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Review

A Research and Development (R&D) roadmap for influenza vaccines: Looking toward the future

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ABSTRACT

Improved influenza vaccines are urgently needed to reduce the burden of seasonal influenza and to ensure a rapid and effective public-health response to future influenza pandemics. The Influenza Vaccines Research and Development (R&D) Roadmap (IVR) was created, through an extensive international stakeholder engagement process, to promote influenza vaccine R&D. The roadmap covers a 10-year timeframe and is organized into six sections: virology; immunology; vaccinology for seasonal influenza vaccines; vaccinology for universal influenza vaccines; animal and human influenza virus infection models; and policy, finance, and regulation. Each section identifies barriers, gaps, strategic goals, milestones, and additional R&D priorities germane to that area. The roadmap includes 113 specific R&D

Abbreviations: ABS, Access and Benefit Sharing; ACT, Access to COVID-19 Tools; ADCC, antibody-dependent cellular cytotoxicity; CARB-X, biopharmaceutical accelerator for combating antibiotic resistant bacteria; CEPI, Coalition for Epidemic Preparedness Innovations; CIDRAP, Center for Infectious Disease Research and Policy; CIVICs, Collaborative Influenza Vaccine Innovation Centers; COBRA, computationally optimized broadly reactive antigen; CHIVIM, controlled human influenza virus infection model; EU, European Union; FVVA, full value of vaccine assessment; GISRS, Global Influenza Surveillance and Response System; HAI, hemagglutination-inhibition; HA, hemagglutinin; HVAC, heating, ventilation, and air conditioning; IIV, inactivated influenza vaccines; IVR, Influenza Vaccines Research and Development (R&D) Roadmap; LAIV, live-attenuated influenza vaccines; LMICs, low- and middle-income countries; ME&A, monitoring, evaluation, and adjustment; NA, neuraminidase; NIAID, US National Institute of Allergy and Infectious Diseases; R&D, Research and Development; SME, subject matter expert; WHO, World Health Organization.

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Seasonal influenza vaccines
Universal influenza vaccines
Broadly protective influenza vaccines
Roadmap

milestones, 37 of which have been designated high priority by the IVR expert taskforce. This report summarizes the major issues and priority areas of research outlined in the IVR. By identifying the key issues and steps to address them, the roadmap not only encourages research aimed at new solutions, but also provides guidance on the use of innovative tools to drive breakthroughs in influenza vaccine R&D.
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1. Introduction

Influenza virus vaccines are the cornerstone of public-health efforts to reduce the burden of seasonal influenza and to respond to the unpredictable emergence of pandemic influenza [1]. Current strategies for generating seasonal influenza vaccines and for influenza vaccine pandemic preparedness, however, are far from optimal. Seasonal influenza vaccines are strain-specific and not designed to provide broad protection against the continual evolution of influenza viruses. Vaccine-induced immunity is short-lived and researchers have yet to identify determinants of durable protective immunity (i.e., lasting 5–10 years). Production of current seasonal influenza vaccines requires up to 6 months and cannot begin until vaccine seed strains are selected for the upcoming season [2]. The lag time between annual vaccine strain selection and vaccine production leaves ample time for changes to occur in the circulation of different virus strains and lineages, which can lead to antigenic distinctions between the vaccine and circulating viruses. Yet even in years when the vaccine is antigenically well-matched with circulating strains, vaccine effectiveness can be suboptimal, partly because of egg-adapted mutations (for vaccines produced in eggs) or the influence of host factors (such as age) on the immune response [3,4]. Furthermore, the need for annual vaccinations is an important barrier to implementing influenza vaccination programs in many low- and middle-income countries (LMICs), leading to variable vaccine uptake around the globe [5] and vulnerabilities in global influenza pandemic preparedness [6]. Even incremental improvements in the efficacy of seasonal influenza vaccines could have a significant impact on the global annual burden of severe seasonal influenza disease (estimated at 3–5 million cases per year) and death (estimated at 290,000 to 650,000 deaths annually) [7]. While public health authorities advocate for annual influenza vaccination programs in all countries, governments faced with many urgent health issues and limited resources are unlikely to act without compelling health and economic data to support this as a priority.

Durable, universal vaccines that protect against all current and future strains of influenza and that are suitable for use in LMICs would be a game-changing public-health breakthrough [8]. Furthermore, this advancement would have a dramatic impact on the entire influenza vaccination enterprise by improving vaccine effectiveness, eliminating the need and cost for developing annual reformulations and annual vaccination campaigns, and simplifying the entire vaccine delivery system to allow broader global implementation and access.

In addition, the occurrence of a severe influenza pandemic remains widely recognized as a critical biological threat, even following the emergence of SARS-CoV-2. Our current strategy of waiting until the next pandemic is detected and then formulating a strain-specific vaccine, primarily using reliable but time-consuming egg-based production methods, is archaic. During the 2009–10 H1N1 pandemic, for example, vaccine arrived after the pandemic peak in many areas, limiting the utility of vaccines during the first year of the pandemic [9–12]. As the COVID-19 experience has shown, delays in vaccine availability during a severe pandemic can have dire consequences.

In recent years, researchers have worked toward improving seasonal influenza vaccines, accelerating development and production of those vaccines, and generating broadly protective and more durable vaccines. New programs have been initiated, such as the Collaborative Influenza Vaccine Innovation Centers (CIVICs) program funded by the US National Institute of Allergy and Infectious

Diseases [13], the European Union (EU)-India Joint Call [14], and the Bill & Melinda Gates Foundation Grand Challenge for Universal Influenza Vaccine Development [15]. In addition, in 2018, NIAID published its strategic plan for universal influenza vaccine development [16] and in 2019, the World Health Organization (WHO) launched the Global Influenza Strategy 2019–2030 calling for the development of better global tools, including improved, novel, and universal influenza vaccines, by 2030 to benefit all countries and instill public confidence and uptake [1]. Researchers are exploring innovative technologies, including new vaccine platforms (such as virus-like particles, nanoparticles, DNA-based, mRNA-based, recombinant proteins, and viral vectors) and novel constructs (such as chimeric hemagglutinin [HA] vaccines, "headless" HA vaccines, or computationally optimized broadly reactive antigen [COBRA] vaccines) to stimulate broadly neutralizing antibodies and cross-reactive T cell immune responses [17–22]. These innovations hold promise toward creating next-generation influenza vaccines and toward streamlining the development process to enhance timeliness and efficiency.

