Global Action Plan on Pandemic Influenza Vaccines (GAP) Technology Transfer Initiative (TTI) programme; in 2023, 14% of global seasonal influenza vaccine capacity was produced by six GAP/ TTI grantees *(40, 85, 88)*.

TABLE 5. Overview of global influenza vaccine production capacity over time *(40)*

Year	Seasonal (billions of doses)	Pandemic – moderate case (billions of doses)	Pandemic – best case (billions of doses)
2006	0.50	0.75	1.50
2015	1.47	3.19	6.37
2019	1.48	4.15	8.31
2023	1.53	4.13	8.26

The current global vaccine production capacity could potentially vaccinate everyone in the world with one vaccine dose in the best-case pandemic scenario, provided that there were no limitations on supplies/reagents, the pandemic strain grew equally well in eggs/cells as seasonal strains, and the same amount of antigen as normally used for each seasonal strain would be enough to elicit an adequate immune response. It may also require accelerated regulatory processes, equitable access and allocation of vaccine supply across countries, and acceptance of available vaccines. Any supply or reagent limitations or changes in amount of antigen or viral growth dynamics could significantly reduce the number of people who could be vaccinated fully. Additionally, these estimates are based on a period of 12 months, during which there may be inequities in vaccine access, as occurred during previous pandemics, including the 2009 H1N1 pandemic *(90–92)*. There may also be a need to administer two or more doses per person to confer adequate protection.

Through the Pandemic Influenza Preparedness Framework, WHO is expected to have access to approximately 11% of future pandemic influenza vaccine production for allocation and distribution to developing countries *(22)*. Manufacturers have reported advance purchase agreements with more than 30 countries *(93, 94)*. Efforts to build vaccine

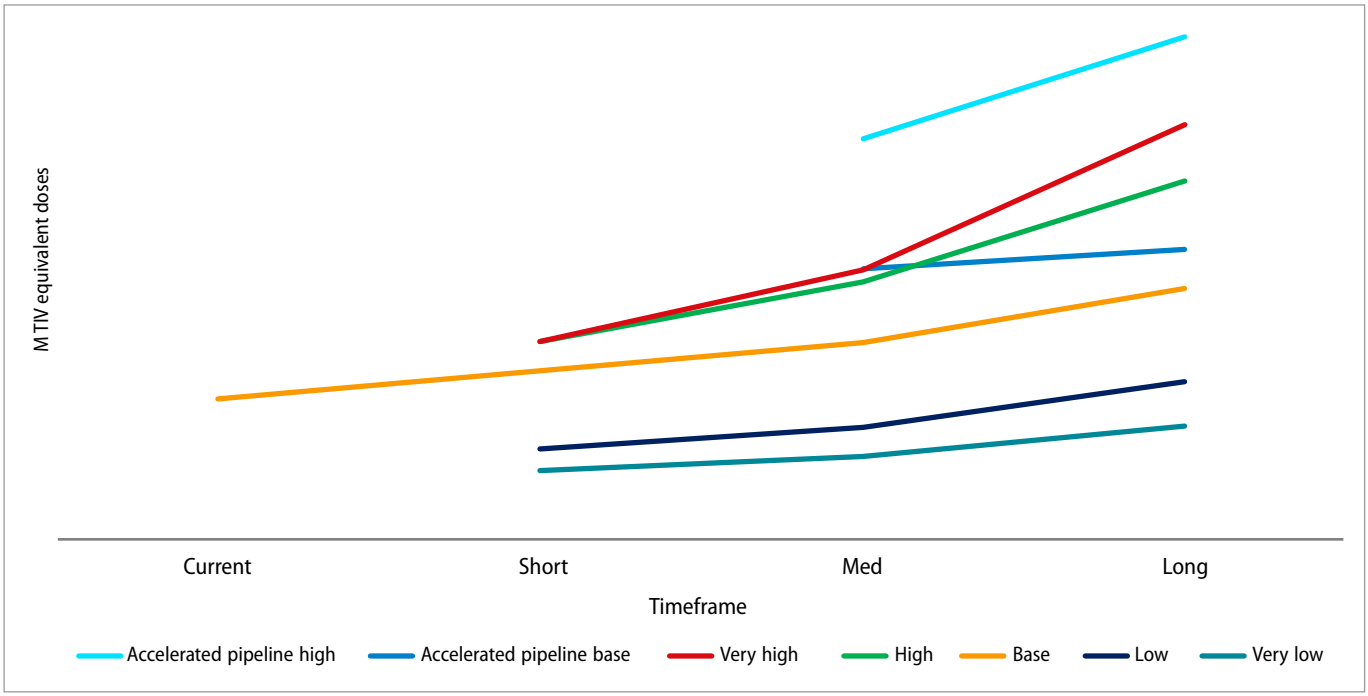
manufacturing capacity in Africa and other low-income settings could also support equitable access to vaccines. New technologies used in improved influenza vaccines, such as mRNA, could help diversify the supply and reduce reliance on egg-based vaccines. They may also strengthen access to vaccines if existing infrastructure, operational and regulatory processes, and technology built up for the COVID-19 vaccine response are leveraged for influenza vaccines.

6.1.4 Available supply for commercialization

Since 2006, efforts have been ongoing to increase manufacturing capacity for influenza vaccines with the goal of achieving full preparedness against an influenza pandemic and to increase global population protection against the virus *(95, 96)*. Manufacturing capacity is a necessary condition for enough vaccine doses to become available to the population. However, this is not sufficient, and multiple factors may prevent installed capacity from translating into available vaccine supply. Understanding the real availability of doses to fulfil demand is paramount for all components of the FVIVA.

Consultations with manufacturers and experts, as well as a review of publicly available information on seasonal influenza vaccines, provided the basis for an assessment of the current and future global available supply for commercialization (ASC) of seasonal influenza vaccines (**Fig. 12**). ASC is defined as the number of doses available for sale at global level in one typical year with utilization of normal production facilities across the various vaccines (not factoring in special market, regulatory or technical events). Current ASC is 1.2 billion trivalent-equivalent doses, which is within the range of production capacity estimates presented in the previous section *(84)*.[4]

FIG. 12. Available supply forecast for commercialization of influenza vaccines over time



M TIV: manufactured trivalent inactivated influenza vaccine equivalent doses

Pipeline vaccines are included in the analysis with assumptions capturing how, in the next decade, progress in development of improved influenza vaccines will contribute to increase the available supply. Importantly, in the base supply scenario, if improved vaccines are assumed to be introduced by producers with other vaccines already in the market, product substitution is assumed, with no increase in the overall supply. Long-term assumptions beyond 2035

[4] All ASC has been standardized to trivalent-equivalent doses to enable a dose-to-dose comparison and because manufacturing capacity is shared between quadrivalent and trivalent doses. It is assumed that each quadrivalent dose is equivalent to 1.25 trivalent doses.

regarding the dynamics of influenza vaccine supply are not included in this assessment due to high levels of uncertainty.

The base scenario which modelled a modest increase of ASC from current producers and typically paced entry of pipeline vaccines resulted in a 1.8-fold increase of ASC in the long term compared to current ASC. In the base scenario, supply is anticipated to remain adequate to support demand for improved influenza vaccines across all demand scenarios modelled as part of the FVIVA.

Additional scenarios were modelled to understand potential supply dynamics based on manufacturer decisions related to the continuation of seasonal influenza vaccine production and levels of vaccine production, as well as the success of pipeline candidates, including improved vaccines, as follows:

- A low scenario modelling limited market exits, minimal increase of ASC from current producers and limited success in pipeline vaccine availability results in a 1.6-fold reduction in ASC in the next 3–5 years.
- A high scenario which modelled no market exits, a modest increase of ASC from current producers, and an optimistic view of the progress of clinical development of pipeline vaccines would result in a three-fold increase in ASC in 8–10 years. Acceleration in the availability of nucleic acid vaccines may lead to ASC increases of up to four-fold in the long-term. All sizeable increases in medium and long-term ASC would materialize only as a response to significantly increased demand; therefore careful coordination and planning are required.
- A very low scenario, which is a worst case with low likelihood of occurrence, and which assumes that several current producers exit the market, was also modelled and would result in a two-fold reduction in ASC in the short term. In the long term, without increases in ASC from remaining producers in the market, or new market entrants, ASC would remain lower than current ASC in the base scenario.

In all supply scenarios, apart from the very low scenario, supply is forecast to be sufficient to support demand for improved influenza vaccines in all of the demand scenarios modelled.

6.1.5 Price benchmarking for improved influenza vaccines

To assess the public health impact and commercial value of improved influenza vaccines, it is critical to understand the potential prices of these innovative vaccines. To support the financial and economic analysis (Chapter 8), public market vaccine procurement prices were estimated for improved influenza vaccine profiles on the basis of a benchmarking approach.

Prices for improved influenza vaccines benchmarks were developed on the basis of price trends identified for current and enhanced seasonal influenza vaccines, other vaccines where performance improvements have been made, vaccine price differentials between markets, and inputs from expert consultations.

Several key assumptions were made to inform the price benchmarking:

1	2	3	4
Price data for enhanced influenza vaccines (i.e. high-dose or adjuvanted) are not yet widely available in the public market. Therefore United States Medicare prices were used to estimate the price differential between non-enhanced and enhanced influenza vaccines.	The observed price differentials in the United States Medicare market between non-enhanced and enhanced influenza vaccines were assumed to be maintained in other markets. However, the base price of non-enhanced influenza vaccines was likely to be lower than in the United States Medicare market.	On the basis of price differentials for other enhanced vaccines in public markets (e.g. improvements made to human papilloma virus vaccine, pneumococcal conjugate vaccine), the price differential for enhanced influenza vaccines will be lower in non- United States public markets than observed in the United States Medicare market.	Compared with other adult vaccines, the price for current seasonal influenza vaccines (i.e. non-enhanced and enhanced) is relatively low (driven in part due to a highly competitive market, seasonal manufacturing requirements and clearing of inventory before the end of the influenza season). Consequently, there is latitude for a wider price differential between enhanced and improved influenza vaccines than for other higher-price enhanced vaccines (e.g. Human papilloma virus vaccine, pneumococcal conjugate vaccine).

The resulting price estimates for improved influenza vaccines were stratified by income strata and, for LMICs, were further stratified by the method of procurement due to its influence on vaccine price (Table 6). Consistent with pricing trends for other enhanced vaccines, prices for improved influenza vaccines are expected to increase as their performance (i.e. efficacy, breadth of protection, duration of protection) improves.

Overall, considering the anticipated additional health benefits to be offered by improved influenza vaccines, the prices of these novel vaccines are likely to be substantially higher than the prices observed for current seasonal influenza vaccines in HICs, UMICs and self-procuring LMICs. Prices for improved influenza vaccines are likely to increase in tandem with the health benefits they provide (see increasing prices for improved influenza vaccine profiles B and C) and are likely to be tiered by different market segments, similar to the pricing of other available vaccines. One exception to these anticipated price evolutions is in LMICs which procure from the United Nations, where the prices of improved influenza vaccines are likely to increase compared to current seasonal influenza vaccines, but will not scale to the same degree as that to which influenza vaccine performance improves because of low tolerance for price increase in these markets.

TABLE 6. Benchmark price estimates for improved influenza vaccines

Scenario name		Performance improvements		Price per dose (public market price)				
				US$	Other HICs	UMICs	Self-procuring LICs and LMICs	United Nations procuring LICs and LMICs
				2022 Volumes / % global market				
		Efficacy (match / mismatch)	Duration	164m (19%)	30 (36%)	367 (43%)	21 (2.5%)	1.4m (0.2%)
0	Current seasonal vaccines	70%/40%	6 months	$24	$10.50	$7.50	$4.50	$4.50
	Enhanced seasonal vaccines	70–90% / 40–70%	6 months	$73	$21	$15	$5.50	$4.50
A1	Improved vaccines (duration or efficacy)	70%/40%	1 year	$80–90	$25–30	$16–18	$5.75–6	$4.50–5.50
A2		90%/40%	6 months					
B1	Improved vaccines (efficacy, duration or breadth, duration)	90%/70%	2 years	$150– 220	$40–60	$20–30	$8.25–11	$5.50–6.50
B2		70%/70%	3 years					
C	Improved vaccines (efficacy, breadth, duration)	90%/90%	5 years	$250– 750	$80–200	$35–105	$11–25	$6.75–.50

6.2 Key gaps in knowledge or research evidence

In-country evaluation of the use cases for influenza vaccines across a range of settings can enable further refinement. The accuracy of the use case sizes could be improved if supported by further operational research to understand the delivery channels and strategies employed in different settings to provide influenza vaccines to recommended target populations.

The precision of demand forecasts could be enhanced with improved vaccination coverage data for different target populations, which could be ascertained through targeted and improved vaccination coverage surveys. If those data could be made available and combined with a more precise sizing of the use case, the demand forecast could be improved and more directly linked to assumptions for specific implementation strategies. Product acceptance testing among different target populations could also support refinements in the assumptions regarding potential changes in vaccination coverage in response to improved vaccines becoming available.

The development of price benchmarks for improved influenza vaccines could be further refined on the basis of the inputs of "willingness to pay" analyses, as well as immunization budget analyses, to assess the financial impact of improved influenza vaccine pricing on broader immunization and health budgets.

