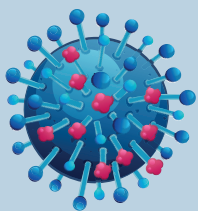


# **Influenza Vaccines**

**R&D**



# **Roadmap**

CIDRAP, IVR Steering Group, IVR Taskforce. Influenza Vaccines R&D Roadmap (IVR). Center for Infectious Disease Research and Policy (CIDRAP), University of Minnesota. September 2021

## Acknowledgments

Stakeholder input has been a critical aspect of the roadmap development process. The IVR steering group, therefore, would like to acknowledge the invaluable input from IVR taskforce members and other subject-matter experts from around the globe who participated in consultation meetings or provided comments on drafts of this document.

# Table of Contents

Preamble	5
Introduction	8
Topic 1: Virology Applicable to Vaccine Development	13
Topic 2: Immunology and Immune Correlates of Protection	20
Topic 3: Vaccinology for Seasonal Influenza Vaccines	30
Topic 4: Vaccinology for Broadly Protective or Universal Influenza Vaccines	38
Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model	43
Topic 6: Policy, Financing, and Regulation	49
References	57
Acronyms	66
Appendix 1	67
Influenza Vaccines R&D Roadmap: Steering Group	67
Influenza Vaccines R&D Roadmap: CIDRAP Core Project Staff	67
Influenza Vaccines R&D Roadmap: Taskforce Members	68
Appendix 2	69
Definitions and Key Features of Universal Influenza Vaccines	69
Appendix 3	71
Summary of Influenza Vaccines R&D Roadmap High-Priority Milestones	71



# Preamble

The COVID-19 pandemic has dramatically illustrated the catastrophic health, social, and economic consequences that a severe pandemic can generate in the 21st century. It also has demonstrated how rapidly viral respiratory pathogens can traverse the planet, leaving little opportunity for just-in-time preparedness. Influenza viruses periodically cause severe pandemics through antigenic shift and generation of novel reassortant viruses, and we don't know when the next one will occur or how severe it will be. While public health officials and others have created a strong foundation for pandemic preparedness, additional efforts are still required.

## Current Influenza Vaccines are Suboptimal

Vaccines are essential for protecting populations from seasonal and pandemic influenza, yet our current influenza vaccines and vaccination programs fall short. First, antigenic mismatches can occur between circulating viruses and viruses used for generating strain-specific vaccines, and the vaccines need to be reformulated and readministered annually. Second, even in years with good antigenic matches, vaccine effectiveness is often suboptimal, particularly in the elderly. Third, researchers have yet to unlock the keys to developing influenza vaccines that generate durable immunity—for example, lasting 5 to 10 years. Fourth, researchers also have yet to develop broadly protective vaccines that can protect against multiple strains of influenza, including novel pandemic viruses. Finally, although seasonal influenza vaccines are widely available, many countries—particularly low- and middle-income countries (LMICs)—do not have robust seasonal influenza vaccination programs in place, and vaccine

uptake varies across nations and populations. Universal and durable vaccines that protect against all current and future strains of influenza would be a tremendous breakthrough by ensuring that vaccines are readily available in sufficient quantities at the onset of future influenza pandemics.

## The Influenza Vaccines R&D Roadmap

The Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, with support from the Wellcome Trust, has created this globally oriented influenza vaccines research and development (R&D) roadmap (IVR). The IVR is intended to serve as a strategic planning tool to facilitate R&D, coordinate funding, and promote stakeholder engagement in R&D aimed at improving seasonal influenza vaccines and generating new broadly protective or universal influenza vaccines. The impetus for this project came from priorities

### Roadmap Vision

To accelerate the development of improved seasonal influenza vaccines and durable, broadly protective influenza vaccines that can reduce illness and death from influenza globally and mitigate the impact of future influenza pandemics.



published in 2019 by the Global Funders Consortium for Universal Influenza Vaccine Development (Bresee 2019). Key components of the IVR include determining critical issues and challenges for improving vaccines, prioritizing research activities, and identifying a set of realistic goals and aligned milestones in key topic areas. The IVR takes into account the potential for different needs regarding influenza vaccine characteristics in different populations, economies, and geographic regions. Primary audiences include scientific and clinical researchers, funders, public health policymakers, industry scientists and business leaders, regulators, and communications/advocacy specialists. Additional audiences may extend to a wider group of global health leaders, policymakers, and government officials.

