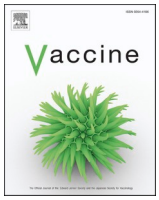
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Review



# Advancing influenza vaccines: A review of next-generation candidates and their potential for global health impact

Jessica Taaffe [a,*], Julia T. Ostrowsky [b], Joshua Mott [a], Shoshanna Goldin [a], Martin Friede [a], Pierre Gsell [a], Christopher Chadwick [a]

[a] World Health Organization, Geneva, Switzerland
[b] Center for Infectious Disease Research and Policy, University of Minnesota, Minneapolis, USA

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ABSTRACT

*Background:* Influenza vaccines are an essential tool for influenza prevention, control and preparedness. However, demand for them and their programmatic suitability globally is significantly influenced by their variable effectiveness against influenza illness annually, limited duration of protection and need for yearly updating and vaccination. As such, the World Health Organization and major funders, such as the United States National Institute of Allergy and Infectious Diseases and Bill and Melinda Gates Foundation, have strongly encouraged developing influenza vaccines with increased efficacy, breadth and duration of protection. Here, we review the next-generation influenza vaccine pipeline, focusing on products in clinical development, and compare their characteristics to currently approved seasonal influenza vaccines.

*Methods:* To identify and characterize next-generation influenza vaccine candidates, we conducted a comprehensive literature review, using the CIDRAP Universal Influenza Vaccine Technology Landscape as a primary reference source and extracting additional information from peer-reviewed manuscripts, clinical trial records and other media in the public domain.

*Results:* Our analysis reveals a robust clinical development pipeline for next-generation influenza vaccines, featuring a diversity of approaches to address existing vaccine challenges and several candidates in advanced stages of development. mRNA vaccines emerged as a predominant platform, as evidenced by the number of candidates focused on improved seasonal protection as well as combination vaccine candidates targeting additional respiratory viruses.

*Conclusion:* While still early in development, results from universal or broadly protective products are promising and warrant continued investment from funders. As most Phase 3 candidates are mRNA-based and include combination vaccines, it is critical to begin considering how these new products may become integrated into the current global influenza vaccine strain selection and manufacturing ecosystems, and existing immunization programmes.

## 1. Introduction

Influenza causes a significant health burden on global populations, with an estimated 1 billion cases annually [1]. Each year, seasonal influenza is responsible for an estimated 290,000–650,000 respiratory-related deaths, not accounting for other influenza-related outcomes [2]. In low-income countries, such as those in sub-Saharan Africa and South-East Asia, rates of illness and death from influenza are estimated to be highest, particularly in older adults and children under 5 years [2]. Influenza also places a large economic burden on global populations, through both direct and indirect costs on governments and societies, particularly among those in at-risk populations [3,4].

WHO, through the Global Influenza Surveillance and Response System [5], continually monitors influenza viruses circulating globally and provides recommendations annually on the composition of seasonal vaccines for both hemispheres. Vaccination is considered a key public health intervention to reduce the burden of influenza and provides a foundation for seasonal epidemic and pandemic preparedness [6,7]. Yet despite the broad use of seasonal influenza vaccines, influenza continues to cause significant disease and economic burden globally.

* Corresponding author.
*E-mail address:* taaffej@who.int (J. Taaffe).

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The annual effectiveness of currently available influenza vaccines typically ranges from < 20% to 60% due to intrinsic and extrinsic factors [8,9]. Vaccine type, dosage and inclusion of adjuvants influence how well a vaccine works in different target populations. The emergence of "drifted" seasonal influenza viruses after vaccine strains are recommended (February for the northern hemisphere season and September for the southern hemisphere season) may also reduce vaccine effectiveness if the vaccine strains do not exhibit a high degree of antigenic similarity to circulating viruses. Effectiveness often varies by influenza virus subtype/lineage in a given influenza season, especially for the H3N2 subtype, which tends to have the poorest performance among vaccine viruses and for which there even may be variation in effectiveness among different phylogenetic subclusters or variants of H3N2 viruses in a single season [10–12]. Additionally, varying immunity and/or previous exposure to influenza viruses within a population, either through vaccination or natural infection, may influence the effectiveness of influenza vaccines [13].

The global market for seasonal influenza vaccines is stable, with approximately 760 million doses procured by countries in 2022 [14]. However, seasonal influenza vaccine use is limited in low income countries [14]. Demand for seasonal influenza vaccines is significantly influenced by the profile of current vaccines, namely their moderate and variable effectiveness against influenza illness from year to year, requirements for annual production and administration, and limited duration of protection. In addition to vaccine price, these characteristics have programmatic and cost implications that challenge seasonal influenza vaccine programmes in low- and middle-income countries (LMICs), which are already strained in implementing vaccination programmes in general. Despite broad availability of seasonal influenza vaccines, many LMICs do not have seasonal influenza vaccination programmes in place, particularly in the African Region and in settings with year-round transmission [15]. Decision-makers in LMICs hesitate to initiate or expand influenza vaccination programmes due to financial constraints, competing priorities and lack of cost-effectiveness evidence [16], even though recent evidence shows cost-saving/efficiency in all target groups in LMICs [4]. Variable global demand influences the global supply of influenza vaccines. Current influenza vaccine manufacturers are not necessarily incentivized by the market to ramp up production of current vaccines, as evidenced by the difference in a maximum annual seasonal influenza vaccine production capacity of 1.5 billion doses in 2019 (estimated by number of seasonal vaccine doses able to be produced in 12 months by manufacturers if operating at full-scale) [17] versus the distribution of approximately 531 million doses globally that same year [18]. Global demand was estimated at 850 million doses for 2024 [14].

Higher vaccination rates globally would reduce morbidity and mortality due to seasonal influenza while also contributing to pandemic preparedness, as seasonal influenza vaccination programmes support manufacturing and operational systems required for a pandemic vaccine response [19]. Furthermore, the right type of immunity from the right type of vaccine, such as a universal influenza vaccine that protects against any influenza A or B virus, could be a tool to prevent the emergence of and mitigate against pandemic influenza [20,21].

WHO and major funders have strongly encouraged developing more efficacious and programmatically suitable influenza vaccines. Continuing the emphasis that WHO's Global Action Plan for Influenza Vaccines gave to developing more effective vaccines, the Global Influenza Strategy 2019–2030 stresses the need for improved, novel and universal influenza vaccines with increased breadth of protection, longer duration of protection, enhanced effectiveness against severe disease and decreased production time [22]. Similar calls for improved influenza vaccines have come from the United States National Institute of Allergy and Infectious Diseases (NIAID) [23], the Bill & Melinda Gates Foundation [24] and the Sabin-Aspen Vaccine Science & Policy Group [25].

In response to these calls, the improved influenza vaccine research and development (R&D) landscape has flourished, with partnerships, initiatives and collaborations supporting this space, such as NIAID's Collaborative Influenza Vaccine Innovation Centers (CIVICs) programme [26], investment in medical countermeasures by the United States Department of Defense's Influenza and Emerging Infectious Diseases Division [27], the European Commission funded Indo-European Consortium for Next Generation Influenza Vaccine Innovation (INCENTIVE) [28] and Flu Lab [29]. In particular, the Influenza Vaccines R&D Roadmap (IVR) [30], led by the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, was initiated to guide vaccine development through R&D priority setting, using a 10-year roadmap to advance priority actions across virology; immunology; vaccinology; animal models and controlled human influenza virus infection models; and policy, financing and regulation. The roadmap is the result of collaboration from over 100 stakeholders from 29 countries [31]. CIDRAP developed the Universal Influenza Vaccine Technology Landscape [32], which is a regularly updated online database of novel influenza vaccine candidates in preclinical and clinical development, including those that aim to be universal or broadly protective influenza vaccines. CIDRAP also tracks R&D funding that aligns with IVR goals and milestones [33].