7. Health impact and economic analysis of improved seasonal influenza vaccines

7.1 Background

Three previous country-specific studies have examined the impact and cost-effectiveness of next-generation influenza vaccines. The first study found that for paediatric vaccination in Kenya, while current and minimally improved vaccines may not be cost-effective, universal vaccines could be cost-effective if priced below US$ 5.16 a dose *(97)*. In Thailand a study found that adopting next-generation influenza vaccines could be cost-effective at prices between US$ 2.80 and US$ 12.90 per dose for minimally improved vaccines, up to between US$ 24.60 and US$ 69.90 per dose for universal vaccines, depending on the age-targeting strategy *(98)*. In the long term, adoption of significantly improved or universal vaccines was potentially cost-saving in Thailand, but in the short term there might be substantial budget impacts of procuring higher-priced vaccines even though they are cost-effective. The third study in the United Kingdom found that replacing current seasonal vaccines with next-generation vaccines could be cost-effective at prices up to £18 for minimally improved vaccines, and as much as £230 a dose for universal vaccines *(98)*.

A recent global modelling study (available in pre-print) projected the potential global impact of next-generation influenza vaccines across 186 countries over a 30-year period from 2025 to 2054 *(100)*. The study estimated the threshold prices, compared to no vaccination, at which different vaccines would be cost-effective, and also explored a range of age-targeting strategies using uniform coverage assumptions across countries. This study found that the current and minimally improved vaccines were unlikely to be cost-effective in many low- and lower-middle-income countries, but at appropriate prices universal vaccines could be cost-effective in most of the countries evaluated. However, the prices at which vaccines were cost-effective varied with the ages targeted, and strategies targeting children were more cost-effective than those targeting older adults.

The analysis conducted for the FVIVA uses the same underlying epidemiological and economic model as the global modelling study, but incorporates different demand projections for the different vaccine types, as presented in Chapter 6. The health impact and maximum threshold prices of improved vaccines (i.e. the maximum price at which vaccination would be cost-effective) are estimated compared to current vaccines and incorporate both the impact of changes in vaccine characteristics, as well as the projected change in the uptake, introduction date and frequency of revaccination.

In the subsequent chapter of this report, the results presented here are combined with benchmarked vaccine prices from Chapter 6 to estimate the global net monetary benefit under different vaccine scenarios.

7.2 Modelling approach

7.2.1 Model framework

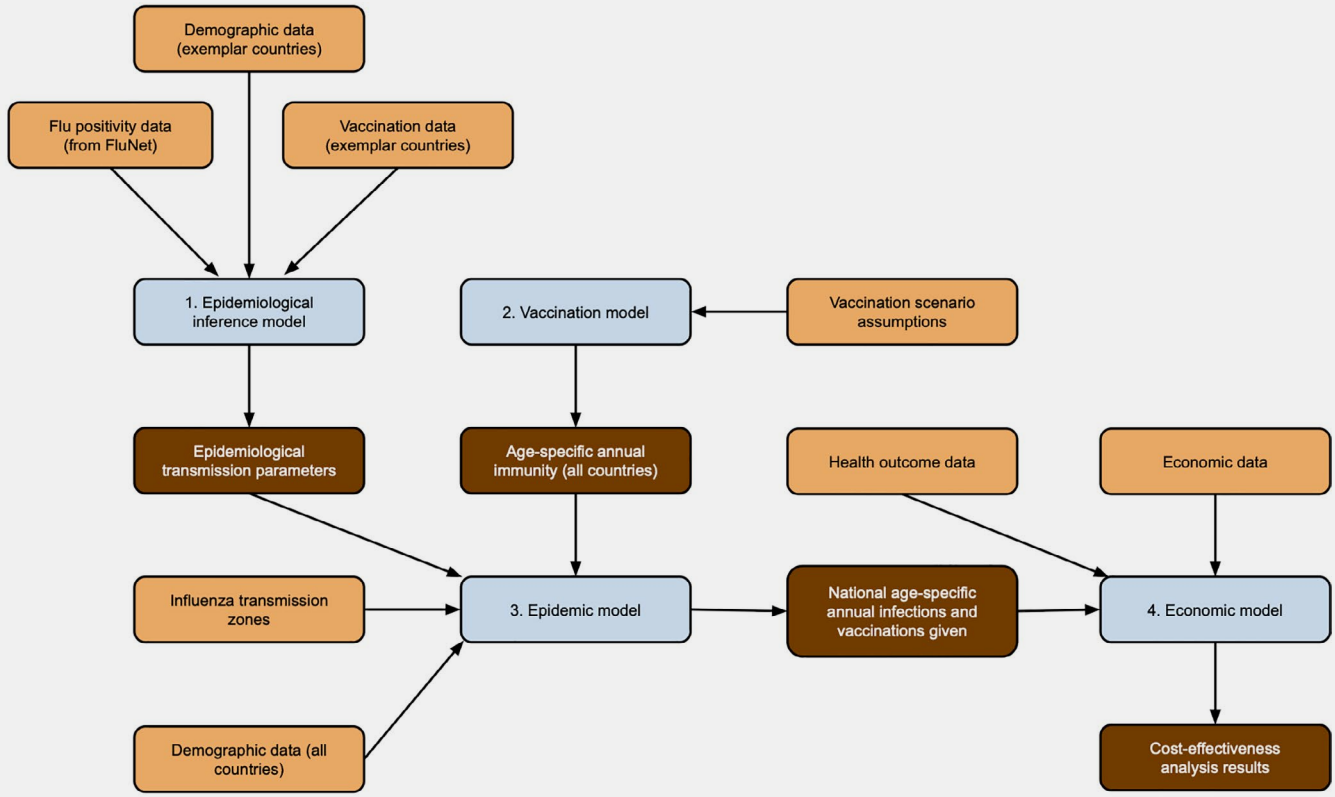
The modelling approach was based on the framework reported by Goodfellow et al. for assessing the future impact of improved influenza vaccines across 186 countries *(100)*. This framework consists of the following four steps (Fig. 13 (a)): 1) inference of current influenza transmission parameters in regions with similar transmission dynamics; 2) use of a vaccination model to project age- and vaccination status-specific populations in each country; 3) use of an epidemic model to simulate future influenza epidemics in each country; and 4) an economic model to estimate the health outcomes and threshold vaccine prices. A list of key model input parameters and associated data sources are presented in Table 7.

The details of the transmission model used for epidemic inference (step 1) and simulating future epidemics (step 3) are shown in (Fig. 13 (b)). In brief, this is an extension of a susceptible (S), exposed (E), infected (I), recovered (R) type compartmental model that is stratified by vaccine status and strain (influenza A or B). The model is further stratified into four age groups, namely 0–4, 5–19, 20–64 and 65 years and older.

FIG. 13. Model framework

(a) Overview of modelling steps

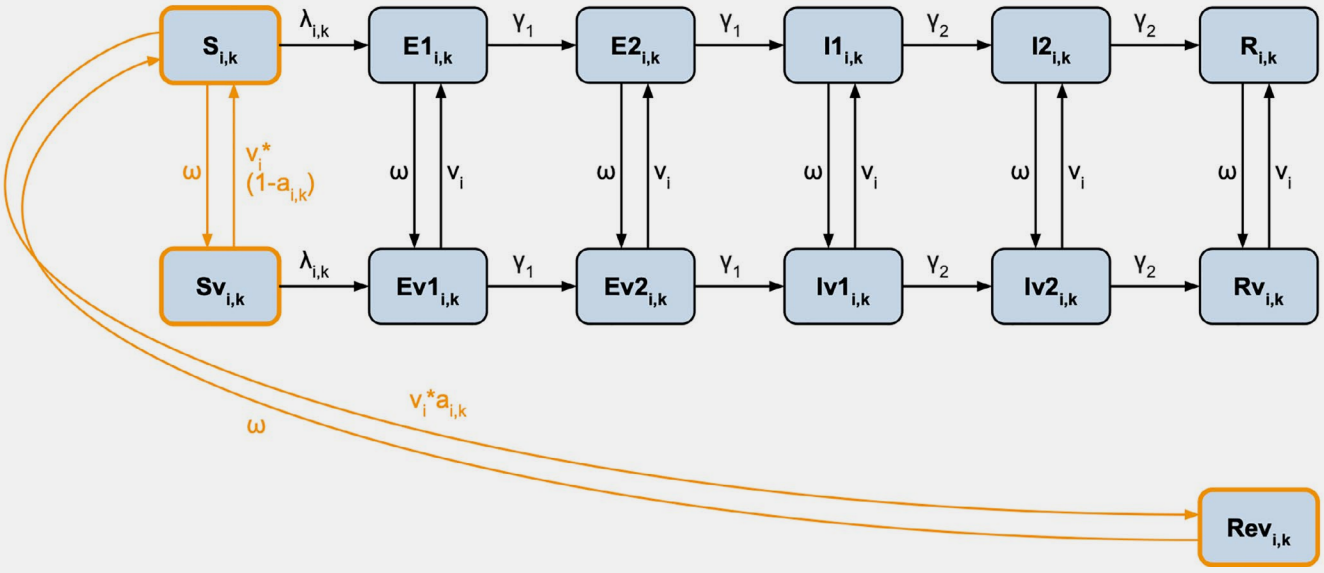
Orange indicates inputs, brown indicates outputs, blue shows the modelling elements.



(b) Vaccination and transmission models

Compartments outlined in orange and transitions in solid orange are included in both the vaccination and the transmission models. Transitions in black are included only in the transmission model.

"v" denotes the age-specific rates of vaccination; "a" denotes the vaccine effectiveness, which varied by age and strain and depended annually on whether the vaccine matched circulating strains in each hemisphere, and "ω" denotes vaccine-derived immunity waning. Each compartment was stratified by age "i" and strain "k". Ageing, births and age-specific mortality are not included in this diagram.



Source: Reproduced from Goodfellow et al. *(100)*

TABLE 7. Epidemic and economic model inputs

Model input	Value	Source
Influenza transmission zones	Seven zones	Chen et al. *(43)*
Laboratory-confirmed weekly influenza infections	Strain-specific, in seven exemplar countries	World Health Organization *(44)*
Demographic parameters	National-level, 2025 values	World Population Prospects, 2022 *(45)*
Contact patterns	National level, scaled to projected demography	Prem et al. *(46)*
Proportion symptomatic	0.669 (95% CI: 0.583–0.745)	Carrat et al. *(47)*
Proportion with fever	0.349 (95% CI: 0.267–0.442)	Carrat et al. *(47)*
Infection-hospitalization ratio	National-level, age-specific	Extrapolated from Paget et al. *(101)*, Cromer et al. *(102)*
Infection-fatality ratio	National-level, age-specific	Extrapolated from Iuliano et al. *(11)*
Disability weights	–	Global Burden of Disease study *(103)*
Cost of hospitalization	National-level, age-specific	Regression using GDP per capita
Willingness-to-pay threshold	National level, scaled to 2022 GDP per capita	Pichon-Riviere et al. *(104)*
Delivery costs	National level	Portnoy et al., regression on additional HIC data *(105)*
Vaccine wastage	10%	Assumption
Discounting	3% annual discounting of costs and benefits, with 0% discounting of benefits as a sensitivity analysis.	World Health Organization guidance *(7)*

Note: GDP = gross domestic product.

7.2.2 Model fitting

The model was used to estimate the global health and cost-effectiveness of improved influenza vaccines. National-level surveillance data on laboratory-confirmed influenza infections vary widely in availability and consistency. Hence, a global categorization of countries with similar influenza epidemiology was used to project characteristics of influenza transmission inferred for a limited number of exemplar countries onto the rest of the world (**Fig. 14**). Using data from FluNet, Bayesian inference was used to estimate key model transmission parameters for influenza A and influenza B epidemics between 2010 and 2019 in seven exemplar countries, each representing an influenza transmission zone (**Fig. 15**).

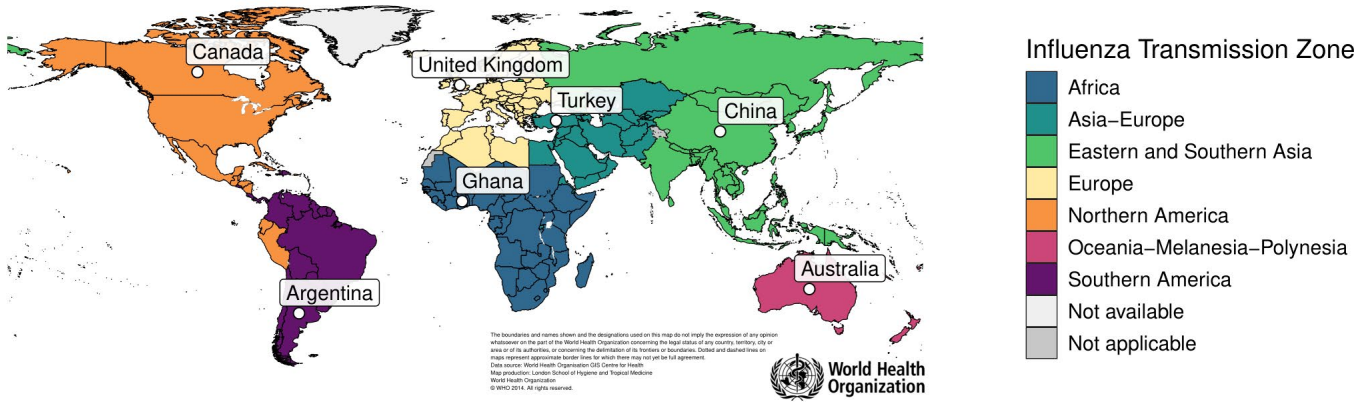
7.2.3 Vaccine scenarios

To project the potential future impact of influenza vaccines, random 25-year periods of epidemics running from 2025 to 2050, inclusive, were simulated in 186 countries or territories using exemplar countries' inferred influenza transmission parameters. National-level demographic changes were incorporated based on projected 2025 birth and mortality rates *(45)*.

The impacts of current influenza vaccines and five different improved influenza vaccine scenarios were estimated on the basis of the WHO PPCs: A1 – minimally improved duration; A2 – minimally improved efficacy; B1 – significantly improved efficacy/duration; B2 – significantly improved breadth/efficacy; and C – improved efficacy, breadth and duration (**Table 8**).