In response to the COVID-19 pandemic, several vaccines against SARS CoV-2 that use novel platforms have been developed and authorized for use. To date, these include mRNA vaccines and adenovirus-vectored vaccines. Other vaccines using additional platforms, such as nanoparticle technology to create subunit vaccines, are in advanced clinical development at the time of this report. This recent experience is providing valuable information about vaccine safety for novel platforms, use of adjuvants, regulatory pathway speed and flexibility, creative funding strategies (such as COVAX, which is the vaccine pillar of the WHO's Access to COVID-19 Tools [ACT] Accelerator), and the critical importance of equitable global vaccine allocation and distribution. Researchers are also exploring multivalent vaccines that combine antigens for SARS-CoV-2 and influenza [23,24] to achieve protection against both viruses as efficiently as possible. As we gain experience with these new approaches, the influenza vaccine research and development (R&D) landscape may change significantly in the near future.

While recent discoveries in immunology, structural biology, and vaccinology have moved influenza vaccine R&D forward, the goal of achieving universal or broadly protective influenza vaccines remains elusive. Immune responses to influenza virus infection and vaccination are highly complex and incompletely understood, and the scientific barriers to creating broadly protective and more durable vaccines are formidable. Furthermore, as noted by the Sabin-Aspen Science and Policy Group, key R&D efforts are constrained by fragmentation and a lack of goal-oriented coordination [25]. Overcoming these persistent issues will likely require innovative, mission-driven collaboration to garner financial investment from around the globe, and consensus-building among stakeholders regarding high-priority activities and strategies. To address these concerns, the Global Funders Consortium for Universal Influenza Vaccine Development [26] called for the development of a global influenza vaccines R&D roadmap. In 2019, the Wellcome Trust established funding to develop the roadmap and identified the Center for Infectious Disease Research and Policy (CIDRAP), University of Minnesota, to coordinate the effort.

2. Roadmap development process

The Influenza Vaccines R&D Roadmap (IVR) [27], is intended to provide a framework for prioritizing global R&D activities, with the goal of improving the production and effectiveness of strain-specific influenza vaccines and advancing the development, licensure, and manufacture of durable, broadly protective or universal influenza vaccines. The IVR lays out a 10-year timeline, with progress on the milestones to be tracked over time and adjustments made to the roadmap as necessary.

In developing the IVR, CIDRAP relied heavily on global stakeholder engagement, using several published methodologic models for guidance [28,29], and the WHO Generic Methodology for Developing and Implementing R&D Roadmaps for Priority Pathogens with Epidemic Potential (unpublished). CIDRAP formed a project steering group that included representatives from the Bill & Melinda Gates Foundation, the Global Funders Consortium for Universal Influenza Vaccine Development, the Sabin Vaccine Institute, the Wellcome Trust, and WHO. Steering group members met in February 2019 to identify experts for a global IVR taskforce and outline a framework for project development. The inital taskforce, which was comprised of experts from 12 countries, was formed in April 2019. The group met several times during the course of the project, provided technical expertise, reviewed roadmap drafts, and identified priority milestones. In fall 2020, CIDRAP convened four online consultations for invited international subject matter experts (SMEs) to review and discuss different sections of the IVR; SMEs represented different areas of expertise and sectors of the influenza research community, including industry and regulation. One hundred forty-seven SMEs, representing nearly 100 different organizations and 20 countries, participated in one or more of the sessions. The last phase of stakeholder engagement was a public comment period, which involved posting the draft IVR online during January and February 2021 and inviting comments, via email and social media, from a broad group of global stakeholders. We received 109 sets of comments from stakeholders in 26 countries; each comment was reviewed by CIDRAP staff and adjudicated as deemed appropriate.

3. Key issues for influenza vaccine R&D

The IVR is organized into six sections: virology, immunology, vaccinology for seasonal influenza vaccines, vaccinology for universal influenza vaccines, animal and human influenza virus infection models, and policy, finance, and regulation. Each section identifies barriers, gaps, strategic goals, milestones, and additional R&D priorities germane to that topic. The IVR includes 113 milestones across the six sections, with 37 identified as high priority (Table 1). The strategic goals are intended to be relatively general, whereas the milestones generally follow the SMART format (specific, measurable, achievable, realistic/relevant, and time-sensitive). The sections below summarize the major issues for each of the six sections, with a particular focus on areas considered high priority.

3.1. Virology

Global influenza virus surveillance tracks antigenic drift of influenza viruses, providing essential data for annual reformulation of seasonal influenza vaccines. The WHO Global Influenza Surveillance and Response System (GISRS), an international network of national influenza centers, WHO collaborating centers and essential regulatory laboratories, and other groups, is responsible for tracking influenza viruses around the globe [30]. The GISAID Initiative is another key organization that promotes the rapid sharing of virologic data to help researchers understand how influenza viruses evolve and spread during epidemics and pandemics [31]. Additional sequence data could also provide critical early information on an emerging pandemic virus. For example, the first SARS-CoV-2 genetic sequences were made available on GISAID's EpiCoV platform on January 10, 2020, which allowed manufacturers to begin the COVID-19 vaccine development process [32]. Although these activities provide an essential function,

Table 1
IVR High-Priority Milestones by Topic Area and Strategic Goal.