The IVR development process has engaged a wide range of stakeholders across scientific disciplines, public and private sectors, and international communities to build consensus on R&D priorities and identify strategies for addressing them. The process has included identifying and reviewing other relevant strategic plans from high-level organizations such as the World Health Organization (WHO) and government entities, discussing scientific challenges and knowledge gaps with a range of subject-matter experts (SMEs), and conducting in-depth reviews of draft roadmap documents (including a public comment period for written feedback). After publication and launch of the roadmap, efforts will focus on dissemination (through targeted communication strategies), implementation, and monitoring, evaluation, and adjustment (ME&A) over time.

## Roadmap Purpose

To provide a 10-year framework that prioritizes research and development (R&D) activities for: (1) improving the production and effectiveness of strain-specific seasonal influenza vaccines and (2) advancing the development, licensure, and manufacture of durable, broadly protective or universal influenza vaccines.

The roadmap is aimed at accelerating progress in influenza vaccine research and stimulating overall investment in influenza vaccine R&D, balancing incremental improvements in conventional seasonal influenza vaccines with transformational changes in technology leading to universal influenza vaccines.

The roadmap highlights key research barriers and gaps, identifies strategic goals and milestones, and encourages synergistic R&D activities to guide advancement in the complex field of influenza vaccines R&D and stimulate overall investment in influenza vaccine development.

The roadmap will also provide a mechanism for benchmarking and tracking progress in influenza vaccines R&D over time. It is intended to be a living document that will be revised and updated as new information becomes available, including lessons learned from COVID-19 vaccine development and use.

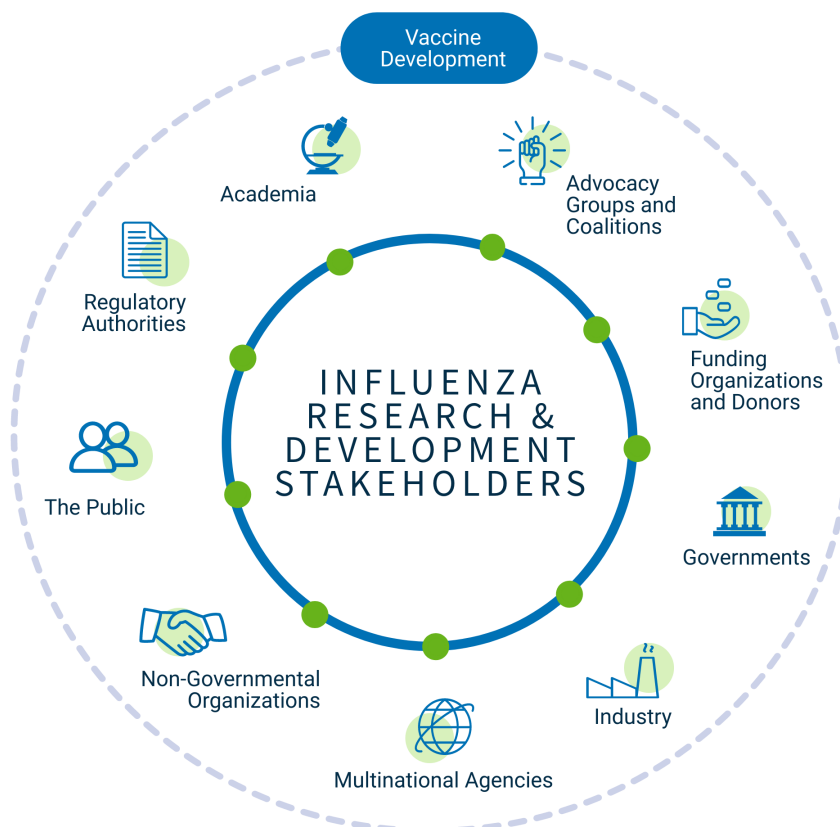


Advising CIDRAP's core team throughout the project is a small steering group of senior leaders from the WHO, the Wellcome Trust, the Sabin Vaccine Institute, the Bill & Melinda Gates Foundation, and the Task Force for Global Health. In early 2019, the steering group advised CIDRAP on the establishment of a global IVR development taskforce of SMEs, who offer a wide range of knowledge and experience in influenza vaccines R&D. (See [Appendix 1](#) for a list of steering group and taskforce members involved during the IVR development phase.)