WHO also provides guidance for improved influenza vaccine development through the WHO Preferred Product Characteristics (PPCs) for Next-Generation Influenza Vaccines. WHO publishes PPCs as guidance for the development of new vaccines in priority disease areas, defining preferences for parameters of vaccines shaped by "global unmet public health need in a WHO priority disease area" [34]. WHO published the PPCs for Next-Generation Influenza Vaccines in 2017 to encourage vaccine innovation that would address the "public health need for improved influenza vaccines conferring broader and longer protection against severe illness, particularly in LMICs" [34]. The document prioritized high-risk groups as its target population, with a focus on children under 5, and set two major strategic goals for next-generation influenza vaccines: (1) vaccines with greater protection against vaccine-matched or drifted influenza strains and protection from severe influenza for at least 1 year, and (2) vaccines that would provide at least 5-year protection against severe influenza A virus illness.

To support investment in their development and use, WHO is conducting a full value of improved influenza vaccine assessment (FVIVA) [35]. This paper supports the FVIVA by describing the landscape of currently available seasonal influenza vaccines and next-generation influenza vaccines in clinical development and reviewing the characteristics of next-generation influenza vaccines in light of current unmet public health needs, particularly those reflected in the PPCs.

## 2. Objectives, definitions and approach

This review analyses currently available influenza vaccines and next-generation influenza vaccine candidates in development, focusing on those in active Phase 1 to Phase 3 clinical trials and using the 2017 WHO PPCs and the IVR roadmap as guiding frameworks to assess how vaccines within the landscape address characteristics desired from new influenza vaccines. This analysis builds on the CIDRAP Universal Influenza Vaccine Technology Landscape and reports on additional information about vaccine candidates' design, indication and performance where indicated. We also report on combination vaccine candidates with a respiratory syncytial virus (RSV) and/or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) component.

Multiple definitions and parameters exist to describe next-generation and universal influenza vaccines, which vary by breadth and duration of protection expected and target population [31]. We propose the following framework to describe the landscape of seasonal influenza vaccines, which includes next-generation and universal influenza vaccine candidates and draws from definitions used in the IVR, WHO PPCs and a systematic review of newer and enhanced influenza vaccines by the European Centre for Disease Prevention and Control (ECDC) [36].

A major goal of influenza vaccine R&D is to develop vaccines that are improved over what is currently available and widely used. We therefore refer to "improved influenza vaccines" as any influenza vaccine designed to provide (as the majority of them are in development) or demonstrating improvement over traditional, unadjuvanted, standard-dose influenza vaccines in terms of durability, efficacy or breadth of protection, or programmatic suitability. These improvements may come through new technologies, vaccine platforms or vaccine design to provide greater efficacy and/or broader and longer-lasting protection from severe influenza disease, including for at-risk populations such as pregnant women, children and older adults. They may also improve upon manufacturing challenges with current vaccines, such as reliance on eggs for egg-based vaccines and manufacturing process timelines.

Improvements may be incremental and modest, such as those expected from vaccines that are building on or using the current influenza technologies. Improvements may also be more dramatic, as in what we consider "next-generation influenza vaccines", which are any vaccines using a different approach or technology in its design than currently licensed vaccines as of the time of this manuscript's writing. Next-generation influenza vaccines include those with the potential to be more effective than current vaccines and those focused on broader or more durable protection. Universal influenza vaccines that would provide protection against all influenza A and B viruses, including seasonal viruses and existing or emergent zoonotic viruses with pandemic potential, are the ultimate goal of next-generation influenza vaccine development. However, broadly protective vaccines could also have significant public health impact, including being subtype-specific (e.g., all strains within a single HA subtype) or providing protection to multiple subtypes within a single influenza A group (e.g., H1/H5/H9). They might also provide pan-group protection, covering all subtypes within a single influenza A group (Group 1 viruses include H1, H2, H5, H6, H8, H9, H11, H12, H13, H16, H17, and H18 viruses; Group 2 viruses include H3, H4, H7, H10, H14, and H15 viruses) [37], or cover all influenza B viruses. While there isn't broad consensus on a threshold for duration of protection from universal vaccines, it would be ideal that they provide multi-year protection, such as five years as noted in the 2017 WHO

**Box 1**
Definitions, characteristics and categories of improved influenza vaccines.

**Improved influenza vaccines:** Any influenza vaccine designed to provide improvement over traditional, standard dose influenza vaccines in terms of durability, efficacy, breadth of protection or programmatic suitability.

Both **enhanced seasonal influenza vaccines** and **next-generation influenza vaccines** are considered improved influenza vaccines.

- **Enhanced seasonal influenza vaccines:** Any influenza vaccine product based on technology and approaches from currently licensed traditional influenza vaccines (i.e., egg-based and cell-based inactivated and LAIV vaccines that target HA from circulating seasonal influenza viruses) that has been enhanced through adjuvants, dosage or manufacturing process (i.e., recombinant technology) to provide improved immunogenicity, efficacy and/or effectiveness over traditional, standard dose seasonal influenza vaccines.

These include [a]:

- o **Adjuvanted inactivated influenza vaccines** that include an adjuvant.
- o **High-dose inactivated influenza vaccines** that are formulated with an increased amount of HA per strain over standard dose vaccines.
- o **Recombinant seasonal influenza vaccines** that have been manufactured through recombinant technology and designed for seasonal and strain-specific use:
  - **recombinant HA protein influenza vaccine** (e.g., Flublok, Supemtek)
  - **virus-like particle vaccine** (Cadiflu-S).

- **Next-generation influenza vaccine**: Any vaccine product using a different approach or technology in its design than currently licensed vaccines.

These include [b]:

- o **Universal influenza vaccines**: Protective against any influenza strain of both influenza A and B viruses, independent of subtype, shift or drift.
- o **Broadly protective influenza vaccines**: Protective against multiple influenza viruses but do not meet the criteria for universal vaccines:
  - subtype-specific (e.g, H1's only)
  - multi-subtype within a single group
  - pan-group (all Group 1 or Group 2 influenza A)
  - all influenza B viruses.
- o **Next-generation seasonal influenza vaccines**: Vaccines containing a formulation based on WHO-recommended strains and/or are designed for seasonal protection that provide better (longer or more effective) protection than currently approved seasonal influenza vaccines against seasonal influenza.
- o **Combination vaccines**: Vaccines that include an influenza component along with another respiratory pathogen.

[a] Ordered alphabetically

[b] Universal, broadly protective, and next-generation seasonal influenza vaccines are ordered according to their intended breadth of protection, with universal influenza vaccines as the most broadly protective

[c] Group 1 viruses include H1, H2, H5, H6, H8, H9, H11, H12, H13, H16, H17, and H18 viruses; Group 2 viruses include H3, H4, H7, H10, H14, and H15 viruses.

Abbreviations: HA = haemagglutinin; LAIV = live-attenuated influenza virus vaccine; WHO = World Health Organization.

PPCs. Box 1 summarizes these definitions and characteristics of improved influenza vaccines, and Fig. 1 illustrates this framework.

We note that this framework and definition of next-generation influenza vaccines, with a focus on new technology or design, differs from the 2017 WHO PPC definition, which focuses on cross-protection. We believe this updated definition is more inclusive and reflective of current influenza vaccine candidates in development and represents leaps in influenza vaccinology versus incremental improvements. As such, it is expected that these new types of influenza vaccines, developed from innovations in vaccine development, may show a greater magnitude of improvement than enhanced seasonal influenza vaccines over currently licensed vaccines, including cross-protection. This definition also aligns with IVR's definition of next-generation influenza vaccines, which focuses on products that use "a different strategy than currently licensed seasonal vaccines to elicit protective immune responses against influenza viruses… demonstrating an improvement over current vaccines in durability, efficacy, or breadth of protection" [38].