Strategic goal*	Milestone*
Virology	
• ***Strategic Goal 1.2:*** Enhance the ability to forecast viruses that are likely to circulate in the upcoming season to improve the antigenic match between circulating influenza viruses and viral strains selected for seasonal vaccine production.	• **Milestone 1.2.e**. By 2025, develop, standardize, and implement methods to improve antigenic characterization of H1N1 and H3N2 influenza viruses.
Immunology and Immune Correlates of Protection	
• ***Strategic Goal 2.2:*** Gain better understanding of human immunology to inform influenza vaccine development through basic research focused on the use of new tools and technologies.	• **Milestone 2.2.c.** By 2027, determine key mechanisms of long-term protection following influenza infection (i.e., immunity lasting at least several years), including the discovery of early biomarkers associated with durable immune responses, to inform the development of durable vaccine-induced protection.
• ***Strategic Goal 2.4:*** Determine the impact of prior influenza virus infection or vaccination on the future immune responses to influenza viruses or vaccines.	• **Milestone 2.4.b.** By 2026, determine through prospective birth-year cohort studies how repeated influenza vaccinations affect the immune response to subsequent influenza vaccinations. • **Milestone 2.4.c.** By 2028, determine how the initial encounter with an influenza virus (i.e., immune imprinting) affects B and T cell responses including immunologic responses to subsequent influenza virus infection or vaccination. • **Milestone 2.4.d.** By 2029, determine if vaccination with IIV vs. LAIV of very young children before their first encounter with influenza virus has a significant impact on future influenza vaccine responses.
• ***Strategic Goal 2.6:*** Improve understanding of the role of mucosal immunity in protecting against influenza.	• **Milestone 2.6.b.** By 2023, further determine the role of mucosal antibodies in protecting against influenza virus infection, disease, and transmission. • **Milestone 2.6.d.** By 2026, determine the role of mucosal T cells in protecting against influenza virus infection, disease, and transmission.
• ***Strategic Goal 2.7:*** Develop novel correlates of protection for assessing seasonal influenza vaccines and broadly protective or universal influenza vaccines, as part of clinical studies that demonstrate efficacy against a disease endpoint.	• **Milestone 2.7.a.** By 2025, develop functional assays to accurately capture the breadth and range of protective responses other than virus neutralization, such as influenza virus-specific ADCC, antibody-dependent cellular phagocytosis, and complement dependent cytotoxicity. • **Milestone 2.7.b.** By 2028, develop new measurement tools, including qualified correlates of protection, for mucosal immunity, particularly for assessing LAIVs or other mucosal vaccines if developed.
Vaccinology for Seasonal Influenza Vaccines	
• ***Strategic Goal 3.2:*** Identify strategies and policies to optimize seasonal influenza vaccines and improve vaccine effectiveness.	• **Milestone 3.2.b.** By 2022, convene a workshop to review the development of novel platforms (e.g., mRNA-based) for COVID-19 vaccines to identify how best to apply them to development of improved seasonal influenza vaccines. • **Milestone 3.2.e.** By 2024, determine optimum methods for assessing vaccine effectiveness of conventional egg-based and cell culture-based vaccines in comparison to vaccines created using new technologies, in coordination with regulatory agencies and using consistent endpoints, to allow data to be combined as appropriate over multiple seasons and to allow better comparability of data across studies. • **Milestone 3.2.h.** By 2028, evaluate the effectiveness of alternate routes of vaccine delivery (e.g., intranasal, oral, intradermal needle-free administration, and topical routes) in preclinical and clinical studies, to identify new mechanisms of immune protection, such as enhancement of mucosal immunity.
• ***Strategic Goal 3.4:*** Further assess the role of existing and new adjuvants in creating next-generation improved seasonal influenza vaccines, informed by recent R&D with adjuvants in new COVID-19 vaccines.	• **Milestone 3.4.b.** By 2026, determine, through clinical studies, if any promising new adjuvant candidates under investigation can substantially improve the immune response to influenza vaccines in the elderly and assess their safety profiles. • **Milestone 3.4.c.** By 2026, determine, through clinical studies, if any existing adjuvants substantially improve the immune response to influenza vaccines in the very young (e.g., as an initial vaccination followed by non-adjuvanted vaccines) and assess their safety profiles.
• ***Strategic Goal 3.5:*** Determine the role of NA as a vaccine antigen for improving vaccine effectiveness and immunogenicity of seasonal influenza vaccines.	• **Milestone 3.5.d.** By 2025, determine if the presence of NA improves seasonal influenza vaccines, and, if so, establish the optimal dose of NA that improves immunogenicity and effectiveness.
Vaccinology for Broadly Protective or Universal Influenza Vaccines	
• ***Strategic Goal 4.1:*** Identify the most promising broadly protective or universal influenza vaccine candidates that elicit durable protection against influenza viruses in preclinical studies, with a focus on targeting conserved regions of the virus.	• **Milestone 4.1.d.** By 2022, convene a workshop to review the development of novel platforms (e.g., mRNA-based) for COVID-19 vaccines to identify how best to apply them to broadly protective or universal influenza vaccines. (See similar milestone under Vaccinology for Seasonal Influenza Vaccines). • **Milestone 4.1.e.** By 2024, identify the most promising influenza vaccine candidates that elicit robust and broadly protective immunity.
• ***Strategic Goal 4.2:*** Evaluate the most promising broadly protective or universal influenza vaccine candidates, using at least several different platforms, in clinical trials, informed by recent experience with SARS-CoV-2 vaccine trials.	• **Milestone 4.2.e:** By 2023, develop consensus on streamlining clinical research for evaluating broadly protective influenza vaccines, drawing on COVID-19 vaccine experience. • **Milestone 4.2.f:** By 2024, identify several vaccine candidates that demonstrate broad—based immunity—humoral, cell—mediated, or both—in preclinical research and assess them for safety and immunogenicity in phase 1 clinical trials in healthy adults.