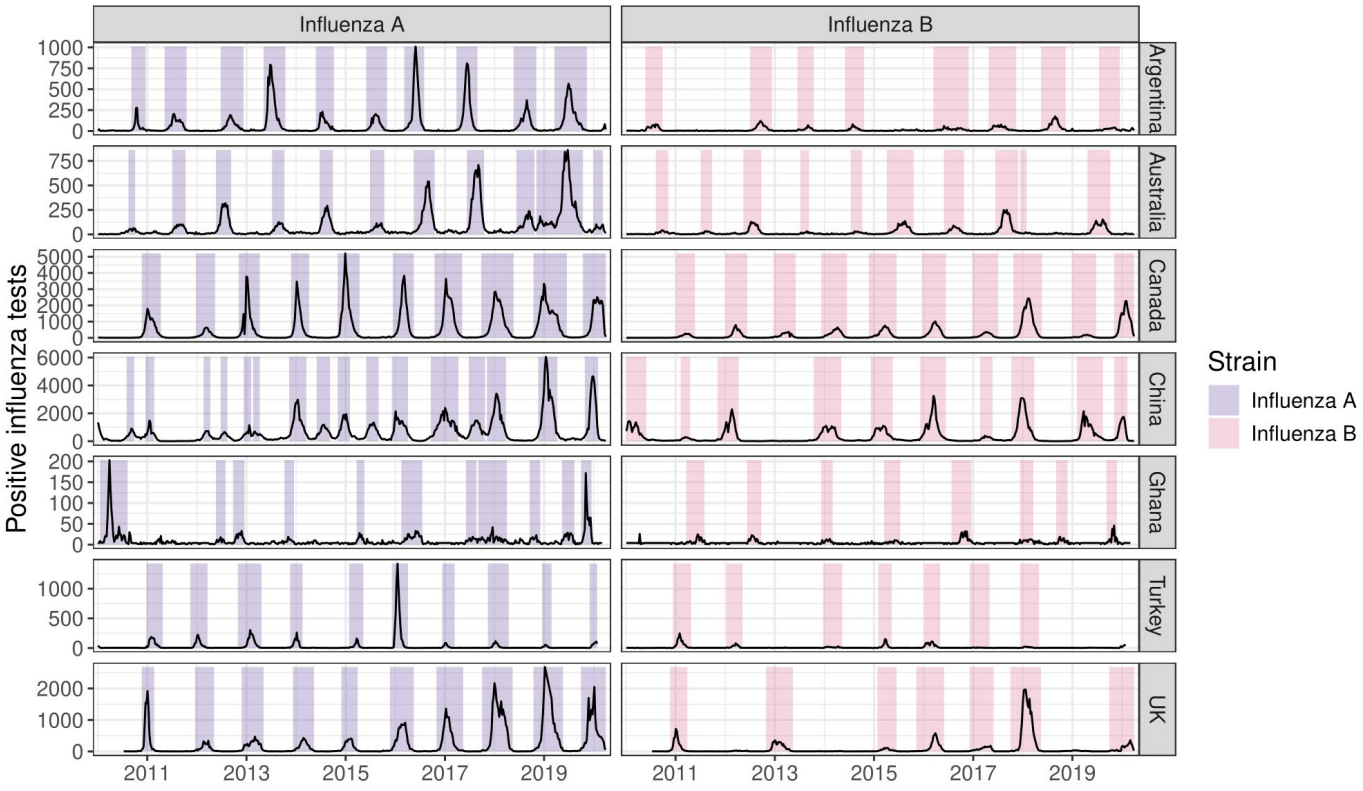
The vaccine coverage in each country, age group and year was based on the demand projections in **Fig. 11**. Vaccine doses were assumed to be distributed independently of previous vaccination and infection status, but with no additional increased protection to individuals receiving multiple doses.

FIG. 14. Map of influenza transmission zones



Note: White dots show exemplar countries for each influenza transmission zone.
Source: Reproduced from Goodfellow et al. *(100)*

FIG. 15. FluNet data in each exemplar country over the inference period



Note: Data are stratified by influenza strain, showing the total number of positive tests. Shaded time periods indicate identified epidemics.
Source: Reproduced from Goodfellow et al. *(100)*

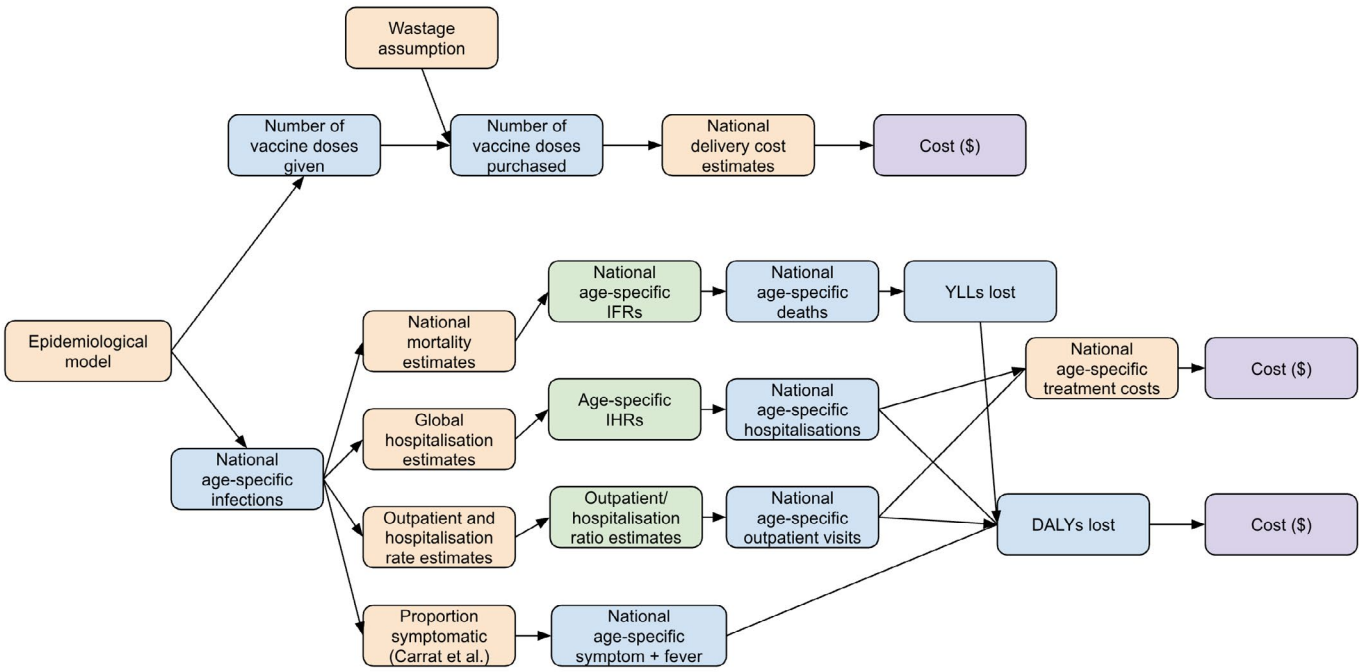
TABLE 8. Assumptions for current and improved influenza vaccine scenarios

Vaccine scenario	0. Current seasonal vaccines	A.1 Minimally improved (duration)	A.2 Minimally improved (efficacy)	B.1 Significantly improved (efficacy, duration)	B.2 Significantly improved (breadth, duration)	C Game changer (efficacy, breadth, duration)
Mean immunity duration	6 months	1 year	6 months	2 years	3 years	5 years
Coverage timing	1 year	1 year	1 year	2 years	3 years	5 years
Efficacy in matched season (0–64, 65+)	70%, 46%	70%, 46%	90%, 70%	90%, 70%	70%, 46%	90%, 70%
Efficacy in mis-matched season (0–64, 65+)	42%, 28%	42%, 28%	42%, 28%	70%, 46%	70%, 46%	90%, 70%
Mismatched seasons?	Yes	Yes	Yes	Yes	No	No

7.2.4 Health and cost outcomes

The links between the epidemiological model and the various health and cost outcomes are illustrated in Fig. 16.

FIG. 16. Links between the epidemiological model framework and the economic model of health and cost outputs



Infected individuals were assumed to experience either asymptomatic or symptomatic influenza infections, with symptomatic infections occurring with or without fever and potentially leading to hospitalization or death. National-level epidemiological and economic data were estimated on the basis of existing data. The number of deaths and hospitalizations were estimated using national age-specific infection fatality ratios and infection hospitalization ratios calculated on the basis of previously published estimates *(11, 101)*.Disability-adjusted life years (DALYs) were then estimated by combining "years of life lost" per death with "years lived with disability" for the different health outcomes calculated using disability weights from the Global Burden of Disease study *(103)*.

Costs were calculated from a healthcare-payer perspective. National costs of hospitalized cases were estimated using data from existing systematic reviews in a regression model predicted by Gross Domestic Product (GDP) per capita. Costs of vaccine delivery were based on estimates from a meta-regression analysis for low- and middle-income countries and extrapolated to HICs using a regression against health-care expenditure per capita *(105)*. In the base case analysis, future costs and DALYs were discounted at 3% annually, and DALYs were discounted at 0% as a sensitivity analysis. All costs were expressed in US dollars at the 2022 rate.

7.2.5 Economic analysis

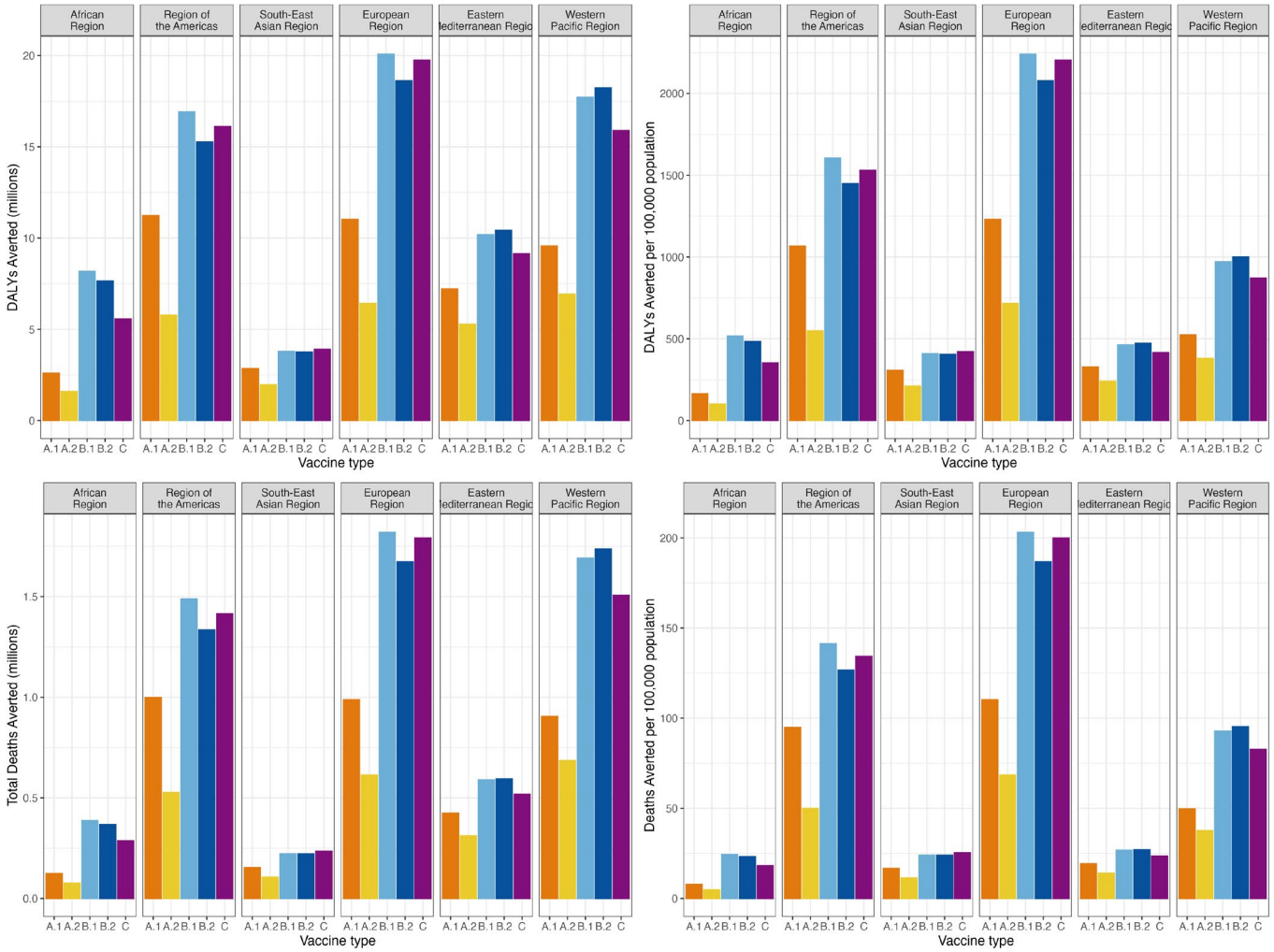
The fitted model was used to estimate the incremental costs and benefits of the projected coverage of different improved influenza vaccine types compared to the coverage (including zero coverage) of current influenza vaccines over the period 2025 to 2050. The vaccine threshold price in each country was then determined by calculating the maximum price per dose at which each type of improved vaccine was cost-effective, using country-specific values of the willingness-to-pay per DALY averted. In the base case, empirical cost-effectiveness thresholds estimated by Pichon-Riviere et al. were used. In sensitivity analysis, fixed thresholds of 0.3 x GDP per capita and 1.0 x GDP per capita were used in each country.