To identify and review next-generation influenza vaccine candidates, we conducted an English-language based literature review to characterize current candidates, drawing significantly from the list of candidates and their source literature in the Universal Influenza Vaccine Technology Landscape [32]. Literature reviewed included peer-reviewed manuscripts, press releases and other material from developers, and clinical trial registry records (clinicaltrials.gov), as of April 2024. Using information about design and performance captured from the above sources, we categorized vaccine candidates by their indication (universal or broadly protective, next-generation seasonal or combination) and vaccine platform (Box 1). Vaccine developers were asked to confirm publicly available information collected on their products. The discussion of current seasonal vaccines draws from publicly known and published literature on current influenza vaccines, including the recent WHO Position Paper on Vaccines against Influenza [39]. While next-generation technology is being used in the development of pandemic influenza vaccines, we chose to exclude these products from our analysis.

## 3. Current seasonal vaccines

Currently licensed seasonal influenza vaccines in the world fall into three main types, as characterized by their production platform: inactivated influenza virus vaccines (IIVs), live-attenuated influenza virus vaccines (LAIVs) and recombinant influenza vaccines (RIVs). IIVs and LAIVs require physical viruses for their development and inclusion of target antigens, while RIVs utilize genetic sequence data to produce target antigens. Of note, viruses used for IIVs and LAIVs can be created through recombinant technology (the HA and NA segments in the licensed LAIV FluMist are produced using reverse genetics) [40,41], however, current IIVs and LAIVs are largely developed and produced from standard methods requiring virus growth and propagation.

We consider currently available IIVs and LAIVs to be "traditional" influenza vaccines, as they have a long history of use as far back as the 1940s. Enhanced seasonal influenza vaccines include RIVs, as well as adjuvanted and high-dose vaccines that use traditional IIV technology as the basis of their design but include either an adjuvant or higher dose of the antigen, respectively. Two different recombinant seasonal influenza vaccines have been licensed globally. Flublok was the first recombinant haemagglutinin (HA) protein vaccine to be licensed in the United States in 2013; it was licensed as Supemtek in the European Union and Canada in 2020 and 2021. Cadiflu-S is the only virus-like particle (VLP) vaccine to have received licensure, in 2016, but it is only available in India.

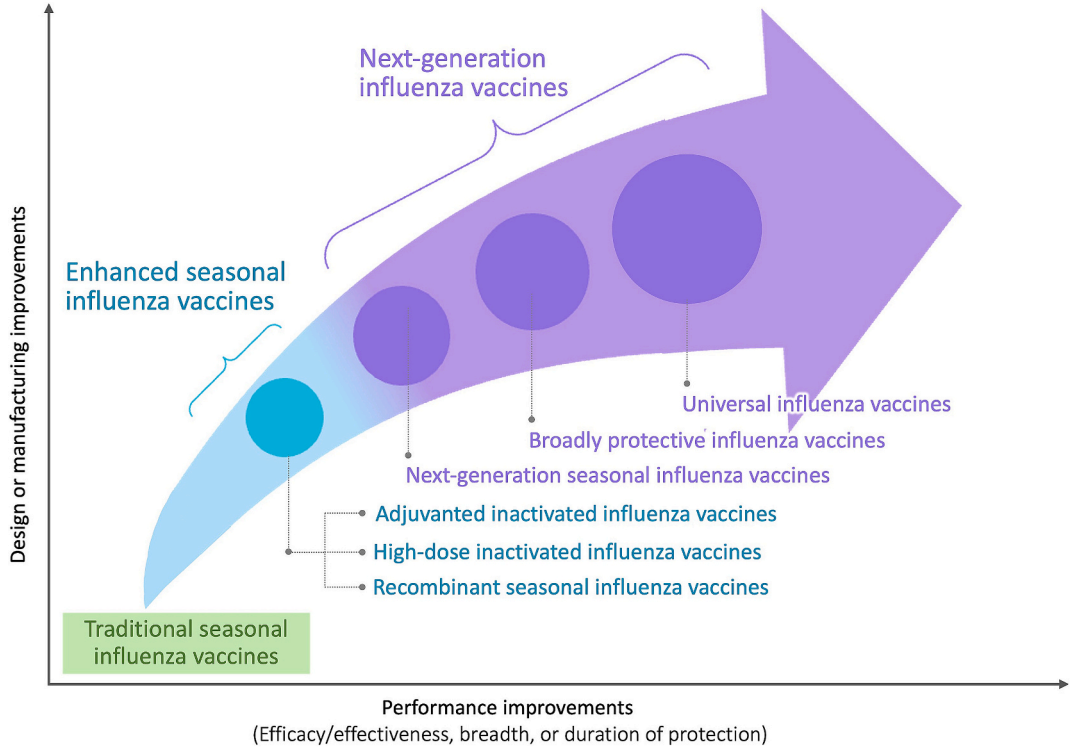



**Fig. 1.** Framework of improving influenza vaccines. Traditional seasonal influenza vaccines serve as a baseline for improvement and include standard dose, egg- and cell-based inactivated and live-attenuated influenza virus vaccines that are designed for seasonal and strain-specific protection. Improvements in vaccine design or manufacturing are expected to lead or have led to improvements in vaccine performance. Both design or manufacturing and performance improvements in enhanced seasonal influenza vaccines* are moderate (vaccines still target HA but use more antigen, recombinant technology or an adjuvant). Improvements from next-generation influenza vaccines are expected to be greater, using novel vaccine targets and design approaches, including platforms, to result in better efficacy/effectiveness, breadth or duration of protection than currently available influenza vaccines, which includes both traditional and enhanced seasonal vaccines.
*Listed order of types of enhanced seasonal vaccines is alphabetical and does not suggest differences in performance)

High-dose vaccines have been available since 2009 when Fluzone High-Dose, a trivalent IIV with four times as much HA per strain, was approved for use in older adults (≥ 65 years of age) in the United States, with Canada following in 2016. As of 2019, a quadrivalent formulation of this high-dose IIV has been available. Adjuvanted IIVs have been in use since 1997, when Italy approved FLUAD for use. By the time it obtained approval from the United States in 2015, it was licensed in 38 other countries [42]. FLUAD uses as its adjuvant MF59, a squalene-based oil-in-water emulsion, and became available in a quadrivalent formulation in 2020. Like the high-dose IIV (Fluzone High-Dose), FLUAD is indicated for adults aged 65 and older; however, FLUAD Pediatric is approved for use in children 6 months to less than 2 years of age in Canada. 3Fluart is an aluminium phosphate-adjuvanted IIV licensed in Hungary [43].

IIVs currently make up approx. 98% of global seasonal influenza vaccine supply, while LAIVs comprise approx. 2%. Estimates of enhanced influenza seasonal vaccine usage and demand are not publicly available, though usage is limited and concentrated in high-income countries [14]. It should be noted that LAIVs are not recommended for several key target groups (e.g., pregnant women, health workers, immunocompromised individuals, children under 2 years of age, older adults), due to the lack of consistently demonstrated vaccine efficacy in these age groups and limited evidence on safety in pregnant women [39].