In September and October 2020, CIDRAP held a series of online meetings to engage a larger group of SMEs, including experts from academia, industry, government, and nongovernmental organizations, to discuss the IVR initiative and provide additional feedback on the draft roadmap. In January and February 2021, CIDRAP posted the revised roadmap online for public comment, receiving critical feedback from over 100 individuals in 26 countries representing 88 different organizations in academia,

government, industry, and nongovernmental organizations. The roadmap was revised further to incorporate feedback from the public comment period.

Implementation of the roadmap will require working closely with partner organizations to determine how the IVR strategic goals and milestones can be achieved. Key steps will include identifying funding sources, establishing ownership for certain activities in the roadmap, and obtaining commitments from organizations to move roadmap activities forward. The IVR will be updated periodically as new information becomes available, goals and milestones are achieved, and new challenges occur. The IVR taskforce will play a key role in guiding implementation of the IVR and determining the need for additional project-management tools, potentially to include detailed implementation plans, an online dashboard of progress, tracking of influenza vaccine R&D funding, and updated summaries of influenza vaccine R&D priorities over time.





# Introduction

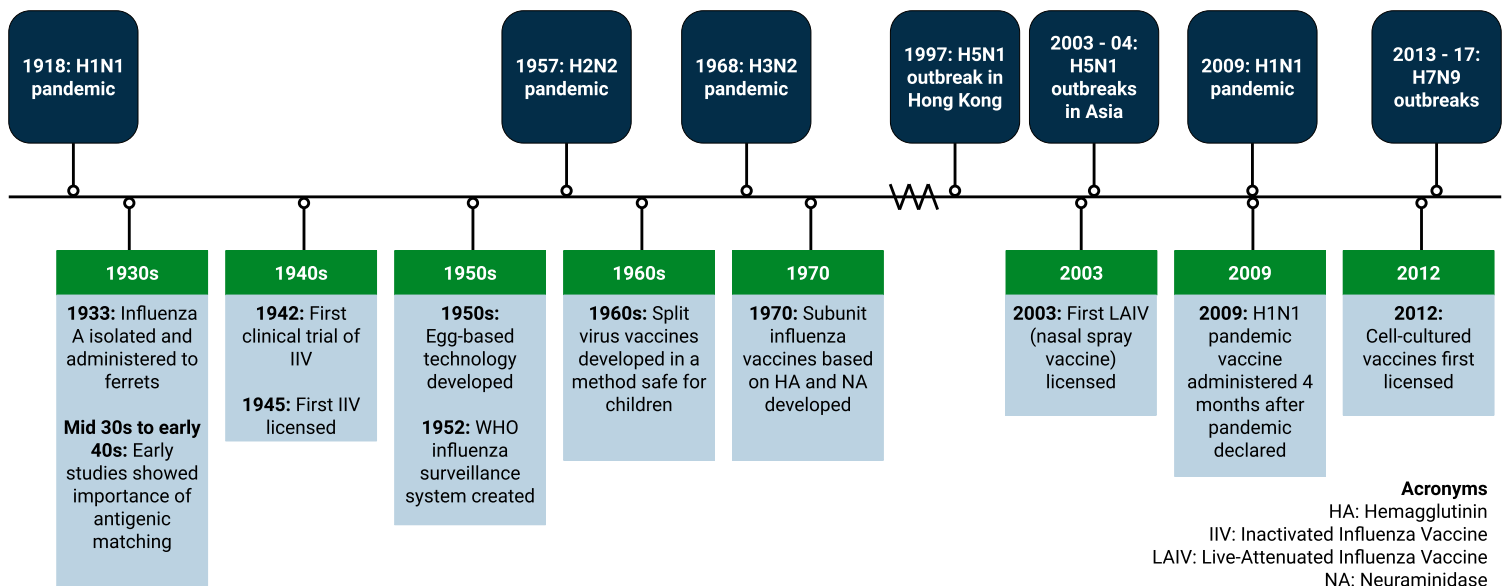
## Influenza Disease Burden

Seasonal influenza epidemics, caused by influenza A and B viruses, account for an estimated 3 million to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths each year worldwide (WHO 2019) and result in substantial economic burdens (Sah 2019). Disproportionately higher rates of illness and death from influenza occur in low-income countries in sub-Saharan Africa and Southeast Asia, particularly among the elderly and children under 5 years (Bartoszeko 2021, Iuliano 2018, Wang 2020). Influenza viruses are maintained in human populations by person-to-person transmission of antigenically diverse viruses that circulate seasonally in the Northern and Southern Hemispheres and year-round in tropical regions (Young 2020). Influenza A viruses from animal reservoirs (mainly wild birds and swine) to which humans have limited immunity can spill over to people, creating the ongoing threat of pandemic

influenza. Novel influenza A viruses with increased pathogenicity and transmissibility have the potential to cause severe pandemics, as occurred with the 1918 pandemic, which is estimated to have caused over 50 million deaths (Morens 2019). Less severe influenza A pandemics occurred in 1957, 1968, and 2009. Influenza B viruses account for about 25% of seasonal influenza infections, with wide variation from year to year (Hensen 2020); no pandemics have been attributed to influenza B.