7.3 Estimated impact of different improved vaccines on the global disease burden

Compared to current seasonal vaccines, improved influenza vaccines were projected to prevent between 6.6 and 18.0 billion additional influenza infections globally between 2025 and 2050. This was estimated to prevent between 2.3 and 6.2 million extra deaths due to influenza and avert between 21 and 57 million additional DALYs. However, the estimated impacts are not distributed equally across regions (**Fig. 17**) with benefits concentrated in European, Americas and Western Pacific regions, reflecting a combination of regional differences in population size and in projected demand, as well as earlier dates of introduction of improved vaccines and higher vaccination coverage. This contrasts with the analysis by Goodfellow et al., which showed the much higher global impact that could be achieved with high and uniform coverage across all regions.

Overall, the additional impact of significantly improved vaccines was substantially higher than that of minimally improved vaccines. Perhaps surprisingly, over the analysis period, "game changer" vaccines were found to have only a similar level of impact to the significantly improved vaccines; however, this finding probably reflects assumptions that the development of these vaccines is expected to take longer and therefore fewer country introductions will occur in the evaluated time period. Another interesting feature of the results is that vaccines with minimally improved duration had a higher impact than vaccines with minimally improved efficacy, although the level of difference varied across regions pointing to the importance of epidemic timing on the impact of vaccines with short protection.

FIG. 17. Estimates of additional deaths and DALYs averted compared to current influenza vaccines by WHO region between 2025 and 2050 for different types of improved influenza vaccine



Note: Totals are shown on the left-hand panels and estimates per 100 000 population are shown on the right-hand panels. Vaccine scenarios: A.1 – minimally improved (duration); A.2 – minimally improved (efficacy); B.1 – significantly improved (efficacy, duration); B.2 – significantly improved (breadth, duration); C. – "Game-changer".

7.4 Cost-effectiveness of different improved influenza vaccines compared to current vaccines

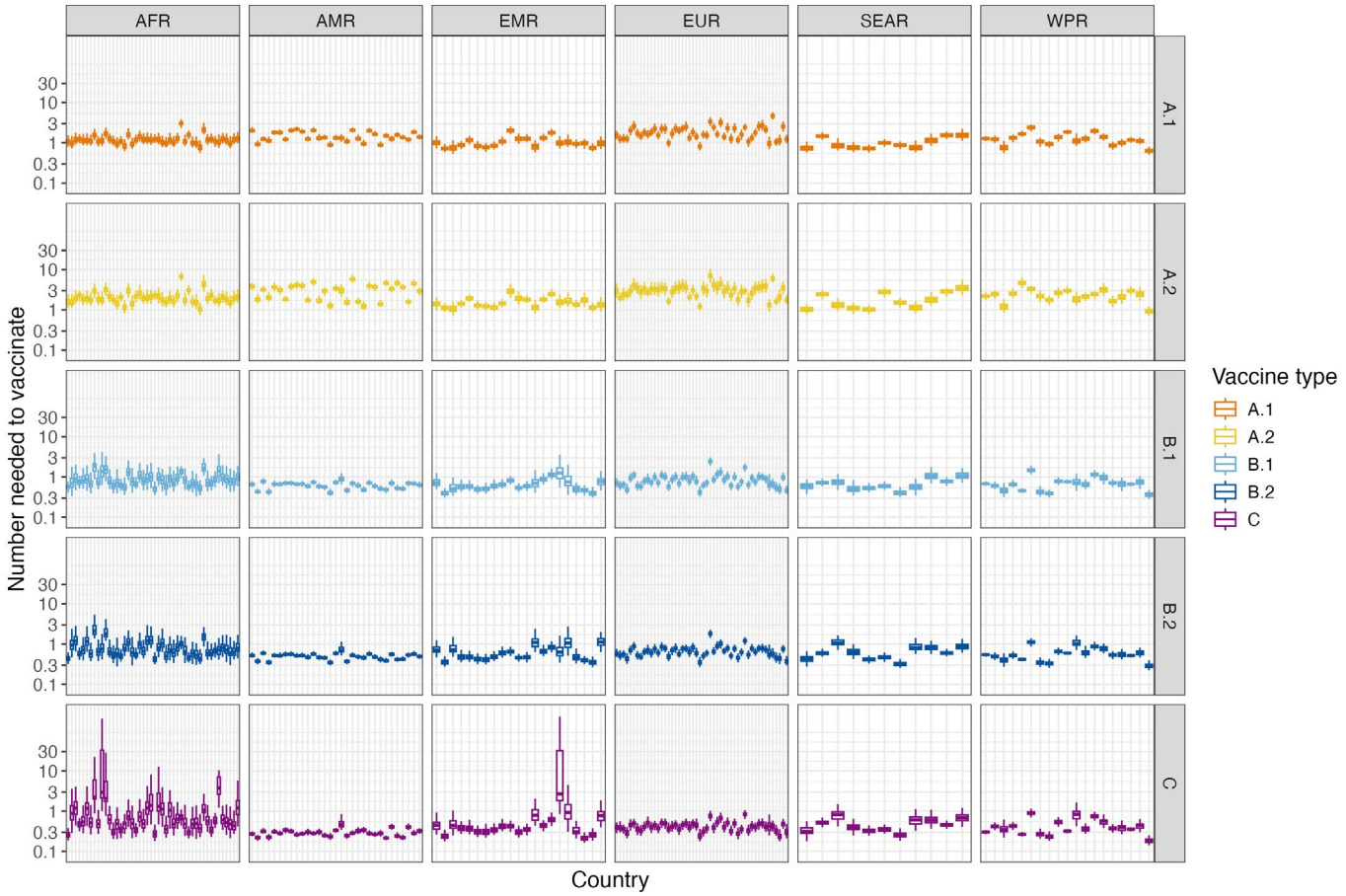
7.4.1 Estimated number needed to vaccinate

The number of individuals who need to be vaccinated (NNV) to prevent one influenza infection provides a measure of the relative efficiency of different types of vaccine. The estimated NNV for the different vaccine types are shown in Fig. 18.

Globally, the NNV was about 2.5 for minimally improved efficacy vaccines, falling to around 1.5 for minimally improved duration vaccines. For significantly improved vaccines and "game changer" vaccines the NNV dropped below 1, indicating that on average each vaccine dose prevents multiple infections.

At the country level there is substantial variation in the NNV, notably for significantly improved and "game changer" vaccines for some countries in the African Region. For these countries, higher NNVs for these vaccine types may reflect late introduction of the vaccines within the time horizon of the model. This in turn may not fully capture the benefits of longer duration protection vaccines.

FIG. 18. Number needed to vaccinate to avert one influenza infection for different vaccine types by country and region between 2025 and 2050 using demand projections

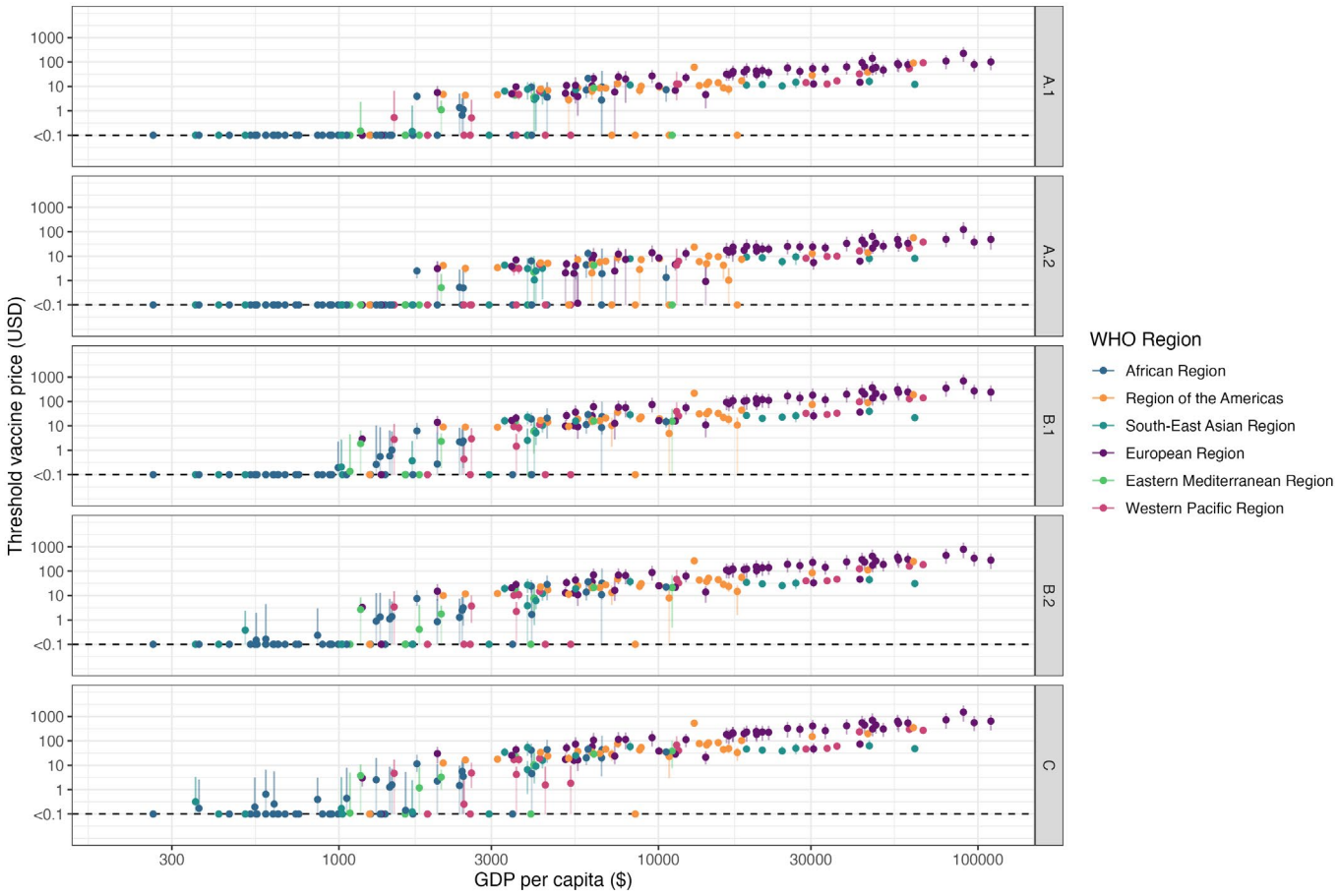


Note: Estimates are shown on a log scale.

7.4.2 Vaccine threshold prices

Estimated vaccine threshold prices at which different vaccine types are cost-effective compared to current vaccines are shown in Fig. 19. As expected, threshold prices increase with increasing country income levels that reflect higher willingness-to-pay in wealthier countries. Across all regions, threshold prices were generally lowest for minimally improved vaccines, and highest for "game changer" vaccines (Fig. 20).

FIG. 19. Threshold prices at which different vaccine types would be cost-effective by country, using demand projections between 2025 and 2050



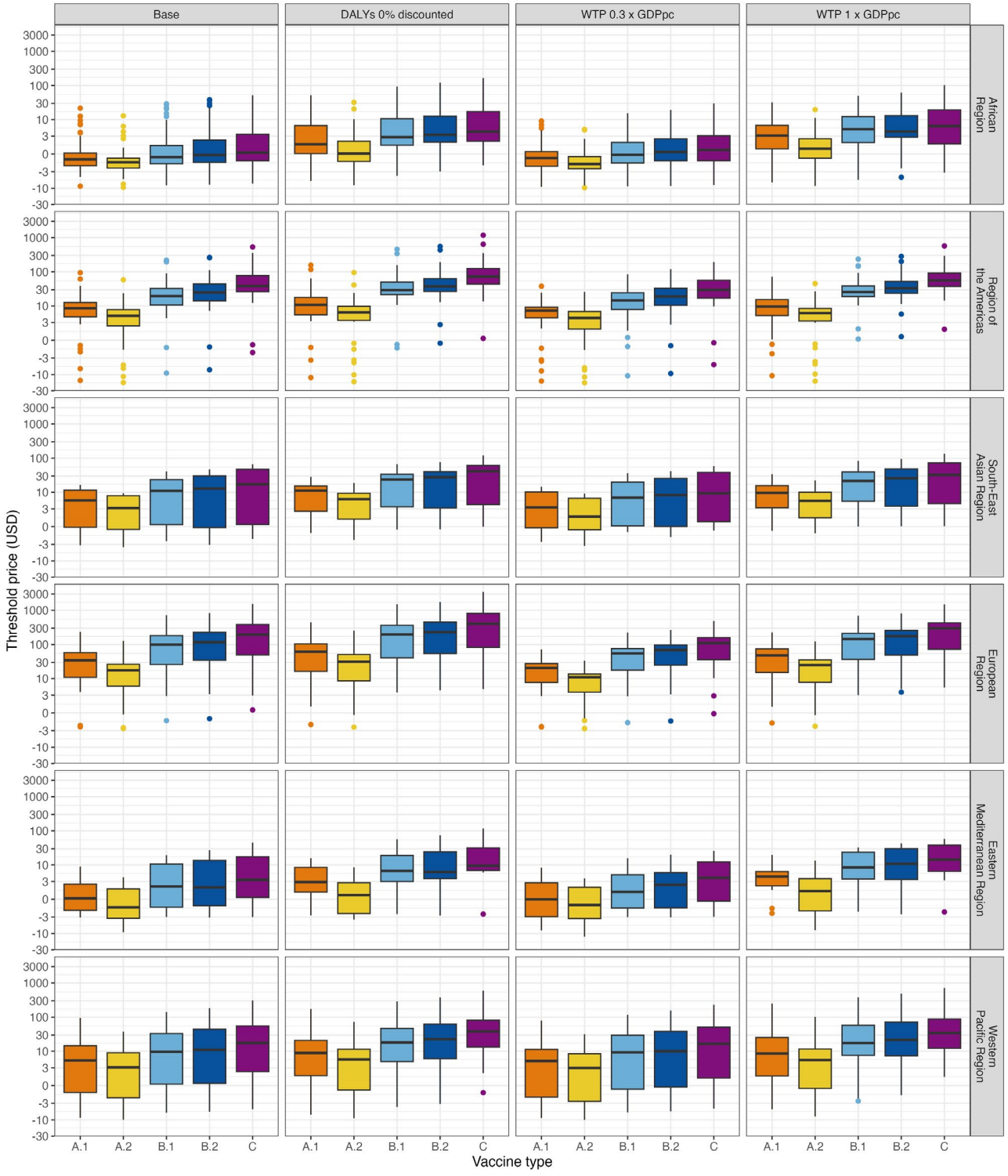
Note: Countries are in order of increasing GDP per capita, and prices are shown on a log scale.