### 3.1. Design and manufacturing

Currently licensed vaccines are designed to provide strain-specific protection. They target or include the HA glycoprotein in their design and are available in trivalent and quadrivalent formulations, using three or four candidate vaccine viruses (CVVs), viruses prepared for potential use in vaccine manufacturing) recommended by WHO each season (two influenza A strains, H1N1 and H3N2, and one or two influenza B lineages, depending on whether the formulation is trivalent or quadrivalent). Of note, as of September 2023, WHO recommends that the B/Yamagata lineage antigen should no longer be included in seasonal influenza vaccines [44]. IIVs contain HA and neuraminidase (NA) proteins from whole influenza virus that have been inactivated through heat or chemical reagents and further processed into split-virion or subunit vaccine forms with concentrated antigen. IIVs used for seasonal vaccines are mostly manufactured in split-virion or subunit forms, as there are higher adverse reaction rates with IIVs from inactivated whole influenza virus [45,46]. While IIVs cannot replicate due to their inactivation, LAIVs contain live influenza virus that has been attenuated to not cause influenza illness. LAIVs contain HA and NA from the target virus strain that has been reassorted into the LAIV backbone virus. Currently licensed RIVs for seasonal use also target and include HA protein which has been produced from recombinant technology and presented in a recombinant HA protein or VLP vaccine platform. The influenza VLP vaccine (Cadiflu-S) also includes recombinant NA and M1 matrix proteins.

IIVs and LAIVs are predominately manufactured in eggs [17], though some use mammalian cell lines to grow CVVs. While the egg-based production process is relatively low cost and its manufacturing process well established [47], production of vaccines ready for deployment can take up to 6 months from initial selection of viruses. During this time, genetic changes that naturally happen externally to circulating virus strains (antigenic drift) or internally to the vaccine virus strains through their adaption and growth in eggs may make the resulting vaccine less effective [48]. Also, there is a risk of allergic reaction for individuals with egg allergy given this vaccine, and availability of eggs could be a limiting factor in the production of pandemic influenza vaccines. The latter is a significant concern given the pandemic risk of avian influenza viruses. The cell-based approach eliminates the issues introduced with eggs and could theoretically be scaled up more quickly from cryopreserved cell lines versus the reliance on egg procurement for egg-based vaccines [49]. However, intellectual property issues, higher manufacturing costs, and access to approved and/or suitable cell lines for vaccine production may limit widespread use of this approach [50]. Similarly, use of the baculovirus expression vector system to express HA protein in insect cells for currently licensed RIVs is a novel method with proprietary and cost barriers.

### 3.2. Current influenza vaccines efficacy/effectiveness

The efficacy, effectiveness and safety of licensed seasonal vaccines, both traditional and enhanced, have been reviewed in several recent reports [9,36]. Seasonal effectiveness against laboratory-documented infection in all age groups, as estimated by the United States Influenza Vaccine Effectiveness Network, was between 19–60% over 15 seasons since 2009, varying by season [8]. Influenza vaccination is also effective against severe outcomes, as evidenced by a 37% reduction in influenza-associated hospitalizations [51] and 32% reduction in severe influenza-associated illness among adults in the United States [52]. Vaccine effectiveness varies by virus type or subtype, vaccine strain component and age [10].

Comparing by vaccine type, a detailed review prepared for the WHO Strategic Advisory Group of Experts (SAGE) on Immunization concluded that vaccine efficacy/effectiveness against medically attended, laboratory-confirmed influenza illness in healthy adults was “good” for LAIVs and “very good” for egg- and cell-based IIVs and RIVs [9]. High-dose and adjuvanted IIVs offer better protection for adults over 65 years of age, followed by cell-based IIVs and RIVs [9]. Cell-based IIVs and RIVs perform best for pregnant women, and the efficacy/effectiveness of traditional influenza vaccines in children and infants is “good” [9]. An ECDC systematic review found vaccine effectiveness/efficacy against laboratory-confirmed influenza in adults aged 65 and older to be 45% and 24% (relative efficacy compared to standard-dose IIVs) for adjuvanted and high-dose influenza vaccines, respectively, and 30% (relative efficacy compared to IIVs) for recombinant HA protein vaccines in adults aged 50 and older [36]. The overall relative vaccine effectiveness of recombinant HA protein influenza vaccines over standard-dose IIVs in adults aged 18 and over during the 2018–2019 and 2019–2020 influenza seasons was 31%, and also significant when stratified by sex (37% in females), age (28% in adults aged 18–65), health (60% in adults with no high-risk conditions) and season (30% in the 2019–2020 season) [53]. A large body of evidence establishes the safety of enhanced seasonal vaccines, with recombinant HA protein vaccines having a reactogenicity profile similar to traditional influenza vaccines while adjuvanted and high-dose IIVs are slightly more reactogenic, as expected due to their composition [36]. Given the available evidence on efficacy/effectiveness, high-dose IIVs, adjuvanted IIVs and recombinant HA protein vaccines are recommended for older adults (aged 65 years and older) [39].

Table 1 summarizes characteristics of current seasonal influenza vaccines.

## 4. Next-generation vaccines

The R&D landscape for improved influenza vaccines is robust in terms of number of vaccine candidates in preclinical and clinical development as well as the number of developers pursuing a vaccine candidate. Previous efforts have documented the influenza vaccine R&D landscape [54–58]. We present our findings to update and complement these efforts, within the context of the WHO PPCs, updated definitions and a broader pipeline of candidates.

### 4.1. Vaccine candidate inclusion and categorization

Fig. 2 and 3 and Supplemental Table 2 summarize the information captured from our literature review of next-generation influenza vaccines currently in development. A total of 56 next-generation influenza

**Table 1**
Summary characteristics of current influenza vaccines.

| | | 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) [93][b]; 23–24 weeks (pandemic) [94] | 6–8 months (seasonal) [93][b]; 21 weeks (pandemic) [94] | 5 months (seasonal) [93][b]; 38 days for production of purified antigen [95] | 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%) [14][f] | Low (approx. 2%) [14] | Estimates unavailable | Estimates unavailable | Estimates unavailable |
| | **Vaccine price** | Moderate | Moderate to high | High | High | High |
| **Other considerations** | **Advantages** | Egg-based: widely used and available<br>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; theoretical scale-up in pandemic is feasible | 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<br>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 [39].

[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 [39,96,97]

vaccine candidates in Phase 1 to Phase 3 trials from 24 developers were reviewed. We only included vaccine candidates that are actively in development and met our definition of a next-generation influenza vaccine. The products listed are those that we consider to be individual vaccine candidates in development and are unique from each other in their design, platform and indication, or a combination of these. Particularly for products in more advanced stages of development, there may have been previous formulations or product versions that led to the current product – here, we only summarize information on the product in its most advanced development phase, noting any relevant information about what has been tested differently or additionally in previous trials or product versions. In cases where a vaccination regimen is heterologous, we consider each unique vaccine candidate used in the regimen as an individual product and enumerate it as such. Candidates that are tested with and without adjuvants are only counted once, as we do not consider the adjuvanted candidate to be an entirely different product than its unadjuvanted version. However, we report immunogenicity and efficacy results by the vaccination regimen, indicating the different products that have been included in the regimen.

Products were categorized by their technology/vaccine platform and by their intended use, as confirmed by developers through direct communication and/or deduced from published or publicly available information on the products. Next-generation influenza vaccine technologies/platforms include recombinant proteins, influenza virus-based, VLPs, virus-vectored, non-VLP nanoparticles and nucleic acid-based. These products have been grouped by their respective intended use/indication as universal or broadly protective or next-generation seasonal; combination vaccines are included as a third category (see definitions in Box 1). For the purpose of this review, we grouped universal and broadly protective vaccine candidates together, as their intended performance and indication go beyond those of the next-generation seasonal category with more of a strain-specific focus.