## Influenza Vaccines

Vaccination remains the cornerstone of reducing the burden of seasonal influenza and enhancing pandemic preparedness (WHO 2020, WHO 2019). While current influenza vaccines reduce infection rates and influenza-related complications and deaths (Chung 2020, Paules 2019a), their overall effectiveness is suboptimal. From 2004 to 2018,







average US estimates of influenza vaccine effectiveness against medically attended illness ranged from 10% to 60% (CDC 2020). During the 2016-17 influenza season, the overall vaccine effectiveness at six international sites (Valencia, Canada, St. Petersburg, Mexico, Moscow, and Turkey) was estimated at 27% (Baselga-Moreno 2019).

---

**“There is an urgent need for better tools to prevent, detect, control, and treat influenza, including more effective vaccines . . . that would instill public confidence and uptake, especially in low- and middle-income countries.”**

---

- WHO Global Influenza Strategy 2019 to 2030

Although the vaccines are reformulated biannually to align with predicted circulating influenza viruses in the Northern and Southern Hemispheres, frequent genetic changes result in different proportions of virus subtypes/lineages circulating. The ability to accurately predict predominant circulating strains is also limited. Therefore, at times vaccine strains may be antigenically distinct from circulating viruses, creating mismatches. Vaccine protection against influenza may still be suboptimal even when the antigenic match appears good, indicating that other aspects may also be involved in determining vaccine efficacy, such as pre-existing partial immunity or the influence of various other host factors on the immune response (Dhakal 2019, Allen 2018, Harding 2018, Lewnard 2018, McElhaney 2020b, Zost 2017). In addition, the duration of protection is notably short, requiring vaccines to be readministered annually,

which poses challenges for immunization programs, particularly in LMICs. Recognizing the limitations of current influenza vaccines, the WHO’s comprehensive Global Influenza Strategy 2019-2030 highlights the urgent need for more effective influenza vaccines to prevent and control seasonal influenza and to enhance pandemic preparedness (WHO 2019).

Several types of influenza strain-specific vaccines are licensed and in widespread use, including split or subunit inactivated vaccines, recombinant vaccines (both administered by intramuscular injection), and live-attenuated influenza vaccines, which are administered intranasally (Gouma 2020a, Mathew 2020). Although some influenza vaccines are produced via cell-culture methods (Rajaram 2020), most of the estimated 1.48 billion doses of seasonal vaccine produced each year are manufactured using conventional egg-based production methods (Estrada 2019, Sparrow 2021). Production of egg-based and recombinant cell-culture influenza vaccines require at least 6 months to complete (Paules 2019a), limiting their usefulness in responding rapidly to the emergence of a pandemic virus.

Because they continually evolve, influenza viruses are often referred to as “moving targets,” given the hypervariable antigenic sites on the virus’s hemagglutinin (HA) and neuraminidase (NA) surface proteins (Francis 2019, McLean 2020, Paules 2019b). These sites have traditionally served as the primary antigens in strain-specific seasonal vaccines. Recent efforts to improve the immunogenicity of these vaccines have focused on the use of high-dose formulations, alternative vaccine delivery methods, and the addition of adjuvants, which can be added to boost the immune response (Wei 2020). Achieving significant reductions in morbidity and mortality worldwide, however—particularly among older adults and other at-risk populations—will require novel approaches (Madsen 2020, McElhaney 2020a).



Several policy initiatives and research funding programs have been launched to stimulate influenza vaccine research and highlight the need for transformative technologies. Examples include the Collaborative Influenza Vaccine Innovation Centers (CIVICs) program from the US National Institute of Allergy and Infectious Diseases (NIAID) (NIAID 2020), the EU-India Joint Call (EEAS 2018), and the Bill & Melinda Gates Foundation Grand Challenge for Universal Influenza Vaccine Development (BMGF 2018a). The ultimate goal of these efforts is to develop durable, broadly protective vaccines suitable for widespread use. Innovations being considered include new vaccine approaches (such as messenger ribonucleic acid [mRNA] lipid nanoparticles and recombinant protein nanoparticles) and novel constructs that target conserved viral epitopes to induce broadly neutralizing antibodies (Wu 2020) and cross-reactive T cell responses (Wei 2020).