In the base case, for most countries with GDP per capita above approximately US$ 1500, improved vaccines could be cost-effective if the vaccines are priced sufficiently cheaply. In high-income countries, minimally improved vaccines could be cost-effective at prices of tens of US$ per dose or less, increasing to hundreds of US$ per dose in the wealthiest countries for substantially improved and "game changer" vaccines. In contrast, for the poorest countries even "game changer" vaccines might not be cost-effective even if the vaccines were donated for free (i.e. their value is estimated to be below the cost of delivery). In sensitivity analyses using undiscounted DALYs or willingness-to-pay based on 1x GDP per capita, the vaccines were more likely to be cost-effective even in low-income countries.

Importantly, these conclusions on cost-effectiveness in different settings could be strongly influenced by the projections of age-specific demand for these countries, with the majority of doses going to adults and older people based on historical patterns of (mainly private sector) use in those settings. The analysis by Goodfellow et al. *(100)* found that universal vaccines targeting older adults would not be cost-effective in low-income countries. However, strategies achieving high coverage of these vaccines in young children

could be cost-effective in most of these countries at sufficiently low vaccine prices as a result of the indirect impact on transmission at the population level. Such strategies – along with other strategies that might be cost-effective such as targeting high-risk groups – have not been explored in the current analysis as it is focused on vaccination in the general population.

FIG. 20. Box-plots showing the distribution of threshold prices across countries within each region for the different types of improved vaccines between 2025 and 2050



Note: Results are shown for the base case scenario and for sensitivity analyses in which DALYs are discounted at 0% instead of 3% and alternative willingness-to-pay thresholds of 0.3 and 1.0 x GDP per capita are used.

7.5 Potential impact of improved influenza vaccines on antimicrobial use

It is common for patients with symptoms of influenza to receive inappropriate prescriptions for antibiotics, particularly when individuals are from vulnerable groups such as pregnant women, older adults and very young children *(37)*. As well as being unnecessary, such prescribing also contributes to over-use of antibiotics that can drive antimicrobial resistance in other pathogens. However, there is good evidence that vaccination against influenza can help reduce antibiotic consumption in some populations *(106)*.

This section presents estimates of the potential impact of different types of improved influenza vaccine on antibiotic consumption that build on estimates of influenza-related antibiotic consumption from a recent WHO report *(107)*. The annual number of influenza infections after accounting for current influenza vaccine coverage was estimated for the first year of the model in each WHO region. This was then then combined with the region-specific estimates of influenza-related antibiotic use from the WHO report to give an estimate of the number of defined daily doses (DDDs) of antibiotic per influenza infection. Finally, this ratio was then applied to the projected number of influenza infections averted for the different improved vaccine scenarios over the period 2025–2050 using the demand projections from Chapter 6.

Table 9 shows the estimated number of DDDs averted by WHO region. Globally, compared to current influenza vaccines, the estimated impact of improved vaccines ranged from about 500 million DDDs averted for minimally improved efficacy vaccines (A.2) to 1.3 billion DDDs averted for significantly improved vaccines. However, the estimates are subject to very wide uncertainty, reflecting both the uncertainty in the estimated impact as well as the underlying uncertainty in the estimates of pathogen-specific antibiotic use *(107)*.

TABLE 9. Potential number of Defined Daily Doses (DDD) influenza-associated antibiotic use averted by improved influenza vaccines between 2025 and 2050

WHO Region	A.1	A.2	B.1	B.2.	C
Africa	48 (4.9–340) million	29 (3.1–210) million	150 (15–1000) million	140 (14–950) million	110 (10.5–690) million
Americas	110 (43–280) million	54 (21–140) million	160 (65–440) million	150 (61–400) million	150 (63–410) million
Eastern Mediterranean	300 (49–1600) million	200 (33–1100) million	380 (59–2100) million	380 (57–2100) million	405 (59–2187) million
Europe	140 (27–630) million	69 (14–340) million	240 (48–1100) million	220 (45–1000) million	230 (50–1100) million
South-East Asia	80 (14–340) million	58 (10–240) million	100 (16–460) million	100 (16–480) million	92 (14–400) million
Western Pacific	140 (29–450) million	89 (19–290) million	250 (52–810) million	260(54–890) million	230 (46–760) million

7.6 Key gaps in knowledge or research evidence

The analysis presented in this chapter shows that improved influenza vaccines could avert a substantial additional burden of influenza compared to existing seasonal vaccines. Such vaccines could be cost-effective in many countries and might be cost-effective even at prices of several hundreds of dollars in the highest-income countries. However, with the projected coverage and year of introduction in various countries, they may not be cost-effective in countries with the lowest incomes.

It should be noted that the projected demand scenarios may not reflect the most efficient use of improved vaccines, particularly for those vaccines offering multiyear immunity where there is a trade-off between the frequency of re-vaccination and the level of immunity in the population. Further work is needed on how to optimize the design of programmes using such vaccines in order potentially to improve the cost-effectiveness profile. A related question concerns the potential for targeting vaccines at high-risk populations as this was not modelled in the current work.

Vaccines offering enduring multiyear immunity with broader protection against different influenza strains might also offer additional benefits by allowing faster responses to future influenza outbreaks with pandemic potential. Further research should be undertaken to better understand these potential benefits.

8. Financing availability and adoption of improved seasonal influenza vaccines

8.1 The producer perspective – financial viability analysis

The availability of new vaccines depends on substantial investment in clinical development, manufacturing and commercialization. With few exceptions, innovative vaccines are taken to market by commercial, for-profit entities seeking to generate an adequate return on the investment to develop the new products. Assessing the return on investment of those development projects is necessary to understand whether the vaccines will become available as a result of favourable market dynamics or if non-market financial incentives will be required.

A financial analysis using discounted cash flow methodology was used to calculate the net present value (NPV) of a project aimed at taking to the market an improved seasonal influenza vaccine *(108)*. This method discounts all financial flows generated by the project under evaluation, namely the revenues and costs linked to production and commercialization, as well as the costs associated with the clinical development of the vaccine and the construction of a dedicated manufacturing plant. An interest rate is used to discount the financial flows that reflect the project's business risk that is specific to the producer. A positive NPV means the initial investment costs can be recovered, rewarding the capital invested at an appropriate rate and generating a surplus. Under these conditions, the investment is viable and a commercial entity can pursue it without external support. The interest rate used to discount future cash flows is defined as a "hurdle rate" and captures the expectation of additional return beyond the cost of accessing financial resources in the capital market or via the borrowing (as measured by the weighted average cost of capital required to remunerate projects that can be considered riskier than the average portfolio.

The analysis covers the period 2025–2045 in order to include a sufficient number of years pre- and post-commercialization and assuming vaccine licensure of different improved influenza vaccines in the early-to-mid-2030s. Different vaccine profiles (as described in section 1.4), different manufacturers' archetypes (one first-to-market based in a HIC that commercialized the vaccine globally and one follower based in a middle-income country that does not pursue marketing authorization in HICs), and different technologies (already available or new to the developer) are explored to capture the different circumstances that may have an impact on the financial return of the project.

The following assumptions were used in the analysis:

- Development and manufacturing costs were assumed to vary on the basis of the improved influenza vaccine profile, the type of manufacturer likely to develop the vaccine, and whether the technology used to develop improved influenza vaccines was already in use by the developer for the production of other vaccines.
- Development costs were assumed to range between ~$175 and $575 million, depending on the combination of the above factors.
  - This analysis assessed the potential financial returns of improved influenza vaccine development for two different kinds of manufacturers: first-to-market with global commercialization plans, and follower (i.e. second-to-market) with commercialization plans focused on low- and middle-income countries (L&MICS).
  - Investment in manufacturing was estimated in a range between ~$140 and $500 million depending on the technology, the type of investment and the location of the production plant.
- The total demand for seasonal influenza vaccines and the penetration of the improved vaccines is based on the forecast detailed in section 6.1.2.
- The seasonal influenza vaccines market is already well established, and the majority of improved vaccines are likely to be developed by existing producers to replace existing vaccines in their portfolio. In those market conditions, the market share of the new entrants will be capped and will be heavily dependent on the improved vaccine profile. The maximum market share for an improved influenza vaccine producer was assumed to be attained by the first-to-market producer of an improved vaccine with profile C vaccine with a 44% market share – double the average of the two producers with the highest market share of current seasonal influenza vaccines.

- The duration of clinical development of improved influenza vaccines will vary according to the extent of their performance improvements compared to current seasonal influenza vaccines. Influenza vaccines with significant improvements (vaccine profiles B.1 and B.2) were assumed to reach registration in eight years, while game-changers (vaccine profile C) in 12 years.
- Improved vaccines from follower developers (i.e. second-to-market) are assumed to attain marketing registration three years after the first-to-market developers and are likely to benefit from extensive technical support.
- Vaccine prices by country income and procurement group are as described in Table 6.
- A proportion of 13% of total revenues was used as the selling, general and administrative expense rate.
- Hurdle rates of 10% and 18% were used to discount the cash flows to reflect two different risk profiles. The former reflects the expectation of a more moderate return from less risk-averse companies or lower-risk initiatives. The latter corresponds to the expectation of a high-return from more risk-averse companies or higher-risk initiatives.

TABLE 10. Estimated development costs of improved influenza vaccines (US$)

	Improved influenza vaccine profile					
	Minimal improvement A.1: 70%/40% – 1 year A.2: 90%/40% – 6 months		**Significant improvement** B.1: 90%/70% – 2 years B.1: 70%/70% – 3 years		**Game changer** C: 90%/90% – 5 years	
	Status of vaccine developer					
	First to market	**Follower**	**First to market**	**Follower**	**First to market**	**Follower**
Target market	Global	L&MICs	Global	L&MICs	Global	L&MICs
Cost of Phases 1 & 2 (US$) *(109)*	**$40m**	**$25m**	**$50m**	**$30m**	**$75m**	**$45m**
Endpoint of Phase 3	Efficacy	Immunogenicity (based on correlates of protection)	Efficacy	Immunogenicity (based on correlates of protection)	Efficacy	Immunogenicity (based on correlates of protection)
Phase 3 trial sites	Multi-country	One or few countries	Multi-country	One or few countries	Multi-country	One or few countries
Cost of Phase 3 (US$)	**$200m**	**$150m**	**$250m**	**$175m**	**$500m**	**$350m**
TOTAL	**$240m**	**$175m**	**$300m**	**$205m**	**$575m**	**$395m**

TABLE 11. Estimated manufacturing investments required for improved influenza vaccines (US$) *(110–113)*[5]

		Type of investment	Target capacity	Investment cost in HICs (US$)	Investment cost in MICs (US$)
Technology	**Technology available to producer**	Expansion of existing plant	100–200 million doses	**$200 million**	**$140 million**
	Technology new for producer	New manufacturing plant	100–200 million doses	**$500 million**	**$350 million**

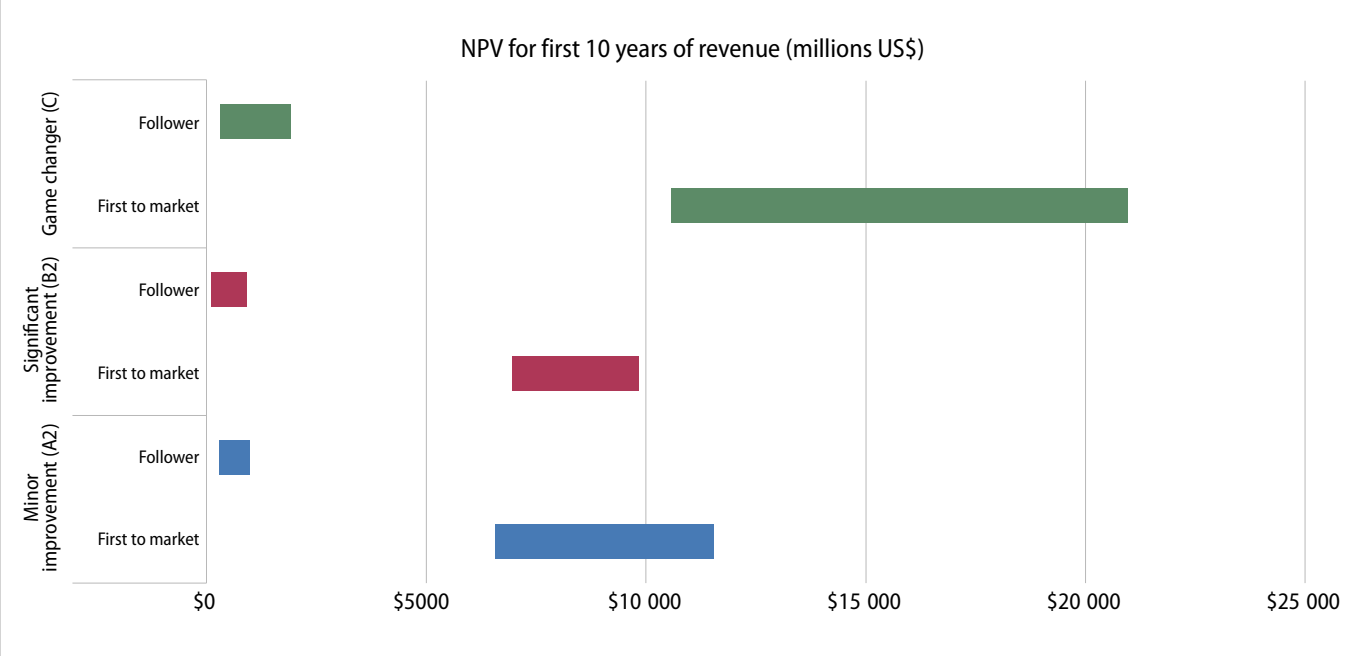
[5] Estimated HIC manufacturing costs informed by manufacturer press releases from Sanofi, Denka, CSL, Changchun BHCT, Moderna.