### 4.2. Vaccine indication, platform, and design

Products falling into the universal or broadly protective category are

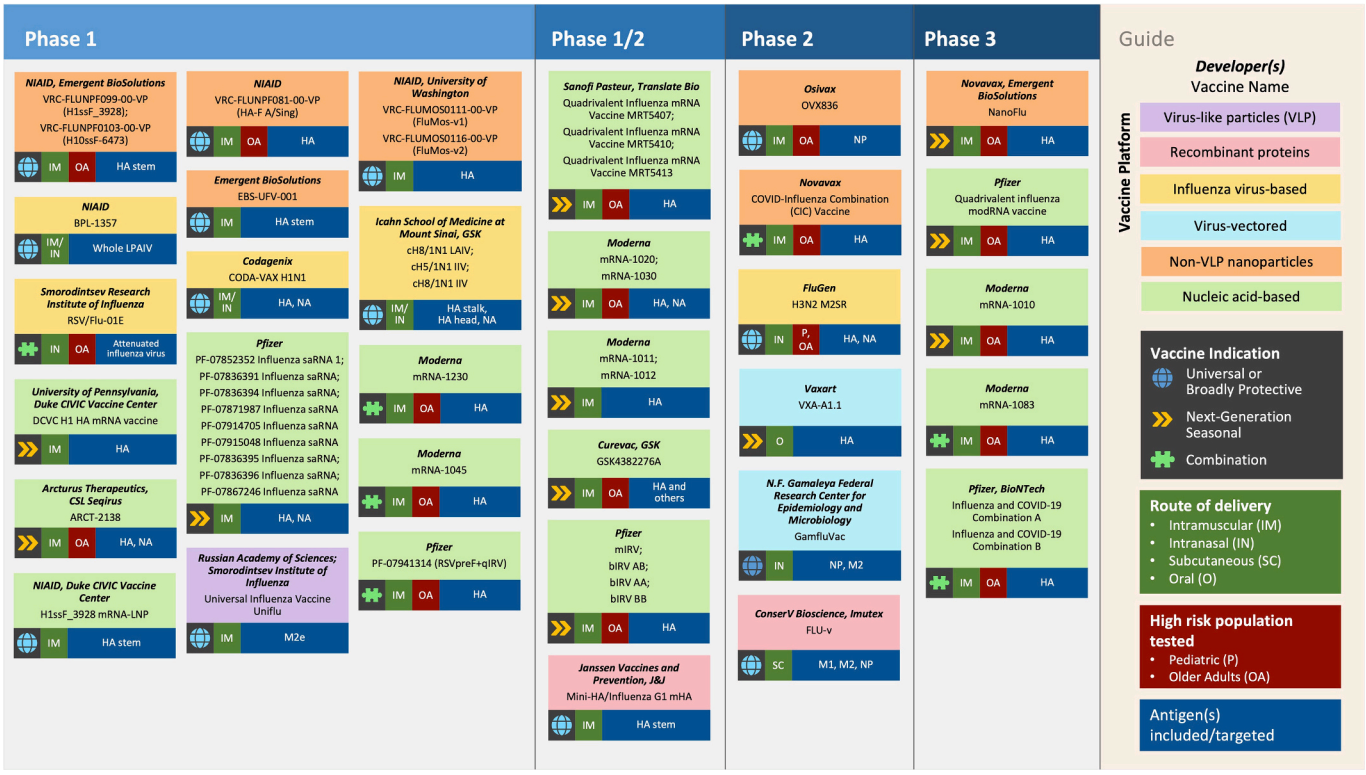



**Fig. 2.** The landscape of next-generation influenza vaccines in clinical development, as of April 2024. Each box represents a unique vaccine candidate or group of candidates, associated with their respective developer(s), and includes key characteristics about the candidate, such as indication, route of delivery, high-risk populations tested and antigens included/targeted.
Abbreviations: bIRV = bivalent influenza modRNA vaccine; BPL = beta-propriolactone; CIVICs = Collaborative Influenza Vaccine Innovation Centers; HA = haemagglutinin; IIV = inactivated influenza virus vaccine; LAIV = live-attenuated influenza virus vaccine; LNP = lipid nanoparticle; mIRV = monovalent influenza modRNA vaccine; NA = neuraminidase; NIAID = National Institute for Allergy and Infectious Diseases; qIRV = quadrivalent influenza modRNA vaccine; RSV = respiratory syncytial virus; UFV = universal influenza vaccine; VRC = Vaccine Research Center.

the most diverse, with 18 total products (Fig. 3). All vaccine platforms/technology are represented in this use category, with the majority of them using influenza virus-based or non-VLP nanoparticle technology/platforms. None of the universal or broadly protective vaccine products are currently in Phase 3 testing, although for two such candidates, development was discontinued after Phase 3 trials were completed (the BiondVax Multimeric-001 candidate, after failing to meet efficacy endpoints [59], and Medicago QVLP [60], following closure of the company in 2023). Many of these products include or target the HA antigen or conserved parts of it, in addition to including or targeting additional antigens – nucleoprotein (NP), M1, M2, NA – for broader protection: Uniflu (Russian Academy of Sciences and Smorodintsev Research Institute of Influenza) includes the M2 ectodomain in a hepatitis B core antigen VLP, Osivax's OVX836 is a self-assembling non-VLP nanoparticle containing NP, GamFluVac (Gamaleya National Center of Epidemiology and Microbiology) is an adenovirus-vectored vaccine targeting NP and M2, and FLU-v (ConserV Bioscience and Imutex) is a synthetic peptide-based vaccine incorporating conserved regions of M1, M2, and NP). Influenza virus-based vaccines from Icahn School of Medicine at Mount Sinai and GSK, Codagenix, and FluGen target both HA and NA in their candidates, whereas vaccine candidates from NIAID, University of Washington, Emergent BioSolutions using the non-VLP nanoparticles platform and mRNA and recombinant protein candidates from NIAID and Duke CIVICs Vaccine Center and Janssen Vaccines and Prevention and J&J, target HA, including its stem region. (Fig. 2 and Supplemental Table 2). Some of the vaccines have been tested with adjuvants, and some have not (Supplemental Table 2).

Next-generation seasonal products are the most abundant in the clinical pipeline, with almost twice as many candidates ($n$ = 30) as universal or broadly protective products in development (Fig. 3). They are also much less diverse. The vast majority of the next-generation seasonal products are mRNA-based and under development by multiple groups and collaborations, including large pharmaceutical companies and vaccine manufacturers, biotech, and academia (Fig. 3, Supplemental Table 1, and Supplemental Table 2). Only two products in this category are not nucleic acid-based - Novavax and Emergent BioSolutions' NanoFlu is a non-VLP nanoparticle candidate that includes a full length HA protein self-assembled into HA nanoparticle structures and Vaxart's VXA-A1.1 is a monovalent adenovirus-based vaccine expressing the influenza HA protein (Supplemental Table 2). No DNA-based vaccines are in active clinical development. All candidates in this category target HA, though products from several developers additionally target NA (saRNA candidates from Pfizer and CSL Seqirus and Arcturus Therapeutics, Moderna's mRNA-1020 and mRNA-1030) (Supplemental Table 2); CureVac reported targeting "HA and others" in their GSK4382276A vaccine (personal communication, November 9, 2023). Adjuvants are only used with the two non-nucleic-acid-based products (Supplemental Table 2), though it should be noted that the lipid nanoparticle packaging of mRNA, widely used in current mRNA vaccines, has its own immunostimulatory effect [61]. Three next-generation seasonal products are in Phase 3 clinical trials, specifically Pfizer's quadrivalent influenza modRNA vaccine, Moderna's mRNA-1010, and Novavax and Emergent BioSolutions' NanoFlu (Fig. 2 and Supplemental Table 2).