Table 1 (*continued*)

Strategic goal*	Milestone*
	• **Milestone 4.2.g:** By 2024, determine correlates of protection for assessing broadly protective or universal influenza vaccines that are appropriate for different stages of vaccine development. • **Milestone 4.2.h:** By 2025, identify the most promising vaccine candidates from phase 1 trials and advance them into phase 2 or directly to phase 3 clinical trials in at-risk populations. • **Milestone 4.2.i:** By 2027, identify the most promising vaccine candidates from phase 2 trials for general and pediatric populations that demonstrate broad protection and provide durable immunity (more than 1 year) and assess them for efficacy in phase 3 clinical trials.
Influenza Research in Animal Models and Human Viral Infection Models	
Strategic Goal 5.1: Optimize animal models for influenza vaccine research.	• **Milestone 5.1.b.** By 2022, ensure that validated reagents, updated viral stocks, and harmonized assays are available to improve understanding of the innate and adaptive immune responses in ferrets and to facilitate cross-comparison of different research studies across different laboratories. • **Milestone 5.1.e.** By 2023, convene a workshop on the development of pre-exposure animal models to address the fact that humans generally have pre-existing immunity to influenza. • **Milestone 5.1.f.** By 2025, complete and publish a comprehensive analysis of the predictive value of different animal models, including natural hosts such as pigs and horses, for influenza vaccine studies (both seasonal and broadly protective vaccines). • **Milestone 5.1.g.** By 2026, develop and validate novel animal models, as needed, for evaluating immune responses—including durability—to broadly protective influenza vaccines.
Strategic Goal 5.2: Address steps needed to further develop and refine the CHIVIM.	• **Milestone 5.2.a.** By 2022, determine the use cases for the CHIVIM and generate guidance, including ethical and safety considerations, for using the model. • **Milestone 5.2.b.** By 2023, ensure that reagents for the CHIVIM are broadly available. • **Milestone 5.2.c.** By 2023, ensure that a biorepository of diverse, accessible, and well-characterized challenge stocks is generated and made available to investigators. • **Milestone 5.2.d.** By 2024, further develop the CHIVIM to ensure that it can be widely operationalized by different investigators.
Policy, Finance, and Regulation	
• ***Strategic Goal 6.1:*** Catalyze broad support and sustained funding for developing improved seasonal influenza vaccines and broadly protective or universal influenza vaccines.	• **Milestone 6.1.a**. By 2022, develop and disseminate a full value of vaccine assessment (FVVA) for improved seasonal and broadly protective, universal influenza vaccines that addresses different vaccine use cases and includes an assessment for LMICs. • **Milestone 6.1.b.** By 2022, develop targeted and creative communications and advocacy strategies and necessary communications tools that build on the FVVA and provide information on economic costs, the risks of future influenza pandemics, and the need for investment in influenza vaccine R&D.
• ***Strategic Goal 6.2:*** Promote innovation for developing improved seasonal influenza vaccines and broadly protective or universal influenza vaccines.	• **Milestone 6.2.a.** By 2022, distill lessons learned from experience with COVID-19 vaccine R&D, including clinical research and study designs, manufacturing, distribution, advocacy, financing, and global collaboration. **Milestone 6.2.b.** By 2023, identify a set of strategies for accelerating the development of universal influenza vaccines through innovative approaches.
• ***Strategic Goal 6.3:*** Promote information sharing aimed at moving influenza vaccine development forward.	• **Milestone 6.3.c:** By 2022, assess the impact of the Nagoya protocol, and possibly related national ABS legislation, on sharing of influenza isolates and gene sequences in relation to influenza vaccine R&D and determine strategies to address potential unintended consequences.
• ***Strategic Goal 6.4:*** Further explore regulatory challenges associated with development and manufacturing of improved seasonal and broadly protective or universal influenza vaccines.	• **Milestone 6.4.a:** By 2022, conduct a workshop that includes regulators and vaccine manufacturers to: (1) clarify regulatory processes related to the development and evaluation of broadly protective or universal influenza vaccines, (2) develop a regulatory science agenda that anticipates the challenges of evaluating and licensing these new vaccines, (3) review the regulatory experience with COVID-19 vaccines and identify ways to streamline the process for new influenza vaccines, and (4) generate additional recommendations regarding how best to provide guidance on vaccine development, manufacture, approval, and delivery. • **Milestone 6.4.b.** By 2023, identify a framework to address post-marketing assessment of safety and effectiveness of new broadly protective or universal influenza vaccines.

Abbreviations: ABS, Access and Benefit Sharing; ADCC, antibody-dependent cellular cytotoxicity; CHIVIM, controlled human influenza virus infection model; FVVA, full value of vaccine assessment; IIV, inactivated influenza vaccines; LAIV, live-attenuated influenza vaccines; NA, neuraminidase; R&D, research and development; SARS-CoV-2; severe acute respiratory syndrome coronavirus 2.

*The milestones identified above reflect only those that were deemed to be of high priority. They are organized by the order in which they appear in the Influenza Vaccines R&D Roadmap and reflect the numbering scheme of the roadmap. To see all goals and milestones, please refer to the complete roadmap.

surveillance is not uniformly distributed globally and there are populations for which surveillance data are limited [33]. To enhance understanding of influenza virus evolution and to improve capabilities to predict changes over time (and thereby create improved seasonal influenza vaccines), greater geographic diversity of influenza virus sequence data and increased metadata collection are needed. Efforts to increase global capacity for SARS-CoV-2 surveillance align with and support this need. Additionally, new tools (such as computational approaches and systems biology) could be more broadly applied to facilitate understanding of influenza virus evolution—particularly the emergence of novel influenza viruses with pandemic potential [16,34]. In part because of continuous viral evolution, antigenic mismatches between vaccine strains and circulating influenza strains occur, particularly for the H3N2 subtype; therefore, continuing efforts are needed to improve methods for antigenic characterization of H3N2 viruses, despite recent progress in this area [35].