Acknowledging the high level of uncertainty regarding the assumptions, the financial analysis was focused on three profiles which, because of their fundamental differences, allow for isolation of the key driving forces of profitability, namely:

- **a minimally improved vaccine with better efficacy compared to current vaccines** (profile A2); this profile broadly corresponds to mRNA-based vaccines that are in-development;
- **a significantly improved vaccine with improved breadth and duration of protection** (profile B2); this profile broadly corresponds to improvements in vaccines with the current design targeting the head region of the haemagglutinin (HA); and
- **a game-changing vaccine that offers significant improvements in efficacy, breadth and duration of protection** (profile C); this profile broadly corresponds to a universal vaccine with a new design that potentially targets different epitopes.
- Profiles A1 and B1 were not included in the financial analysis, given their similarities with profiles A2 and B2 from a commercial perspective.

The analysis indicates that the seasonal influenza vaccine market is very profitable, as confirmed by the continued presence of suppliers who have divested themselves of other less profitable vaccines. The profitability of influenza vaccines depends primarily on access to high-priced HIC markets (particularly the United States market). Fig. 21 presents the NPV ranges that the two manufacturer types could achieve for each of the improved influenza vaccine profiles evaluated (A2, B2, C). Those ranges reflect the differences in the technology (whether new or already used by the manufacturer), and in the hurdle rate (10.5% or 18%).

FIG. 21. Net Present Value (NPV) ranges for each of the improved influenza vaccine profiles



The financial analysis shows a positive NPV for all vaccine profiles under all combinations of assumptions analysed concerning the technology adopted (new or available to the developer), the market entry positioning (first-to-market or follower), the geographical reach (marketing authorization in HIC markets or not) and the hurdle rate (low or high). Sensitivity analyses were also performed, and the profitability of each vaccine profile was confirmed under significant changes in the key variables influencing the NPV: demand, price and cost of goods sold.

These results highlight some important findings that are relevant for the future of improved seasonal influenza vaccines:

- The large investments in manufacturing capacity and clinical trials required for improved seasonal influenza vaccines are not a major barrier in terms of the return-on-investment. Nonetheless, constraints to accessing the required capital could be a problem for developers primarily focused on LMIC markets.
- Successful development of vaccines with high efficacy are likely to command a high premium price, particularly in HICs. Pursuing marketing authorization in HICs is the key driver of profitability and can de-risk the investment since even large variations in key drivers (demand, price, cost of goods sold) do not endanger profitability if commercialization is possible in HICs.
- Commercialization strategies that do not include HICs can still be profitable, albeit significantly less so than those including HICs, but require the cost of goods sold to be not higher than United Nations procurement prices.
- Overall, if the technical issues can be addressed, significant financial barriers that can hinder the availability of improved seasonal influenza vaccines are not foreseen. However, financial constraints may be a factor that could hinder the establishment of a supplier base that is sufficiently diversified from a geographical standpoint.

8.2 The country perspective – global distribution of economic benefit

This section presents estimates of the economic benefit, estimated by using the analysis framework from Chapter 7 if countries were to adopt the different types of improved influenza vaccines according to the demand projections and at the benchmark prices presented in Chapter 6. The model was used to estimate the "incremental net monetary benefit" (INMB) – i.e. the health-care cost savings and the value of health gains minus the costs of the vaccine programme in each country. If a country's INMB is negative, this means that vaccination is not cost-effective and there is an economic loss. Conversely, for positive INMBs there is an overall economic gain.

Fig. 22 shows the INMB by country at the lower and upper benchmarked prices for the different types of improved vaccines presented in Table 6 for the base case analysis (3% discounting of costs and DALYs, and use of empirical cost-effectiveness thresholds). Notably, even under the lower benchmarked vaccine price assumptions, improved influenza vaccines would not be cost-effective in many countries. In particular, minimally improved (efficacy) vaccines were only cost-effective in 9% of countries, and minimally improved (duration) vaccines were cost-effective in 26% of countries. Significantly improved and "game changer" vaccines were much more likely to be cost-effective, with a positive INMB in up to 48% of countries at the lower benchmarked prices. In sensitivity analyses using undiscounted DALYs or willingness-to-pay of 1.0 x GDP per capita, these vaccines were cost-effective in around two-thirds of countries at the lower price point (Fig. 23).

To estimate the global economic benefit, the country-level INMBs were summed together under two scenarios: 1) all countries were assumed to purchase improved vaccines according to the benchmarked prices and demand projections regardless of cost-effectiveness; and 2) countries were assumed only to purchase vaccines if a vaccine scenario was cost-effective at the benchmarked price. The global INMBs under these different scenarios are presented in Fig. 24 for both the base cases analyses and sensitivity analyses.

In the base case analysis under scenario 1 the global benefit could be negative under some scenarios (minimally improved efficacy vaccines and "game changer" vaccines at the upper price point). However, at the lower prices, all types of improved vaccines, with the exception of minimally improved efficacy vaccines, led to global economic gains that ranged from US$ 114 billion to US$ 440 billion. This suggests that there could be sufficient economic surplus globally to subsidize the delivery of these vaccines in countries where they would otherwise not be cost-effective.

FIG. 22. Incremental net monetary benefit (INMB) of different improved vaccine types by country in the base case analysis under lower vaccine price (left panel) and higher vaccine price (right panel) assumptions from Table 6

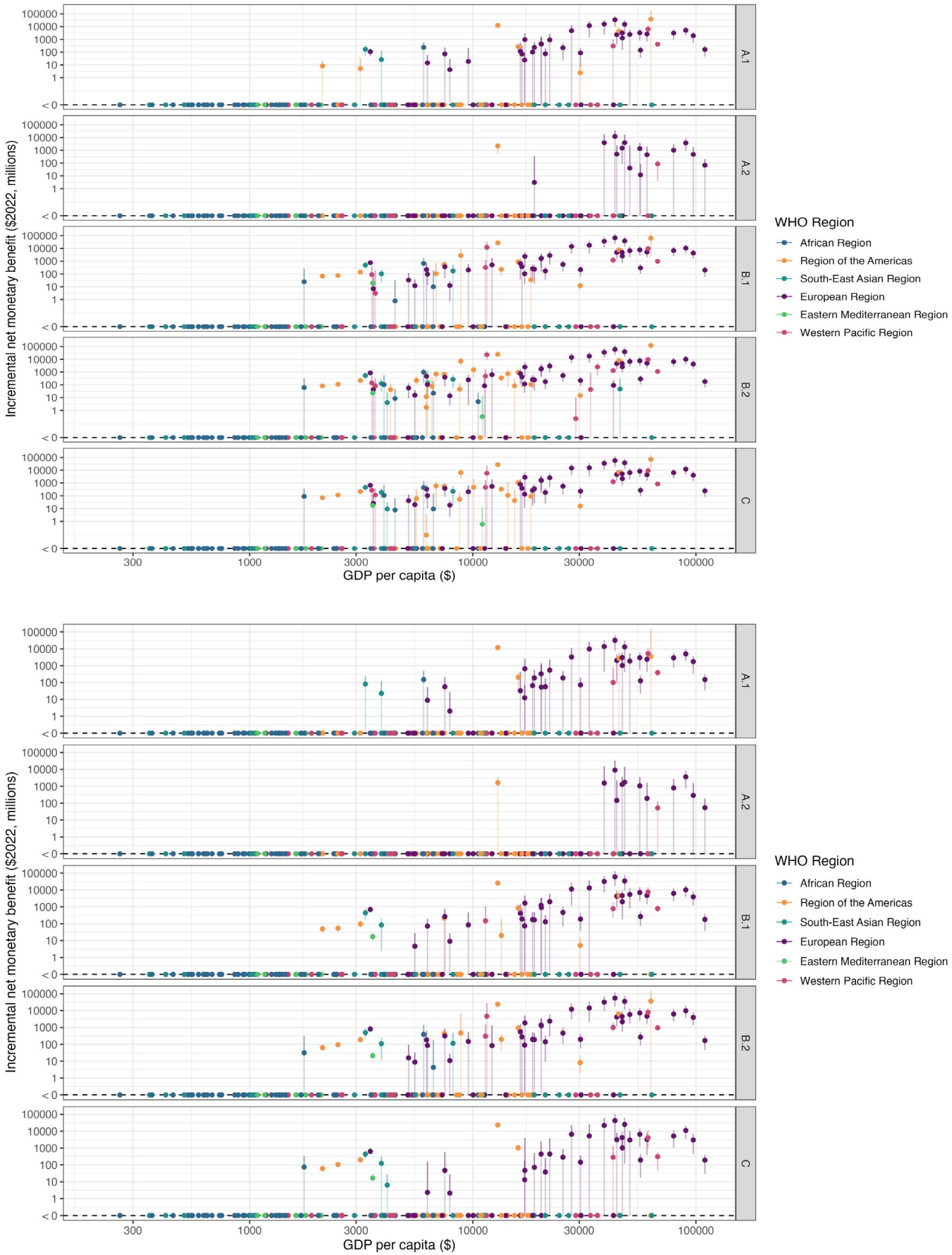


FIG. 23. Proportion of countries where improved vaccines are cost-effective under the lower and upper vaccine price assumption for the base case and sensitivity analyses in which DALYs are discounted at 0% instead of 3% and using alternative willingness-to-pay thresholds of 0.3 and 1.0 x GDP per capita

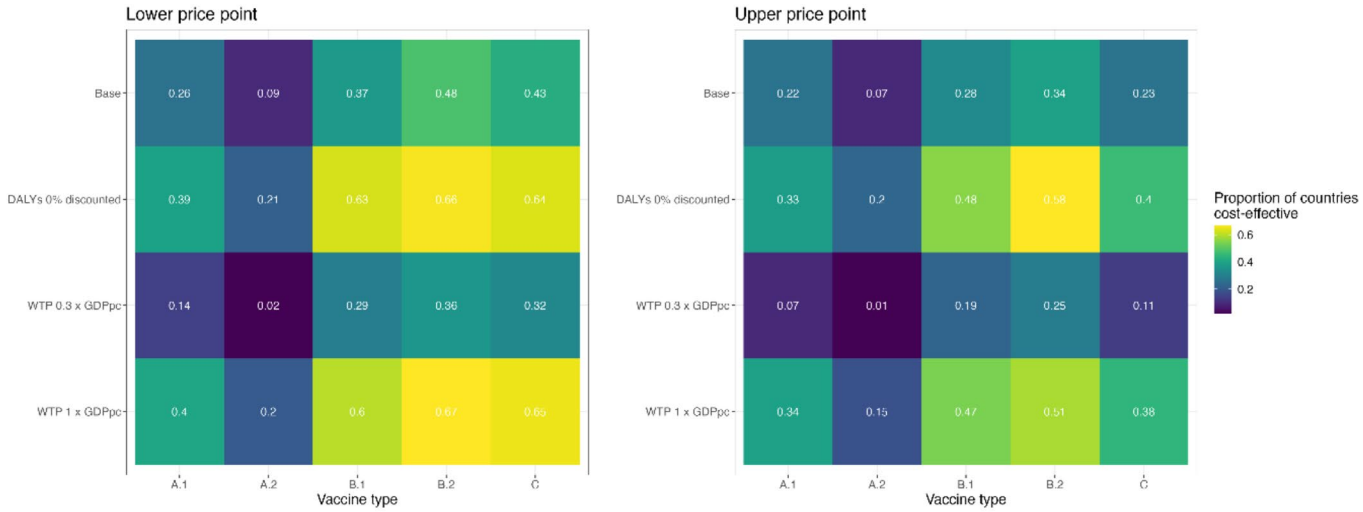
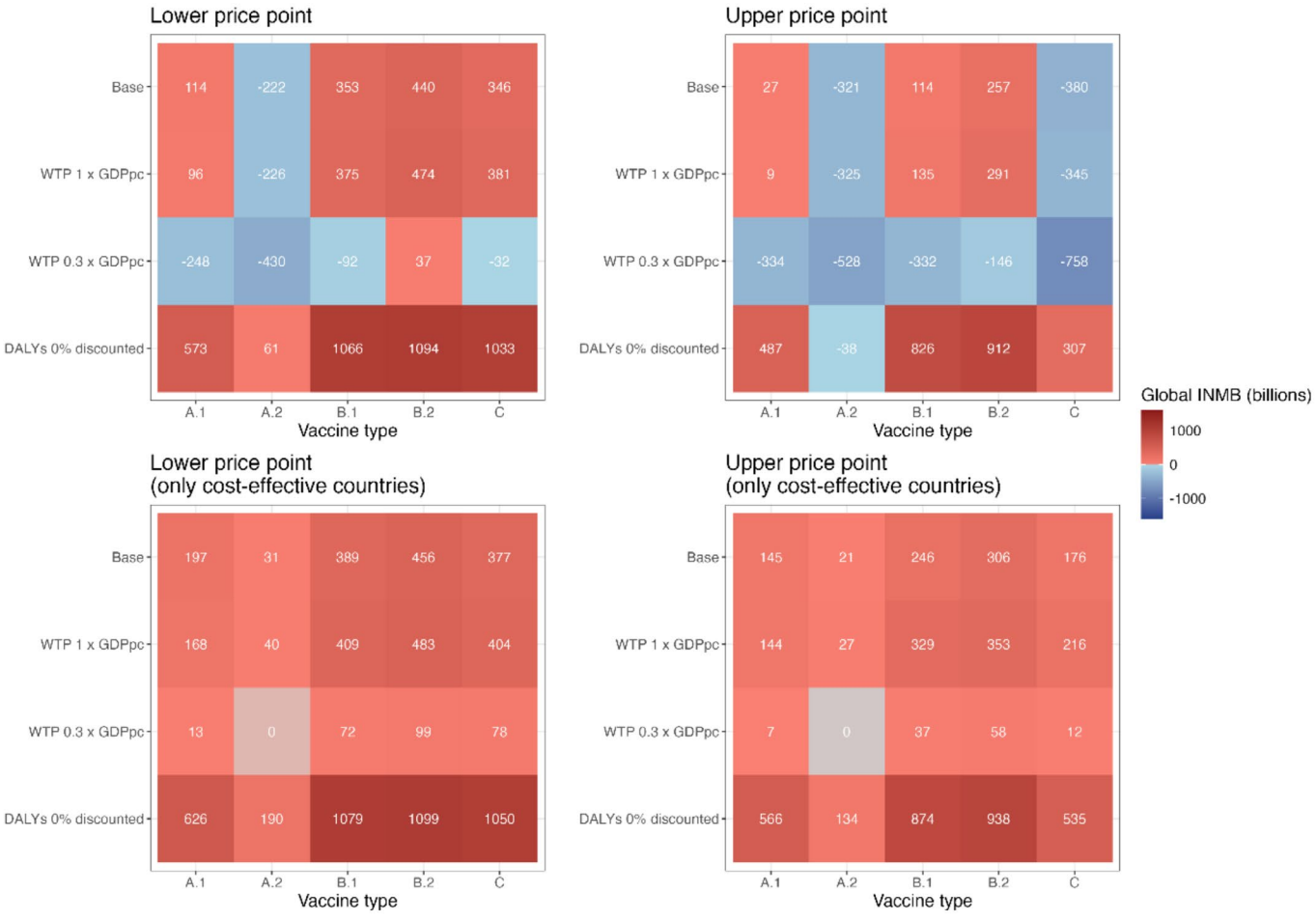