There is significant investment in developing combination vaccine products that include an influenza component, with eight candidates in the clinical pipeline (Fig. 2 and Supplemental Table 2). The vaccine products in the combination vaccine category generally mirror what is

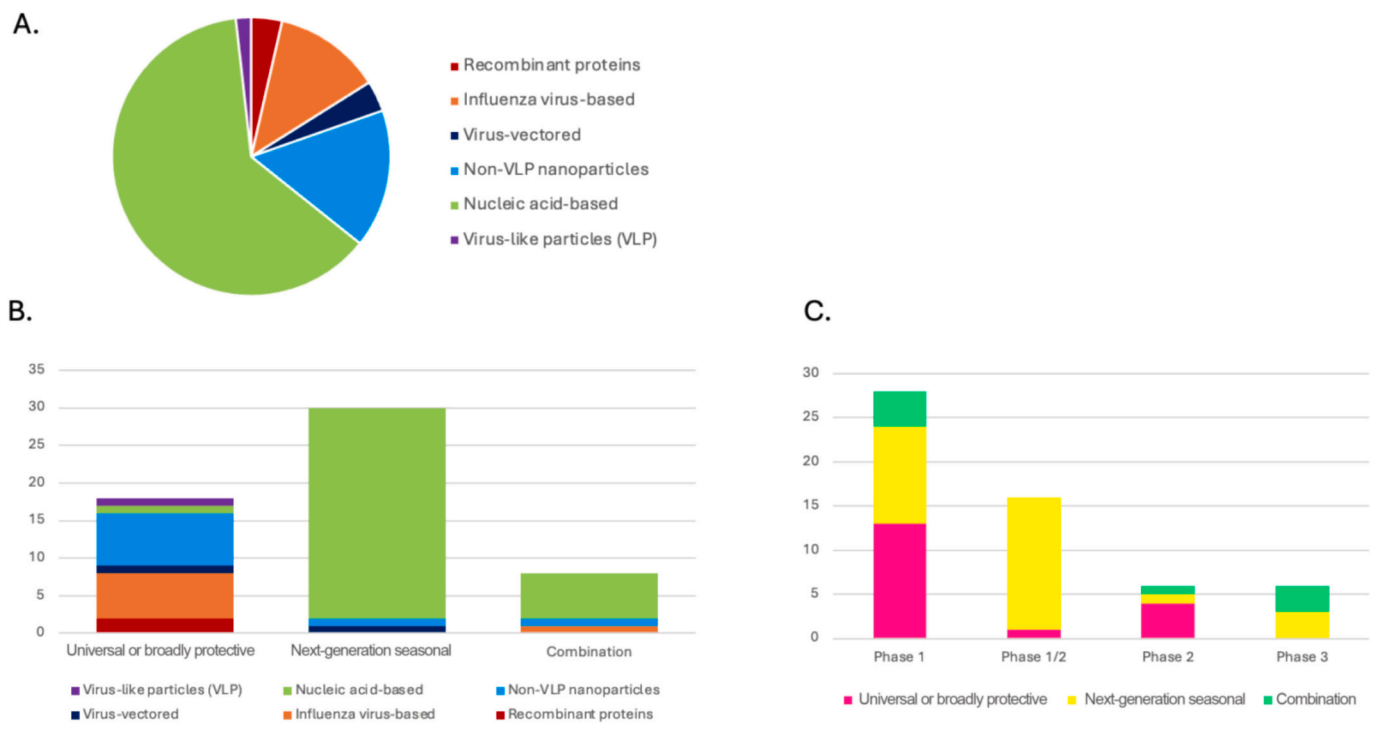



**Fig. 3.** Next-generation influenza vaccines in clinical development tallied by vaccine platform, indication and clinical development phase. (A) The share of each vaccine platform among all next-generation influenza vaccine candidates in clinical development. (B) The number of candidates among universal or broadly protective, next-generation seasonal and combination influenza vaccines, as characterized by vaccine platform. (C) The number of vaccine candidates in or having completed Phase 1, Phase 1/2, Phase 2 or Phase 3 clinical trials, as characterized by vaccine indication.

in the next-generation seasonal vaccine category. Novavax, Moderna and Pfizer are developing combination vaccine candidates with technology and approaches similar to their standalone next-generation seasonal influenza vaccine candidates. Two candidates use a vaccine platform other than mRNA: Novavax's non-VLP nanoparticle combination SARS-CoV-2/influenza vaccine and the Smorodintsev Research Institute of Influenza's combination RSV/influenza vaccine, which uses an attenuated influenza virus as its platform. Both Pfizer and Moderna are developing combination SARS-CoV-2/influenza and RSV/influenza mRNA vaccines, and Moderna is also testing a triple-pathogen SARS-CoV-2/influenza/RSV mRNA vaccine. Three of the combination products are in Phase 3 trials.

In general, administration of next-generation vaccines is limited to one or two doses, and most of them are being tested for intramuscular delivery, with a few notable exceptions. Vaxart's VXA-A1.1 is administered orally in tablet form, and its efficacy against influenza-positive illness in a Phase 2 homologous challenge study was comparable to that of a licensed intramuscular quadrivalent IIV [62]. FLU-v (ConserV Bioscience and Imutex) has been tested with subcutaneous administration. All of the influenza virus-based vaccines have been tested intranasally.

### 4.3. High-risk population testing

Many of the vaccine candidates across platforms, use categories and stages of development have included or focused specifically on testing in older adults (≥ 65 years of age), including all candidates in Phase 3 trials (Fig. 2 and Supplemental Table 2). FluGen's H3N2 M2 Deleted Single Replication Live Virus Vaccine (M2SR) is the only product that has been tested in children, having completed a Phase 1 trial in children aged 9–17 years. The results of that trial, NCT03553940, are reported in the ClinicalTrials.gov registry but have not been formally analysed and reported. An updated strain version of this product is currently in Phase 1 testing (NCT04960397) with participants from age 6 months to 17 years.

### 4.4. Immunogenicity measures and efficacy

While many vaccine candidates are still in early testing, those that have completed initial safety testing have been reported as safe, with no serious adverse events. In addition to dosage finding studies and safety testing, the immunogenicity and efficacy of many candidates have also been measured. Supplemental Table 3 summarizes the immunogenicity and efficacy of candidates that have reported results.

Each platform has some candidates that measure both humoral and cell-mediated immune responses, though this is most common with virus-based vaccines. The most frequently used assays to measure immunogenicity include HA inhibition (HAI), virus neutralization, enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunosorbent spot (ELISpot); however, actual immunogenicity measures and which assays are used vary widely across trials and studies. For example, an HA antibody response could be measured through HAI and reported as seroconversion rates, as defined by a specific fold increase over baseline antibody titre threshold, or the actual titres themselves may be used. Antibody or cell-mediated immune responses may be measured against homologous or heterologous antigens and may be specific to only a part of the antigen. The variability in how immunogenicity is measured and reported makes it challenging to compare different vaccine products.

Only five vaccine products, including both universal or broadly protective and next-generation seasonal candidates, have reported efficacy results, derived from human challenge and seasonal cohort studies and focused on protection from influenza infection and clinical symptoms. Osivax's NP-based nanoparticle vaccine, OVX836, showed an 84% level of protection against RT-PCR confirmed influenza A infection during the 2021–2022 influenza season [63]. Pfizer's Phase 3 quadrivalent mRNA vaccine candidate's efficacy data have not been published, but the developer has reported non-inferior and superior efficacy compared with a licensed influenza vaccine at primary analysis which remains non-inferior by the end of the season [64]. In a Phase 2 human

challenge trial with FluGen's H3N2 M2SR vaccine, only individuals with at least a twofold microneutralization response achieved statistical significance in reduction of infection and influenza symptoms; otherwise, the difference between vaccine and placebo groups was not significant [65]. While Vaxart's adenovirus-based VXA-A1.1 protected against laboratory-documented infection, it did not significantly reduce influenza illness; neither did the licensed vaccine comparator in this challenge study [62]. Recipients of FLU-v (ConserV Bioscience/Imutex) were significantly less likely to develop mild-to-moderate influenza disease after challenge versus those receiving placebo (32.5% vs 54.8%) [66].