To address these considerations, the IVR virology section highlights the following key activities relevant to influenza vaccine R&D: (1) improving understanding of human and animal influenza virus evolution, particularly using functional assays to identify relevant epitopes, with the goal of enabling predictions of phenotypes from genotypes [36,37]; (2) enhancing the ability to forecast the range of viruses likely to circulate in the upcoming season to improve the antigenic match between circulating influenza viruses and viral strains selected for vaccine production; (3) developing, standardizing, and implementing methods to improve antigenic characterization of influenza A H1N1 and H3N2 viruses [38–40]; and (4) improving the ability to detect and understand the emergence of novel influenza viruses with pandemic potential.

3.2. Immunology

The current lack of a comprehensive understanding of human immunology and interactions among the many components of the immune system limits the pace and direction of influenza vaccine R&D [41]; innovative new strategies needed for improved influenza vaccines may result from discoveries not yet identified in existing research. Furthermore, many critical issues remain unresolved. For example, differences between immune responses to influenza virus infection versus influenza vaccination are inadequately understood and require further research [42]. Second, more information is needed on the immune factors required for inducing broad protection against influenza viruses [16,43,44] and the mechanisms that induce durable immunity, such as activation of long-lived plasma cells in the bone marrow [45]. This involves improving scientific understanding of both the humoral and cell-meditated immune responses to influenza virus infection and vaccination, particularly regarding immunodominance hierarchies of the antibody response and how immunodominance can be overcome [4,46–48]. Third, the role of mucosal immunity is a critical research topic for influenza vaccine development, including determining the potential magnitude of mucosal immunity elicited by influenza virus infection or vaccines and understanding the drivers of myeloid and lymphoid cell differentiation and migration to protect upper and lower respiratory airways [45,49,50]. Fourth, the role of immune imprinting from early childhood exposure on influencing subsequent immune responses to influenza virus infection or vaccination requires further understanding [51–53]. A related issue is the need to clarify the roles that repeated influenza virus infection and/or annual seasonal vaccination play in determining the immune response to subsequent vaccinations [54–57]. Finally, efforts are needed to further clarify the role of the T-cell response in protecting against severe influenza disease [58], since protection against severe disease is of particular importance for vaccines formulated for use in LMICs.

To date, the most commonly used marker for immune response to influenza virus infection or vaccination is the serum hemagglutination-inhibition (HAI) antibody titer; however, HAI titers have limitations in predicting vaccine effectiveness, particularly for older adults, and do not provide a comprehensive assessment of immunity [59,60]. Additional correlates of protection, potentially involving multiple correlates or complex correlates, are needed to evaluate immune responses from universal or broadly protective influenza vaccine candidates [61–63]. A correlate of protection is also needed for assessing mucosal immunity (e.g., through measurement of mucosal antibodies). Additionally, reagents, and standardized, harmonized assays are needed to evaluate non-HA head immune responses [59,64] and to assess and quantify T-cell immune responses [65,66]. Systems biology has the potential to identify molecular predictors or correlates of protection and may be able to provide insights into some of the key immunologic questions.

To address these issues, the IVR immunology section focuses on: (1) ensuring availability of critical tools for immunologic research involving next-generation influenza vaccines; (2) conducting basic research aimed at achieving a more comprehensive understanding of human immunology to inform influenza vaccine development, including the use of new tools, such as systems biology; (3) determining key mechanisms of long-term protection (i.e., lasting at least several years), including clarifying the roles of CD4 and CD8 T cells and antibodies to various epitopes (e.g., HA, NA [neuraminidase], M2e, and epitopes in conserved internal proteins) [64]; (4) determining the impact of prior influenza virus infection or vaccination on future immune responses to influenza viruses or vaccines [53,67–69]; (5) improving understanding of the B-cell immune responses to influenza that are important for development of broadly protective immunity, particularly in the context of partial pre-existing immunity from continual exposure to influenza viruses; (6) clarifying the role of T cells in generating or supporting protective immunity to influenza virus infection and vaccination (including prevention of severe disease); (7) determining the critical role of mucosal immune responses in protecting against influenza virus infection, disease, and transmission; and (8) developing novel correlates of protection for assessing next-generation influenza vaccines, as part of randomized controlled clinical trials that evaluate vaccine efficacy.

3.3. Vaccinology for seasonal influenza vaccines

Critical limitations with seasonal influenza vaccines are suboptimal vaccine effectiveness (particularly in the elderly), variable effectiveness from year to year, and long production times. From 2004 to 2018 in the United States, average annual estimates of influenza vaccine effectiveness against medically attended illness ranged from 10% to 60% [70]. Also, during the 2016–17 influenza season, the overall vaccine effectiveness at six international sites in Canada, Mexico, Russia, Spain, and Turkey was estimated at 27% [71]. Even a 10% to 15% improvement in vaccine effectiveness for seasonal vaccines could have an important impact on the global annual health burden of influenza as evidenced by a recent study in the United States [72]. Potential strategies to incrementally improve vaccine effectiveness of current seasonal influenza vaccines include evaluating alternative platforms to deliver HA antigens (e.g., mRNA-based vaccines) or combinations of licensed products (potentially as part of prime-boost regimens), adjusting HA antigen doses for different populations and age groups, expanding the use of adjuvants, and determining the role of NA as a vaccine antigen [17,73–76]. The development of alternative approaches to vaccine delivery (such as microarray patches or other needle-free injection systems) may also lead to significant advantages to enhance seasonal vaccination programs in LMICs and pandemic-response

capabilities. Second, current production methods lead to a long lag time (i.e., 5–6 months) for annual seasonal influenza vaccine development. New platforms, such as those applied to COVID-19 vaccines, could reduce the production time significantly. Third, seasonal influenza vaccines need to be more suitable for use in LMICs by offering better protection against severe disease and providing more durable protection to avoid the need for annual reformulations and vaccinations [8].