FIG. 24. Global incremental net monetary benefit (INMB) of improved influenza vaccines under the lower and upper vaccine price assumption for base case and sensitivity analysis in which DALYs are discounted at 0% instead of 3% and using alternative willingness-to-pay thresholds of 0.3 and 1.0 x GDP per capita



8.3 Key gaps in knowledge or research evidence

The discounted cash flow analysis would benefit from additional investigation into the clinical trial and manufacturing investments required to develop improved influenza vaccines once more specific product profiles are defined and initial clinical development plans are available from developers. The availability of more specific vaccine profiles should inform market research aimed at assessing acceptability, adoption intentions, willingness and ability to pay. This information is critical for a more precise estimate of demand and market share for the improved influenza vaccines. Lastly, more accurate information about the developers and their manufacturing strategies should be followed by analyses of the cost of goods sold to allow for the refinement of the NPV estimates.

9. Implementation of the vaccine in low-resource settings

9.1 Barriers and enablers to seasonal influenza vaccine access and implications for improved influenza vaccines

While improved influenza vaccines are likely to offer improved health benefits compared to existing seasonal influenza vaccines, realizing the full public health impact of the improved vaccines will require addressing many of the same programmatic barriers to the uptake as encountered to date.

An extensive literature review was performed in order to: 1) investigate the barriers and enablers to the use of current seasonal influenza vaccines across all of WHO's recommended target population groups (health workers, older adults, pregnant women, individuals with comorbidities and underlying health conditions) and other populations often prioritized for vaccination (children 6–59 months, older children and adolescents, other adults); and 2) inform the planning and implementation of future improved influenza vaccines as part of life course immunization approach.

The summary results of the literature review can be found in Table 12.

TABLE 12. Summary of cross-cutting barriers and enablers of seasonal influenza vaccines

	Barriers	Enablers
Influenza epidemiology and surveillance	**Lack of data and surveillance:** • Inadequate surveillance infrastructure limits reporting of influenza cases • Absence of robust data on local burden of influenza among key population groups hinders effective vaccination decision-making and implementation **Gaps in data analysis capacity:** • Challenges with data analysis and reporting despite availability of relevant data	**Comprehensive surveillance system:** • Strong sentinel surveillance systems to track influenza trends, inform influenza vaccination adoption and implementation, and monitor impact of vaccination • Use of surveillance data or burden studies to enable better resource allocation **Capacity-building:** • Investment in improvement of knowledge and capabilities to perform data analysis and reporting
Influenza vaccine characteristics	**Scepticism about vaccine effectiveness:** • Public scepticism regarding the effectiveness, breadth of protection and duration of protection of influenza vaccines **Concerns about vaccine safety:** • Fear of allergic reactions and other adverse events	**Proven effectiveness and safety:** • Continuous availability, dissemination, and awareness by providers and patients of evidence to boost public confidence and uptake • Continued research and development of improved influenza vaccines
Institutional and policy context	**Inconsistent or weak policy implementation:** • Limited availability of national burden of disease data and/or limited capacity of national immunization technical advisory groups (NITAGs) for formulation of vaccine policy and consideration of introduction/optimization of seasonal influenza as part of national immunization strategy processes • Top-down policy formulation and implementation omitting key stakeholder engagement • Inconsistent and insufficient communication causing policy discrepancies between public, private and informal providers	**Supportive vaccination policies and institutions:** • Strengthening of NITAG capacity and capabilities • Robust institutional frameworks and WHO guidance to support policy formulation, evidence review and decision-making • Implementation of national vaccination policies

Table 12 (continued)

	Barriers	Enablers
Financial context and access mechanisms	**Limited financial resources:** • Limited health budget, with many competing health priorities, leading to limited funding • Lack of costing of influenza vaccination programme	**Prioritization of vaccination activities:** • Sustained leadership support and financial commitment to influenza vaccination activities, including campaigns • Pooled procurement of influenza vaccines to obtain lower prices (e.g. most countries in Latin America and the Caribbean procure seasonal influenza vaccines through the PAHO Revolving Fund)
Health system and infrastructure	**Infrastructure and resource limitations:** • Segmented organizational structure, with division of influenza and immunization programme roles and responsibilities • Data gaps (particularly for vaccination occurring in the private sector) resulting in under-reporting of national vaccine use • Inadequate health-care infrastructure and resources, creating challenges for human resources and supply chains • Variability in vaccine availability leading to variability in vaccination coverage • Lack of awareness by health workers regarding influenza vaccination recommendations • Extra workload for health-care workers	**Improved collaboration and more robust health-care infrastructure:** • Strengthening of existing immunization and data infrastructures • Increasing awareness of health workers through education and training • Integration of seasonal influenza vaccination services with other disease control initiatives and into routine primary health-care services for populations at higher risk of influenza (e.g. general practitioners, cardiologists, pneumologists, obstetricians, gynaecologists etc.) • Tailoring of influenza vaccination campaign materials and activities • Conducting acceptance and demand studies to inform targeted interventions that can increase uptake among recommended groups
Accessibility and convenience	**Logistical, accessibility and financial constraints:** • Geographical and logistical challenges, including lack of time, lack of transportation and distance to vaccination sites • Cost barriers for individuals, including the price of vaccines and lack of insurance coverage	**Accessible vaccination services:** • Economic support (e.g. vaccines free of charge) • Providing vaccines at convenient times and locations • Use of outreach vaccination clinics and mobile immunization teams for remote communities and house-to-house delivery
Communication and awareness	**Lack of knowledge and misinformation:** • Inconsistent and insufficient communication from health-care providers to the public • Insufficient knowledge in the community about influenza, severity of the disease, vaccine indications and the benefits of vaccination • Misinformation and myths about vaccines	**Effective communication strategies:** • Risk communication and community engagement focused on influenza disease and influenza vaccine to build trust and confidence in vaccines • Strong cultural endorsement of vaccination within communities
Personal and cultural beliefs	**Negative attitudes and beliefs:** • Fear of injections • Perception of low personal risk of disease, low severity of influenza, and beliefs that vaccination is unnecessary • Decrease trust in vaccines • Previous negative experiences with influenza vaccine or anecdotes of adverse events	**Positive perceptions of vaccination:** • Effective use of communication channels by health-care providers to deliver information about influenza vaccines • Emphasis on the personal, family, and community health benefits of vaccination

To enhance the positive impact of influenza vaccination programmes across all priority populations, particularly adults, it is critical to address the barriers related to both the vaccine characteristics and the broader contextual programmatic factors influencing vaccine uptake and sustainability of influenza vaccination programmes.

For concerns about the vaccine characteristics, vaccine manufacturers involved in the research and development of improved influenza vaccines should prioritize enhanced effectiveness and safety profiles to build public trust and confidence, particularly among groups such as pregnant persons and the elderly who often have more concerns about adverse events and vaccine effectiveness. These manufacturers should continue to focus on creating vaccines that provide broad-spectrum and long-lasting immunity against multiple influenza strains in order to reduce the need for annual vaccination and thus improve convenience and increase uptake, as well as help mitigate concerns about mismatches between the vaccine and circulating virus strains. Additionally, improving vaccine delivery to include more convenient, more thermostable and less invasive options – such as intranasal sprays or microarray patches – could increase acceptance among those who fear injections or those in low-resource settings where the cold chain is limited.

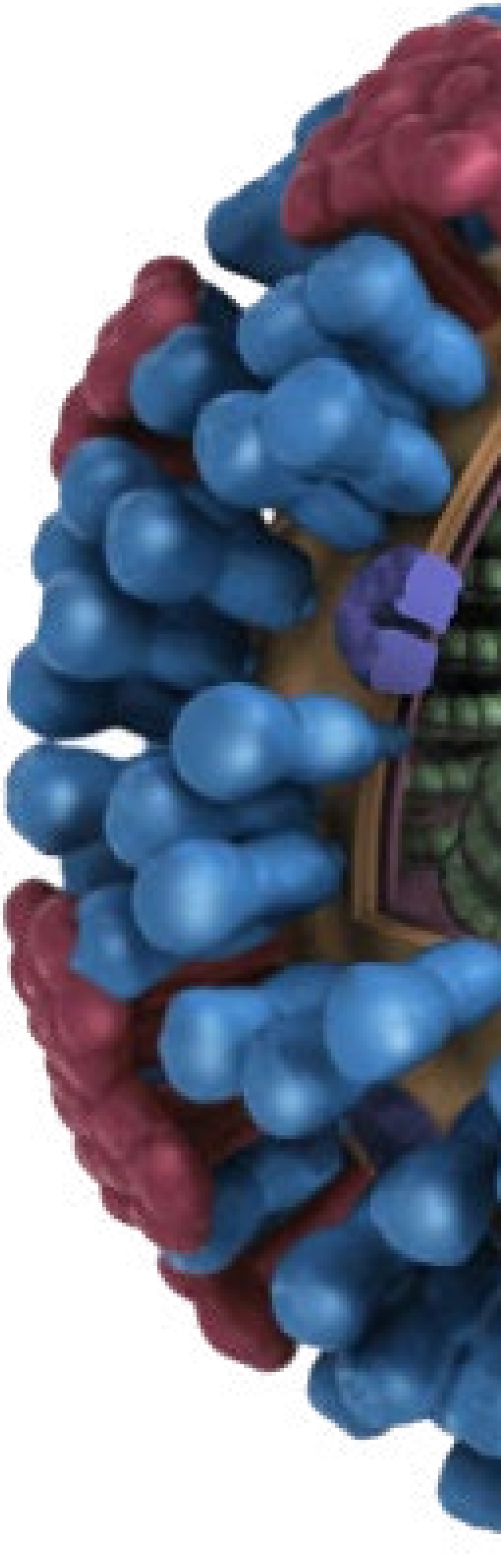
Beyond the characteristics of the vaccine, it is essential to consider the systemic and societal factors that influence vaccination uptake and the adoption and health impact of future improved influenza vaccines. Effective policy frameworks and robust health-care infrastructure play critical roles in supporting widespread immunization with influenza vaccine. Policies that integrate influenza vaccination into routine health-care visits, provide free or subsidized vaccines and leverage existing health-care programmes such as national immunization programmes or antenatal care visits (for pregnant individuals) can substantially improve accessibility. The integration of influenza vaccination along with other adult vaccines into national immunization programmes can also reduce systemic issues that may prevent vaccine uptake. Equally important are risk communication and community engagement strategies that address specific misconceptions and inform populations about the benefits and safety of vaccines. Tailored messaging and strong recommendations from trusted health-care providers and community leaders can overcome cultural resistance and personal beliefs that act as barriers to vaccination. Future strategies must also ensure equitable access, especially for highest priority populations, by addressing challenges such as vaccine availability and geographical barriers.

The majority of the barriers described above are likely to persist even as improved influenza vaccines become available. These new vaccines will primarily enhance effectiveness and the breadth and duration of protection, addressing crucial but limited aspects of the barriers to use of influenza vaccines. Consequently, without proactive and coordinated efforts across relevant stakeholders at global, regional and national levels, other critical issues will remain unchanged. A comprehensive plan of action to strengthen and/or establish adult immunization platforms is essential to reduce these barriers and support the adoption and uptake of improved influenza vaccines. By taking a holistic approach that combines improvements in vaccine technology with supportive policy and infrastructure, future influenza vaccination programmes can achieve higher uptake and can better protect the population.