### 4.5. Performance compared to current influenza vaccines

A main goal of next-generation vaccines would be to elicit an improved immune response or be more efficacious than, or at least show non-inferiority to, currently licensed influenza vaccines. Most of the products with reported results, including candidates from each of the indication categories and all but one (FLU-v) reporting efficacy, have been tested and compared against licensed vaccines, usually testing against the standard of care or recommended vaccine for a specific age group (traditional seasonal vaccines for healthy adults, enhanced seasonal vaccines for older adults). As enhanced vaccines do show better efficacy/effectiveness in and are recommended for older adults, it is important that these vaccines are used as comparators when testing in this population.

Among the next-generation seasonal candidates, several have shown non-inferiority to or even superiority over currently licensed vaccines in immune responses elicited or protective efficacy. Novavax's NanoFlu vaccine has been shown to be non-inferior or even superior to a licensed IIV with regard to eliciting antibody and T-cell responses to homologous and heterologous strains in older adults [67]. The latest Phase 3 trial results from Moderna's mRNA-1010 demonstrate higher geometric mean titres (GMTs) and seroconversion rates for both A and B virus strains than the licensed standard-dose vaccine comparator [68]. mRNA-1010 also induces higher (influenza A strains and B/Victoria) or comparable (B/Yamagata) HAI titres in older adults, as compared to an enhanced seasonal influenza vaccine (Fluzone High-Dose). Pfizer's Phase 3 quadrivalent mRNA candidate demonstrated non-inferior and superior efficacy compared with a licensed influenza vaccine, though immunogenicity end-points were only met for A strains [64]. Similarly, CureVac and GSK's Phase 2 mRNA candidate GSK4382276A elicited higher antibodies than its licensed vaccine comparator in both younger and older adults for A strains, but antibodies were lower against B strains in both age groups [69]. In another Phase 2 study, orally administered VXA-A1.1 significantly reduced laboratory-documented infection from homologous challenge over placebo, with protection similar to licensed IIVs [62]. However, HAI and neutralization titres were inferior to the licensed vaccine, and instead, induction of immunoglobulin A (IgA)-antibody-secreting cells specific to HA correlated with VXA-A1.1's efficacy [62].

Combination candidates have demonstrated non-inferiority as well. Novavax's COVID-Influenza Combination (CIC) vaccine, whose influenza component is based on its stand-alone NanoFlu design, performed similarly to NanoFlu [70,71], and Pfizer's combination SARS-CoV-2 and influenza vaccine candidates exhibited point estimates for HAI GMT ratios greater than 1 relative to a licensed quadrivalent influenza vaccine for all vaccine-matched strains [72]. Moderna's mRNA-1083 similarly achieved HAI GMT ratios greater than 1 relative to licensed quadrivalent influenza vaccines in adults 50–79 years old for all four influenza vaccine strains [73].

Among the universal or broadly protective candidates, the immunogenicity of H3N2 M2SR in older adults was compared to that from Fluzone High-Dose. H3N2 M2SR elicited increased secretory IgA antibodies and T-cell responses in a greater proportion of subjects than the enhanced vaccine alone, as did coadministration of H3N2 M2SR and Fluzone High-Dose; HAI and neuraminidase inhibition assay responses were increased in a greater proportion of subjects that received H3N2 M2SR and Fluzone High-Dose together versus Fluzone High-Dose alone [74]. NP-specific antibodies and the interferon gamma T-cell response from OVX836 were increased over those from quadrivalent seasonal influenza vaccine (Influvac Tetra) [75]. However, Influvac Tetra is an inactivated surface antigen (subunit) influenza vaccine, enriched specifically for HA and NA. Any trace amounts of NP in this vaccine should be negligible, so it functions more like a placebo in this study.

### 4.6. Breadth and duration of immune responses

Results based on duration and breadth of immune responses are almost exclusively found in products from the universal or broadly protective category, with the exception of Novavax's NanoFlu and CIC vaccines, which showed cross-reactivity against drifted strains [67,70]. The ferritin-based nanoparticle vaccines [VRC-FLUNPF081-00-VP (HA-F A/Sing), VRC-FLUNPF099-00-VP (H1ssF_3928)] demonstrated heterosubtypic responses within Group 1 influenza A viruses that lasted at least 6 months [76,77]. The influenza-virus-based vaccines also were effective at eliciting a cross-reactive immune response. Chimeric influenza virus vaccines in a live-attenuated form or inactivated with adjuvant (Icahn School of Medicine at Mount Sinai/GSK) generated heterosubtypic responses within Group 1 persisting through 420 days [78], and FluGen's H3N2 M2SR vaccine is able to induce immune responses to drifted strains [65,79]. FLU-v, an adjuvanted recombinant protein vaccine consisting of a mix of lyophilized synthetic peptides from conserved regions of M1, M2 and NP proteins, elicited a cell-mediated immune response that was cross-reactive against both influenza A (Groups 1 and 2) and B strains and persisted along with antibody responses for 180 days [80,81].

## 5. Discussion

The global public health need for improved influenza vaccines is clear due to programmatic challenges for current influenza vaccines and calls from major global health R&D stakeholders to develop better vaccines against seasonal influenza. Vaccine developers are equally invested in this goal, as our evaluation reveals a robust clinical development pipeline for next-generation influenza vaccines, with diverse approaches to improve the performance and programmatic suitability of influenza vaccines.

We evaluated next-generation influenza vaccine candidates in context with currently approved influenza vaccines, both traditional and enhanced seasonal vaccines, noting potential technological and performance improvements from candidates in the pipeline, and through the frameworks of the IVR Roadmap and the 2017 WHO PPCs for Next-Generation Influenza Vaccines. We drew heavily from these two frameworks in our definitions of improved and next-generation influenza vaccines and the characteristics we chose to evaluate in pipeline candidates.

The 2017 WHO PPCs for Next-Generation Influenza Vaccines specifies desired characteristics for improved seasonal and universal-like influenza vaccines. Although no new types of seasonal influenza vaccines have been approved since publication of the PPCs, the pipeline review shows that considerable resources have been allocated to developing next-generation influenza vaccines and that progress in the clinical development and licensure of these vaccines is underway, with 56 candidates in clinical trials. Over half of the candidates are categorized as next-generation seasonal, with the potential to address the first strategic goal in the PPCs for a vaccine offering better protection for at least 1 year against vaccine-matched or drifted influenza strains than non-adjuvanted, non-replicating influenza vaccines. Eighteen universal or broadly protective candidates are in development with the potential to address the PPC's second strategic goal of a vaccine with better protection against vaccine-matched AND drifted influenza strains that is maintained for at least 5 years. Combination vaccines in the pipeline

could address either strategic goal, depending on their performance, though current candidates are based on technology and approaches more likely to be limited in their breadth and duration of response. We are unable to assess the potential of pipeline products in meeting duration of protection parameters, as most trials have not measured performance beyond 1 year.

Protective efficacy against severe influenza illness is the desired outcome identified in the WHO PPCs for Next-Generation Influenza Vaccines, as it would have significant impact in an LMIC context. Efficacy has only been reported in a small subset of candidates, including only one Phase 3 candidate, and it is evaluated against laboratory-documented infection or clinical influenza symptoms, not severe influenza illness specifically. Evaluation of severe influenza illness would require much larger and more costly clinical trials; this assessment may not be obtained until post-licensure studies are conducted with next-generation influenza vaccine products.

Current WHO guidance on influenza vaccines recommends consideration of seasonal influenza vaccination in high-risk groups, such as health workers, individuals with comorbidities and underlying conditions, older adults and pregnant women, as well as groups that countries may deem a priority (e.g., children) [39]; the WHO PPCs indicate a preference for children aged 6 weeks through 59 months, older adults, persons with chronic medical conditions and pregnant women as the target populations for next-generation influenza vaccines. Despite this emphasis on influenza vaccines suitable for high-risk populations, current candidates have not been tested in most of these populations. Many candidates are being evaluated in older adults, but only one candidate has been tested in children. Healthy adults are the primary focus of most next-generation influenza vaccine clinical trials, excluding pregnant women. It is critical that next-generation influenza vaccines be evaluated in all high-risk populations to ensure that safe and more effective vaccines are available to reduce morbidity in the most vulnerable populations.