With regard to optimizing seasonal influenza vaccine effectiveness, key strategic goals outlined in the IVR include: (1) promoting strategies that shorten the lag time from identification of candidate vaccine viruses through the vaccine development and distribution process, such as exploring use of new platforms (e.g., mRNA-based); (2) determining strategies and policies to optimize vaccine effectiveness, including identifying key lessons learned from the COVID-19 pandemic; (3) improving the ability to assess the impact of seasonal influenza vaccines on preventing severe disease (particularly for use in LMICs) and to support development of influenza vaccines that protect against severe disease; (4) further assessing the role of existing and new adjuvants for improving vaccine effectiveness [76,77] and possibly offering cross-protection [78]; and (5) clarifying the role of NA in improving vaccine effectiveness.

3.4. Vaccinology for universal influenza vaccines

The definitions for universal or broadly protective influenza vaccines have not been standardized and several have been proposed (Table 2) [15,22,25,26,75,79]. Most have suggested that a truly universal vaccine should provide long-term (several years to life-long) protection against all drifted and shifted influenza A and B strains (including pandemic strains and zoonotic strains). The US NIAID strategic plan for guiding research toward improved influenza vaccines identified the goals for universal influenza vaccines as: (1) at least 75% effective against symptomatic influenza virus infection, (2) protective against phylogenetic groups 1 and 2 influenza A viruses, (3) capable of providing durable protection for at least 1 year, and (4) suitable for all age groups [16]. For the purposes of the IVR, a universal influenza vaccine "is one that offers protection against all influenza A and B viruses, including seasonal viruses and existing or emerging zoonotic viruses with pandemic potential." A broadly protective influenza vaccine "offers protection against multiple influenza viruses (i.e., is not strain-specific) but does not meet the criteria for a universal vaccine. For example, a broadly protective vaccine could confer protection against all strains within a single HA subtype (subtype-specific), multiple HA subtypes within a single group (multi-subtype), all group 1 or group 2 influenza A viruses (pan-group), or all influenza B viruses."

To generate universal or broadly protective influenza vaccines, new approaches are needed for immunogen design to achieve robust immune responses to conserved regions of the influenza virus [79–81]. This may require identifying successful strategies for overcoming immunodominance of the HA globular head domain [82,83]. Universal influenza vaccine constructs may also need to include multiple antigenic targets to provide broadly protective and durable immunity against a wide range of influenza viruses [84], particularly including conserved antigens targeted by T cells, given that broad T-cell responses appear to be associated with asymptomatic or mild disease [85].

While many promising vaccine candidates for broadly protective or universal influenza vaccines are under study, clinical development requires overcoming a variety of significant logistical challenges, such as conducting clinical trials over multiple seasons with different circulating viruses and demonstrating immunogenicity without well-established correlates of protection [19,22]. Furthermore, resources for conducting large efficacy trials are limited, necessitating the selection of the most promising candidates for advancement through clinical trials [50,63]. The strategic goals

Table 2
Universal Influenza Vaccines: Definitions and Key Features.

Source	Definitions	Target viruses	Duration of protection	Target population
Bill & Melinda Gates Foundation Grand Challenges Initiative [15]	• *Universal influenza vaccines*: "protection from morbidity and mortality caused by all subtypes of circulating and emerging (drifted and shifted) influenza A subtype viruses and influenza B lineage viruses for at least 3–5 years."	All influenza A viruses and influenza B viruses	Minimum of 3–5 years	All age groups, especially in developing countries
European Commission European Union–India Collaboration for Next Generation Influenza Vaccines [14]	• *Next-generation influenza vaccines*: improved efficacy and safety; improved duration of immunity; reactivity against an increased breadth of influenza strains and/or from the outset of a large-scale influenza pandemic; suitable for different populations and LMICs.	Increased breadth of influenza strains	Improved duration of immunity	Different populations and LMICs
Global Funders Consortium for Universal Influenza Vaccine Development [26]	• *Universal influenza vaccine*: high efficacy; induces immunity to a broad array of influenza A viruses (and perhaps influenza B viruses); prevents severe disease; confers more durable immunity than current vaccines; prevents seasonal and pandemic influenza; cost-effective for low- and high-resource settings.	Influenza A viruses and perhaps influenza B viruses	More durable than current influenza vaccines	All
National Institute of Allergy & Infectious Diseases A Universal Influenza Vaccine: The Strategic Plan for the NIAID [16]	• *Universal influenza vaccine*: goal of at least 75% effectiveness against symptomatic influenza virus infection; protects against Groups 1 and Group 2 influenza A viruses (secondary target, influenza B viruses); durable protection for at least 1 year and preferably through multiple seasons; suitable for all age groups.	Group 1 and Group 2 influenza A viruses	Durable protection for at least 1 year	All age groups
Sabin-Aspen Vaccine Science & Policy Group Accelerating the Development of Universal Influenza Vaccine [25]	• *Universal influenza vaccine*: safe and highly effective in all age groups, against any strain; confers lifelong immunity.	All influenza viruses	Lifelong	All age groups
World Health Organization Preferred Product Characteristics for Next-Generation Influenza Vaccines [8]	• *Universal-type influenza A vaccines:* protection against severe influenza A virus illness for at least 5 years; suitable for high-risk groups in LMICs.	Influenza A viruses	At least 5 years	High-risk groups in LMICs

Abbreviations: LMICs, low- and middle-income countries; NIAID, US National Institute of Allergy and Infectious Diseases.

and milestones in the universal vaccines section of the IVR, therefore, focus on identifying the most promising broadly protective or universal influenza vaccine candidates that elicit durable protection against influenza viruses in preclinical studies [80,81,86] and evaluating those candidates in phase 1 through phase 3 clinical trials, with a particular focus on determination of efficacy rather than just immunogenicity. Recent experience with COVID-19 vaccines suggests that the clinical trial process could be streamlined to move more quickly to phase 2/3 clinical trials or to run clinical trials in parallel once vaccine safety is established.