9.2 Key gaps in knowledge or research evidence

Many of the operational concerns highlighted above can be addressed with appropriate planning and support during the time we have until improved influenza vaccines become available.

10. Summary of findings and recommendations



10.1 Summary of findings and recommendations to stakeholders

The FVVA outlines key considerations for advancing influenza vaccine development and describes the potential impact that improved influenza vaccines can have.

The research summarized in this FVVA shows the following:

- The investment in improved influenza vaccine development is supported by its anticipated health and economic benefits.
- The market for current influenza vaccines is concentrated in high-income and upper-middle-income countries and is expected to grow marginally in the next 10 years unless improved influenza vaccines become available, countries currently using seasonal influenza vaccines expand their current policies or more countries introduce seasonal influenza vaccines.
- UMICs and LMICs consider vaccine efficacy to be the most important criterion in their decision-making regarding the adoption of improved influenza vaccines.
  - Country demand is projected to increase substantially if improved vaccines with increased efficacy become available.
  - Vaccines with broader and longer duration of protection offer the additional benefit of reduced annual vaccination requirements.
- Improved influenza vaccines are likely to have a positive global net monetary benefit and could be cost-effective in most countries if the vaccine is both affordably priced and optimally delivered.
- Improved influenza vaccine development is financially sustainable and is likely to be profitable from the manufacturers' perspective globally – even those manufacturers who focus on markets in LMICs.
- It would be feasible in principle to implement vaccination programmes using improved influenza vaccines. However, existing challenges related to current seasonal vaccines (e.g. surveillance capacity, low demand and vaccine hesitancy, financial constraints, logistical difficulties) must still be addressed to realize higher vaccination coverage and additional health benefits.

Table 13 outlines in more detail the key findings of this paper, linking the findings with quantitative results and calls to action to specific stakeholders.

TABLE 13. Principal findings, quantitative results and recommendations

Principal findings	Quantitative results	Recommendations for next steps
Market supply and demand dynamics • **Production and access disparities:** Vaccine production remains concentrated in high- and upper-middle-income countries. Expanding local manufacturing in all WHO regions is key to equitable access in pandemic circumstances. Increases in available supply will depend on both country demand signals and manufacturers' strategic approaches and pipeline developments. • **Demand for improved vaccines:** The demand for improved vaccines, with their increased health benefits, is expected to exceed that for seasonal vaccines. Vaccines with greater breadth and duration of protection reduce revaccination requirements, reducing annual demand but increasing the number of people vaccinated over time. • **Affordability and pricing strategies:** Additional health benefits offered by improved vaccines could result in higher prices. Tiered pricing to ensure access in low- and middle-income countries is likely to be necessary.	**Global production capacity of influenza vaccines primarily in HICs** • ~80% of global pandemic production capacity in HICs • ~20% of global pandemic production capacity in UMICs as well • <1% in LMICs. **Global demand varies depending on characteristics of improved vaccines** • As of 2022, 128 WHO Member States had a formal national seasonal influenza vaccination policy, and 143 Member States reported that influenza vaccines were able in the public and/or private sectors. • Demand for current seasonal influenza vaccines (~850m doses) is anticipated to grow ~10% by 2050. • Minimally improved influenza vaccines forecast to exceed current demand by ~30–75%. • Improved influenza vaccines with extended breadth and duration of protection can increase or decrease by ~15% (reduced need for annual vaccination versus higher population coverage). • Future prices of improved influenza vaccines likely to be higher than current seasonal vaccines • In HICs prices could increase by ~2–7 times (depending on additional health benefits) • In UMICs, LMICs and low-income countries price increases are expected but not at same rates.	**Recommendations to all stakeholders:** To ensure the successful development and introduction of improved influenza vaccines, **the collaboration between countries, vaccine developers, the research community, regulatory agencies, vaccine procurement and financing entities is crucial**. • Stronger collaboration between R&D funders and manufacturers is needed to accelerate vaccine development. This should include incorporating country perspectives from this FVVA to ensure alignment with national preferences and needs. • Exploration and evaluation of regulatory pathways for novel vaccines by vaccine developers and regulatory agencies is relevant to accelerate the development and licensure of improved influenza vaccines. • As vaccines reach maturity in development, implementation funders and countries should collaborate to prepare key stakeholders for vaccine introduction. This includes engaging communities, informing populations and NGOs about the benefits of new vaccines, and proactively countering misinformation and rumors.
Health and economic impact • **Health benefits:** Enhanced vaccines have the potential to lower significantly the global influenza burden by reducing infections, hospitalizations and mortality rates. This impact will be particularly pronounced in LMICs due to higher efficacy and longer-lasting protection. • Cost-effectiveness: These vaccines could be highly cost-effective in many countries if appropriately priced. Substantially improved or "game changer" vaccines, in particular, may offer strong economic value in HICs, UMICs and selected LMICs. • Implementation challenges: Existing barriers to seasonal influenza vaccine use and uptake could limit the additional health and economic benefits of improved vaccines, and require proactive, comprehensive efforts at global, regional and national levels for benefits to be realized.	**Globally, when compared to current seasonal vaccines, between 2025 and 2050 improved influenza vaccines could prevent:** • between 6.6 and 18.0 billion additional influenza infections • between 2.3 and 6.2 million extra deaths due to influenza and • avert between 21 and 57 million additional influenza DALYs. **Cost-effectiveness** • In HICs, minimally improved vaccines could be cost-effective at prices of tens of $ per dose, increasing to hundreds of dollars per dose in the wealthiest countries for substantially improved and "game changer" vaccines. • In some LMICs, improved vaccines may be cost-effective only if they are both affordably priced and optimally delivered.	

Table 13 (continued)

Principal findings	Quantitative results	Recommendations for next steps
Technical and regulatory considerations to accelerate vaccine development • **Enhancing effectiveness and durability:** Advancements in vaccine platforms, such as mRNA and other innovative strategies, have the potential to improve significantly protection and programmatic suitability in the short term. • **Challenges in development:** Large-scale clinical trials are essential to demonstrate efficacy, particularly for novel platforms targeting different viral components. The absence of well-defined biomarkers or correlates of protection further complicates efficacy evaluation, leading to resource-intensive trials. • **Innovative vaccine platforms:** Technologies such as mRNA, recombinant protein and virus-like particles offer faster production timelines, enhanced immunogenicity and broader protection against influenza strains. The development of combination vaccines targeting multiple respiratory viruses is also increasing in the R&D landscape.	**Next-generation influenza vaccine pipeline analysis** • As of April 2024, there were 56 next-generation influenza vaccines in clinical development; over half of them use the mRNA vaccine platform. • Eight combination vaccine candidates are in clinical trials, including three in Phase 3 testing.	**Recommendations to vaccine developers** • Prioritize the development of vaccines with superior **efficacy, broader and longer-lasting protection, and faster production times**. • **Design vaccines that are suitable for a diverse set of use cases** which are compatible with both mobile and fixed delivery systems. Additionally, consider the logistical challenges posed by different populations across the life course. • **Leverage new technologies to minimize dependence on egg-based production methods** and address supply chain vulnerabilities by exploring advanced technologies, such as mRNA vaccines, which offer greater flexibility accelerating manufacturing processes that lead to earlier distribution. **Recommendations to funders of vaccine development** • **Ensure equitable access** by funding the development of affordable vaccines, promoting technology transfer, and removing procedural and legal barriers, particularly for low- and middle-income countries. This could include subsidizing production costs, facilitating technology transfers and advocating tiered pricing across countries to ensure fair access as part of immunization strategies across the life course through global health organizations. • **Invest in innovative vaccine technologies** (e.g. mRNA, nanoparticle-based platforms) and encourage diversification of manufacturing methods to address challenges posed by traditional vaccine production. Consider new investment modalities (e.g. joint ventures, public-private partnerships) to support the development of vaccines suitable in all settings. • **Support the development of competencies and knowledge** in influenza vaccine research and manufacturing by funding training programmes, resource exchanges and capacity-building initiatives.
Financial viability to develop improved influenza vaccines • **Investment Feasibility:** Using the "discounted cash flow" methodology, the analysis confirms a positive net present value (NPV) across all vaccine profiles, indicating that large-scale investments in clinical trials and manufacturing are financially viable. • **Value:** If these vaccines achieve higher efficacy and longer protection duration, they could provide substantial global net monetary benefits, particularly in HIC markets. • **Ensuring equitable access:** Strong financial and implementation strategies are necessary to bridge accessibility gaps, particularly in LMICs. Coordinated efforts are needed to expand local manufacturing and mitigate logistical and financial barriers to vaccine adoption.	**Positive NPV for all improved vaccines under all scenarios** (depending on vaccine profile) • First-to-market manufacturers (focus on HIC/global market): ~$6.5–20 billion US$ • Follower manufacturers (focus on LMIC market): ~$120 million–1.9 billion US$. • Global net monetary benefit • The value of improved influenza vaccines between 2025 and 2050 could be as high as $456 billion depending on vaccine pricing.	

Table 13 (continued)

Principal findings	Quantitative results	Recommendations for next steps
Policy development and decision-making • **Key factors for vaccine adoption:** Vaccine efficacy is the most critical factor for inclusion of improved influenza vaccines in national immunization programmes. Other important attributes include duration and breadth of protection, safety, temperature stability and shelf-life. • **Integration into life-course vaccination:** Even with more effective vaccines, successful uptake will require strong life-course vaccination programmes, ensuring that delivery platforms exist to reach and reduce the disease burden effectively in all populations targeted for vaccination • **Future advancements and distribution innovations:** Medium-term innovations, such as broader protection against influenza A and B strains and novel delivery methods such as microarray patches, could simplify vaccine administration, particularly in resource-limited settings.	• N/A, findings supported by literature reviews, surveys, focus groups and workshops.	**Recommendations to funders of vaccine introduction/ implementation** • **Provide funding to countries** that lack influenza pandemic preparedness in order to ensure access to seasonal vaccines that offer protection beyond one influenza season, thereby reducing the need for annual vaccinations and improving cost-effectiveness. • **Reassess funding strategies to strengthen the life course** in LMICs, considering the cost-effective use of vaccine candidates and vaccination approaches integrated with other health interventions to reduce costs for the implementing countries. • **Support countries to pre-emptively address implementation logistical challenges, including logistics** (e.g. cold chain infrastructure, mobile vaccination units, integrated adult vaccination platforms) and vaccine acceptance to ensure that vaccines reach all target populations, particularly in resource-constrained settings. • **Promote pooled procurement of improved influenza vaccines** across countries to create a larger vaccine market demand able to negotiate affordable, cost-effective vaccines, while allowing manufacturers to achieve a positive return on investment due to economies of scale. **Recommendations to countries – policy development** • **In countries without seasonal influenza programmes, NITAGs should use newly-available evidence to inform local decisions** regarding the adoption and integration of improved influenza vaccines into the national immunization schedule. These policies should adopt a life-course approach to enhance vaccination coverage among vulnerable populations, particularly where strategies targeted at these populations are highly cost-effective. Health and economic impact data from influenza vaccines used in other settings should also be reviewed to inform local decisions. • **Anticipate vaccine adoption timelines and coordinate national policies** to ensure the timely integration of improved vaccines into existing frameworks, informed by the local disease burden and economic analysis. • **Advocate for improvement of data accuracy** of vaccination coverage and influenza virology/diagnostic tests of burden. This will enable more effective and efficient national vaccination strategies and the measurement of impact through economic evaluations. Understanding the size of target populations and use case scenarios will also help optimize vaccine delivery. • **Initiate data collection and analysis at national and, if possible, regional/subregional** levels to assess the economic impact and cost-effectiveness of different strategies for the introduction of improved influenza vaccines within the local context.

Table 13 (continued)

Principal findings	Quantitative results	Recommendations for next steps
Proactive mitigation of implementation barriers • **Identifying barriers to uptake:** Low-resource settings face challenges such as inadequate surveillance infrastructure, vaccine hesitancy, financial constraints, and logistical difficulties that limit adoption and uptake of current seasonal and improved influenza vaccines. • **Enablers for success:** Political will, strengthening sentinel surveillance, ensuring continuous availability of safety and efficacy data, and implementing supportive policies can enhance vaccine acceptance and uptake. • **Programmatic considerations:** Beyond vaccine improvements, addressing systemic barriers such as policy frameworks, health-care infrastructure and communication strategies is critical for maximizing public health impact.	• N/A, findings supported by literature reviews, surveys, focus groups and workshops.	**Recommendations to countries – implementation** • **Early planning is essential for adapting vaccine delivery strategies** to local contexts, utilizing both fixed and mobile facilities. Where institutionalized routine vaccination is not feasible, or in addition to health facility-based delivery, prioritize mobile units to reach specific high-risk groups and rural or hard-to-access populations. • **Raise awareness and address vaccine acceptance issues within communities (health workers and vaccine recipients)** about the benefits of improved vaccines to enhance uptake, especially in underserved communities and through existing adult vaccination platforms. Vaccine manufacturers should prioritize enhanced effectiveness and safety profiles to build public trust and confidence. • Regularly, and as continuously as possible, evaluate the effectiveness and reach of vaccination programmes using **monitoring and evaluation (M&E) data**. Adjust strategies to improve vaccine uptake, particularly in underserved populations and vulnerable groups in society.

10.2 Conclusions

This FVVA presents some of the important challenges and opportunities for the development and implementation of improved influenza vaccines. It summarizes the latest research findings on disease burden, potential vaccine cost-effectiveness, financial sustainability and operational issues that must be addressed to enable broad acceptability and uptake. This evidence can be used by a range of stakeholders to prioritize activities and to mobilize the required financial resources to accelerate progress towards the development and use of improved influenza vaccines.

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