In addition to the progress made in developing next-generation influenza vaccines, the COVID-19 pandemic has spurred considerable focus on combination vaccines that would target multiple respiratory viruses, including influenza, SARS-CoV-2 and/or RSV. The pipeline review has shown that eight candidates are in clinical development, with three in Phase 3 testing. This strategy of integrating multiple respiratory viruses that cause significant disease and economic burden could allow for comprehensive protection against a spectrum of respiratory infections, streamlined and integrated immunization schedules that support a life-course approach to vaccination [82], and optimal health system resource allocation. The ongoing evaluation of combination products and of vaccine coadministration in preclinical and clinical settings has suggested that development of these products is feasible with safety maintained and performance not significantly affected by the combination of different respiratory pathogen antigens in one vaccine product [83–86]. However, the behavioural and social drivers of vaccination must also be considered, as any hesitancy to receive a vaccine including antigens for one respiratory virus in a particular target population could then conceivably alter vaccine uptake for other included antigens. Also, a complication with the manufacturing and usage of combination vaccines could be different timing of antigen composition updates and recommendations for frequency of administration between the pathogens targeted. At present, recommendation of COVID-19 revaccination within 6-12 months of the last dose is only for priority-use groups [87], and evidence review related to vaccine performance in context with SARS-CoV-2 evolution happens approximately every 6 months, with WHO recommending composition changes as needed [88]. While RSV vaccines are recommended for similar target groups (older adults, pregnant women), revaccination is not currently recommended for older adults [89].

While the prospects of next-generation influenza vaccines are promising, their potential limitations must also be acknowledged. Challenges such as scalability, affordability, supply chain specificities and uncertainties regarding long-term effectiveness necessitate a pragmatic approach. It is crucial that these novel vaccines be not only efficacious but also financially viable and logistically feasible. The programmatic suitability section outlined in the WHO PPCs highlights these aspects, which are important for ensuring access by vulnerable populations in LMICs. Strategies aimed at enhancing vaccine access and affordability, such as technology transfer initiatives and tiered pricing models, promote equitable distribution and mitigate economic barriers to vaccination. Additionally, investments in health system infrastructure, cold-chain logistics and vaccine delivery systems strengthen vaccine supply chains and enhance vaccine coverage in resource-limited settings. Moreover, advances in vaccine delivery systems, including microneedle patches and intranasal formulations, offer alternative routes of administration that could enhance vaccine acceptability and coverage. Collaborative partnerships between governments, international organizations, academia, nongovernmental organizations and industry foster innovation, capacity-building and knowledge exchange, allowing for greater access to and sustainable use of next-generation influenza vaccines.

The diversity of vaccine candidates and design within the pipeline is impressive, though it makes comparison of performance, especially immunogenicity, between vaccines very challenging. As more novel candidates enter late-stage clinical trials, it is imperative to focus on identifying correlates of protection and requirements for clinical evaluation, which are essential for licensing next-generation influenza vaccines. Robust correlates of protection serve as surrogate markers for vaccine efficacy, enabling comparative assessments of vaccine candidates and informed decision-making in clinical trial design and interpretation. They also de-risk product development of new vaccines for manufacturers [90]. Additionally, scientific consensus and regulatory guidance on how to define and evaluate breadth of protection for regulatory review are greatly needed. Furthermore, transparent and flexible regulatory pathways and expedited approval processes facilitate timely access to safe and effective vaccines, particularly during public health emergencies and influenza pandemics. These issues have been emphasized in recent meetings in the next-generation influenza vaccine development community [90,91], though a structured path forward has not been established. It is imperative that vaccine developers and regulators work together to do so.

The continued detection and notification of human infections with zoonotic influenza viruses (including H5 viruses) from countries around the world reminds us of the ongoing threat of an influenza pandemic which is a global concern. Both effective vaccines and robust influenza vaccination programs are needed to respond to this threat, and seasonal influenza vaccination programs provide a foundation for pandemic influenza preparedness and response. Next-generation influenza vaccines could further strengthen this foundation if they can be produced faster, provide breadth of protection against emerging influenza viruses, and overcome programmatic barriers previously identified by immunization managers in LMICs [16].

Looking ahead, policy-makers face the critical task of strategically navigating next-generation influenza vaccine development and licensure. Sustained funding for R&D initiatives is critical for advancing innovative technologies, supporting preclinical and clinical development, and translating promising candidates into effective vaccines that are accessible by all countries. Countries are encouraged to develop and strengthen national influenza vaccination policies and programmes utilizing currently available vaccines, especially for high-risk populations. Continued investment in these programmes remains crucial to mitigate the burden of influenza while simultaneously providing a foundation for use of next-generation influenza vaccines once they become available. In addition to technical support, WHO and other stakeholders, such as the Partnership for International Vaccine Initiatives, provides financial support to eligible LMICs in establishing/enhancing their national seasonal influenza vaccination programmes. To ensure policy-makers and developers continue to think through the

optimal characteristics and programmatic components for next-generation influenza, WHO is also developing an updated version of the PPCs for Next-Generation Influenza Vaccines. This updated document will reflect an evolved influenza vaccine R&D landscape, updated WHO guidance and strategy on influenza, and perspectives gained from the COVID-19 pandemic.

The abundance of mRNA-based vaccine candidates in the pipeline indicates significant interest and investment from developers in this platform for influenza. Several mRNA-based vaccine candidates, both stand-alone influenza and combination products, are in or have completed Phase 3 trials and may enter the market in high-income countries in the coming years. As such, it is important to begin considering how these mRNA vaccines may become integrated into the current global influenza vaccine manufacturing ecosystem and existing immunization programmes, keeping in mind issues such as vaccine access and equity, cost and other implementation or roll-out issues. Additionally, it will be critical to monitor activities to develop and transfer mRNA vaccine production technologies to LMICs, such as the WHO/Medicine Patent Pool mRNA Technology Transfer Programme [92], to understand which countries are prioritizing influenza vaccine development.

The timeline from the start of production to the release of future vaccines has the potential to be shorter for next-generation vaccines than for current egg-based vaccines, and some future vaccines also have the potential for longer duration of protection. This means that current global approaches to vaccine strain selection and vaccine composition should now consider how these and other decision-making processes will need to incorporate the coming technologies. While the influenza vaccination pipeline is both robust and promising, it is also important to acknowledge that current influenza vaccines have been shown to reduce medically attended and severe illness associated with seasonal influenza in high-, middle- and low-income countries. Current vaccines have also been shown to be cost-effective and/or cost-saving in many specific target groups. As the horizon of future vaccination products approaches, it remains imperative to continue to support and expand current global influenza vaccination programmes to reduce annual morbidity and mortality, and to support pandemic preparedness efforts as well.

## 6. Conclusion

Our review of the current next-generation influenza vaccine clinical pipeline highlights the robust efforts underway to develop improved influenza vaccines. With 56 candidates in development, including late-stage mRNA and combination vaccines and promising universal or broadly protective products, there is significant potential for enhanced efficacy and programmatic suitability. Continued investment and strategic planning will be essential to ensure the successful development and integration of these new vaccines into global influenza prevention efforts and vaccination programmes, aligning with the goals outlined by WHO and other major stakeholders.

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## Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

## CRediT authorship contribution statement

**Jessica Taaffe:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Julia T. Ostrowsky:** Writing – review & editing, Validation. **Joshua Mott:** Writing – review & editing. **Shoshanna Goldin:** Writing – review & editing. **Martin Friede:** Supervision, Conceptualization. **Pierre Gsell:** Writing – review & editing. **Christopher Chadwick:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

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