3.5. Animal and human influenza virus infection models

Experimental animal models provide an important research tool for evaluating influenza virus transmission, pathogenesis, and immune responses to vaccination. Currently, a number of animal models exist for studying influenza (e.g., mice, ferrets, guinea pigs, swine, horses, and nonhuman primates [NHPs]). While these models provide valuable information, an ideal animal model for influenza has not yet been identified and further efforts are needed to bridge the gap between animal studies and human outcomes. For example, influenza disease in certain animal models does not accurately mimic disease in humans and the complex exposure history to influenza virus in humans is difficult to recreate in animal models [87–90]. Key activities in the IVR for optimizing animal models include: (1) ensuring that validated reagents, harmonized assays, and updated viral stocks are available for use in key models such as ferrets; (2) clarifying issues around development of pre-exposure animal models [88]; (3) publishing a comprehensive analysis of the predictive value of different animal models for influenza vaccine studies; and (4) developing and validating novel animal models, as needed, for evaluating immune responses and durability to broadly protective influenza vaccines [88].

The controlled human influenza virus infection model (CHIVIM) could be used to surmount certain important clinical research hurdles in developing broadly protective or universal influenza vaccines. Although much progress has been made recently in moving the CHIVIM forward [91,92], important issues remain, such as lack of standardization for certain key elements of the model, limited access to challenge viruses, lack of harmonized protocols, the need for better definition of endpoints (particularly for determining mucosal immunity), the need for agreed-upon criteria for selection of challenge strains, regulatory challenges, and environmental considerations (such as heating, ventilation, and air conditioning [HVAC] systems) [91]. Key issues in the IVR for advancing the CHIVIM include: (1) determining the use cases for the CHIVIM and generating guidance (to include ethical and safety considerations) for using the model; (2) ensuring that reagents for using the CHIVIM are broadly available to investigators; (3) ensuring that a biorepository of diverse, accessible, and well-characterized challenge stocks is generated and made available to investigators; and (4) further developing the CHIVIM to ensure that it can be widely operationalized by different investigators around the globe. Two human infection studies for COVID-19 have recently been launched in the United Kingdom [93,94]; these efforts may yield important information applicable to the CHIVIM.

3.6. Policy, financing, and regulation

The majority of the estimated 1.48 billion doses of seasonal influenza vaccine produced each year are manufactured using relatively time-consuming but reliable conventional egg-based production methods [95]. The size and scope of this existing global market for influenza vaccines is a barrier to investment in new, durable, and broadly protective influenza vaccines, since the companies that profit from this commercial model may be resistant to change. Furthermore, bringing new vaccines to market requires overcoming significant financial hurdles. For example, a new product must cross the "valley of death" during the development process. This period encompasses early clinical trials through phase 3 trials to the point of regulatory approval and early commercialization. During this time, substantial costs are incurred while outcomes are uncertain and no revenue is generated [96]. A root cause of the "valley of death" for new vaccines is that an asymmetry of risk exists, where manufacturers take on much of the risk and the public sector is not balancing that risk with sufficient commitments and funding. Additional creative mechanisms (such as push/pull incentives and non-dilutive funding [i.e., funding that does not drain company equity]) are needed to further de-risk influenza vaccine R&D [97,98].

Currently, a coordinated commitment to sustained funding for developing next-generation or universal vaccines is lacking. Efforts are needed to catalyze broad support and funding for developing next-generation seasonal influenza vaccines and broadly protective or universal influenza vaccines. The IVR calls for development of a full value of vaccine assessment (FVVA) [99] for improved influenza vaccines that addresses different vaccine use cases for preventing seasonal and pandemic influenza and includes an assessment for LMICs. The IVR also advocates for targeted and creative communications and advocacy strategies that build on the FVVA. These need to be explicitly designed to highlight the impact of influenza, the urgency of the global need for a universal influenza vaccine, and the social and economic costs of not developing improved vaccines for seasonal and pandemic influenza. These tools should be aimed at informing policy makers, funders, researchers, healthcare providers, and the general public about influenza-related health and economic costs, the risk of future influenza pandemics, and the need for investment in influenza vaccine R&D [25,100]. One priority milestone in the IVR is to distill the lessons learned from recent experience with COVID-19 vaccine R&D to inform future work on influenza vaccines and to address a number of these considerations.

The IVR also calls for efforts to explore the feasibility of creating a new public-private enterprise with robust funding, aimed at mission-driven R&D for universal influenza vaccines, similar to the biopharmaceutical accelerator for combating antibiotic resistant bacteria (known as CARB-X), which was established in July 2016 [101]. Another approach is to align the work of the IVR with that of the Coalition for Epidemic Preparedness Innovations (CEPI) [102]. CEPI will continue to focus on pandemic and epidemic preparedness in the future, with an emphasis on global equitable access for medical countermeasures; implementation of the IVR could potentially be folded into that work. As we emerge from the COVID-19 pandemic, there will likely be an evolving global ecosystem of vaccine R&D with new organizational coalitions forming that could also be engaged in moving the IVR milestones forward.

Another key issue is the need for improved data sharing around the globe. While GISRS and GISAID have successfully fostered international sharing of influenza virus isolates and gene sequences for years, certain provisions of the Nagoya Protocol [103] may restrict utilization of influenza viruses. Additionally, mechanisms to improve data management and sharing among academic, industry, and government developers are needed. Also, challenges with mapping (and potentially sharing) of intellectual property and proprietary technologies continue to be barriers to influenza vaccines R&D. Finally, improved innovation and coordination are needed to maximize the value of research on influenza vaccines, such as exploring options for reuse of influenza vaccine study data.

Clarity regarding regulatory requirements, potentially including the use of innovative approval pathways, will be needed for licensing broadly protective or universal influenza vaccines. Alternative

pathways will likely require the development of additional tools, such as new potency assays and new correlates of protection or immune markers likely to predict protection. Different vaccine goals (such as short- vs. long-term protection or protection against severe vs. mild disease) may require different clinical trial designs, which pose challenges for clinical evaluation. Key activities in the IVR related to regulatory science include: (1) clarifying regulatory processes for developing and evaluating broadly protective or universal influenza vaccines, (2) developing a regulatory science agenda that anticipates the challenges of evaluating and licensing new broadly protective or universal influenza vaccines and incorporates lessons learned from recent experience with COVID-19 vaccines, (3) promoting international regulatory harmonization, and (4) developing a framework to improve post-marketing assessment of safety and effectiveness of new broadly protective or universal influenza vaccines.

4. Roadmap implementation and monitoring

In late July 2021, the IVR expert taskforce met virtually to begin considering active strategies for implementing the IVR. This meeting focused on developing ongoing structures and mechanisms to: (1) promote ownership and "buy in" of the IVR by key R&D partners, (2) enhance coordination of activities across the influenza vaccine R&D ecosystem, (3) monitor and assess roadmap progress over time, and (4) identify gaps in progress and create strategies to address them. A website is being established at CIDRAP for monitoring, evaluation, and adjustment (ME&A) related to the IVR over time; current and future versions of the IVR can be accessed through this site [27]. The site will also contain a brief executive summary and other communications tools to increase accessibility of the roadmap. During the implementation meeting, taskforce members discussed the most critical and immediate needs for influenza vaccine R&D, using the high-priority milestones as a starting point; during this discussion the taskforce developed consensus on several issues. First, for immunology, the taskforce agreed that a critical need is to determine the key mechanisms of long-term protection following influenza infection to inform the development of durable influenza vaccines. Second, for vaccinology, the taskforce agreed that an immediate need is to review the novel platforms (e.g., mRNA-based) for COVID-19 vaccines to determine how best to apply them to developing improved seasonal vaccines and to enhance pandemic preparedness. A third critical need, also under vaccinology, is to draw on the COVID-19 vaccine experience to streamline clinical research for evaluating broadly protective or universal influenza vaccines. A fourth critical need is to clarify regulatory processes for developing broadly protective or universal influenza vaccines, including developing a regulatory science agenda that anticipates and addresses challenges in evaluating and licensing new products. Part of this process will be to provide guidance to industry on vaccine development, manufacture, approval, and delivery.

5. Conclusion

The COVID-19 experience has clearly illustrated the global impact of a severe pandemic respiratory virus and demonstrates the value of rapid vaccine development and delivery in preventing the potentially devastating health, social, and economic effects. A preparedness mindset—in advance of a pandemic—could prevent the catastrophic consequences that the global community has endured since early 2020 and that will continue to impact global health, social, and economic systems for years to come [104,105]. Furthermore, efforts to improve seasonal influenza vaccines and to generate universal or broadly protective vaccines go hand-in-hand. For example, improving seasonal influenza vaccines will enhance their usefulness in LMICs, leading to expansion of country-based influenza vaccination programs, which will reduce the burden of season influenza and also provide critical infrastructure for global pandemic preparedness. Development of universal vaccines will dramatically enhance pandemic preparedness by ensuring that vaccines are available at the onset of the next pandemic. Achieving the high-priority milestones identified in the IVR, however, will require enhanced coordination and potentially new public-private partnerships, including increased investment by industry and sustained funding from government agencies and philanthropic organizations.

By defining the specific barriers and gaps, the roadmap invites not only current influenza investigators to generate new solutions, but also provides initial direction for transdisciplinary innovators to apply emerging tools that can drive breakthroughs in influenza vaccine R&D. The IVR can also serve as an important catalyst for generating and focusing the resources necessary to make improved seasonal influenza vaccines and broadly protective or universal influenza vaccines a reality before the next pandemic strikes.

CRediT authorship contribution statement

Kristine A. Moore: Conceptualization, Writing – original draft, Writing - review & editing. **Julia T. Ostrowsky:** Conceptualization, Writing – original draft. **Alison M. Kraigsley:** Conceptualization, Writing - review & editing. **Angela J. Mehr:** Conceptualization, Writing - review & editing. **Joseph S. Bresee:** Conceptualization, Writing - review & editing. **Martin H. Friede:** Conceptualization, Writing - review & editing. **Bruce G. Gellin:** Conceptualization, Writing - review & editing. **Josephine P. Golding:** Conceptualization, Writing - review & editing. **Peter J. Hart:** Conceptualization, Writing - review & editing. **Ann Moen:** Conceptualization, Writing - review & editing. **Charlotte L. Weller:** Conceptualization, Writing - review & editing. **Michael T. Osterholm:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Kristine Moore, Julia Ostrowsky, Angela Mehr, Michael Osterholm report financial support was provided by Wellcome Trust. Kristine Moore, Michael Osterholm report a relationship with Wellcome Trust that includes: funding grants.

Coauthor received grants to the organization from Sanofi Pasteur, received grants from US CDC, PATH, Wellcome Trust, South African MRC. (CC)

Coauthor is a former Director of one of the WHO International Reference Centres for influenza and was part of the biannual strain selection group. His family superannuation fund holds some shares in companies which produce vaccines, including Influenza vaccine (Pfizer, Merck and CSL) and specific antiviral agents (Vaxart). (IG)

Coauthor is an independent Director of two organisations that support vaccine development, the Coalition for Epidemic Preparedness Innovations and MSD Wellcome Trust Hilleman Laboratories Pvt; Ltd. Neither is working on influenza vaccines. (GK)

Coauthor has the following declarations: The Icahn School of Medicine at Mount Sinai has filed patent applications relating to universal influenza virus vaccines, SARS-CoV-2 serological assays and NDV-based SARS-CoV-2 vaccines which name me as inventor. I would also like to note the following, which could be perceived as a conflict of interest: I have previously published work on influenza virus vaccines with S. Gilbert (University of Oxford); have consulted for Curevac, Merck and Pfizer (before 2020); I am currently

consulting for Pfizer, Seqirus and Avimex; my laboratory is collaborating with Pfizer on animal models of SARS-CoV-2 and with Dynavax on influenza virus vaccines; my laboratory is collaborating with N. Pardi at the University of Pennsylvania on mRNA vaccines against SARS-CoV-2 and my laboratory was working in the past with GlaxoSmithKline on the development of influenza virus vaccines and two of my mentees have recently joined Moderna. (FK)].

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