## Influenza Vaccine Definitions

There is no commonly accepted definition of “universal” influenza vaccines, which is often used interchangeably with “broadly protective” or “next-generation” vaccines. Krammer and colleagues (Krammer 2018a) suggest that “universal” refers to “lifelong protection against all drift and shift variants, including seasonal influenza A and B, pandemic, and zoonotic strains,” whereas “broadly protective” refers to protection against a subset of influenza viruses (such as all current seasonal strains and their drift variants or against all influenza A viruses) for at least several years. The NIAID strategic plan states that the ultimate goal is to develop universal vaccines that are at least 75% effective against symptomatic influenza infection, protect against phylogenetic groups 1 and 2 influenza A viruses, provide durable protection for at least 1 year, and are suitable for all age-groups (Erbelding 2018).

“Next-generation influenza vaccines” can also be defined according to their various potential roles, such as: *high-performance seasonal* vaccines (improved existing vaccines); *supraseasonal* vaccines (seasonal vaccines with consistent annual efficacy without reformulation over two or more seasons); *vaccines for pandemic preparedness* (stockpiled for immediate use during a pandemic); *vaccines for pandemic response* (rapid production at the onset of a pandemic); and *universal vaccines* (consistent efficacy against all influenza A and B viruses, including drifted seasonal and pandemic viruses, ideally for at least 3 years, achieving at least 75% reduction in medically attended lower respiratory tract disease or hospitalization) (Kanekiyo 2020).

In a research context, the term “universal influenza vaccine” serves as an aspirational concept that ideally encompasses four attributes: (1) *breadth of protection* against diverse influenza viruses (including influenza A and B viruses); (2) *robust immunogenicity and safety* in different age-groups and special populations (e.g., immunocompromised individuals, pregnant women); (3) *durability* (at least several years’ protection against seasonal influenza viruses); and (4) *suitability* for global use. Outcomes of the research may include one or more influenza vaccine products for different purposes, markets, or populations, each with different characteristics and target product profiles. If durable, universal influenza vaccines can be developed that are suitable for use in LMICs, this will have a dramatic impact on the entire influenza vaccination enterprise.

This roadmap uses the following definitions regarding influenza vaccine R&D:

- **Universal influenza vaccine:** Offers protection against all influenza A and B viruses, including seasonal viruses and existing or emergent zoonotic viruses with pandemic potential.



- **Broadly protective influenza vaccine:** Offers protection against multiple influenza viruses 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.
- **Next-generation influenza vaccine:** Involves a different strategy than currently licensed seasonal vaccines to elicit protective immune responses against influenza viruses (e.g., uses different vaccine platforms or targets antigens other than, or in addition to, the variable HA head epitopes), demonstrating an improvement over current vaccines in durability, efficacy, or breadth of protection. Both universal vaccines and broadly protective vaccines could be considered next-generation vaccines, but next-generation vaccines also could include strain-specific vaccines if they offer significant public health advantages, such as greater durability or a 15% to 20% increase in effectiveness.

Examples of how other groups have defined the above terms can be found in [Appendix 2](#).

## Roadmap Scope and Structure

Recent efforts to develop R&D roadmaps in other fields, such as medical countermeasure development for WHO priority diseases (WHO R&D Blueprint Initiative), have informed the structure of the IVR. Each IVR section contains an overview of key issues, barriers, and knowledge gaps. High-level strategic goals within these topics are identified, followed by associated actions (milestones) required to achieve them. The milestones include target dates for completion and reflect SMART (Specific, Measureable, Achievable, Realistic/Relevant, and

Time-sensitive) criteria, to the degree feasible. High-priority milestones, listed in the text and in Appendix 3, are those that are on the critical path to improving seasonal influenza vaccines or to generating universal influenza vaccines or are considered essential to advance influenza vaccine R&D, based on consensus agreement among IVR taskforce members.

The IVR is organized into six topic areas:



VIROLOGY applicable to vaccine development



IMMUNOLOGY and immune correlates of protection



VACCINOLOGY for seasonal influenza vaccines



VACCINOLOGY for broadly protective or universal influenza vaccines



ANIMAL MODELS and the controlled human influenza virus infection model



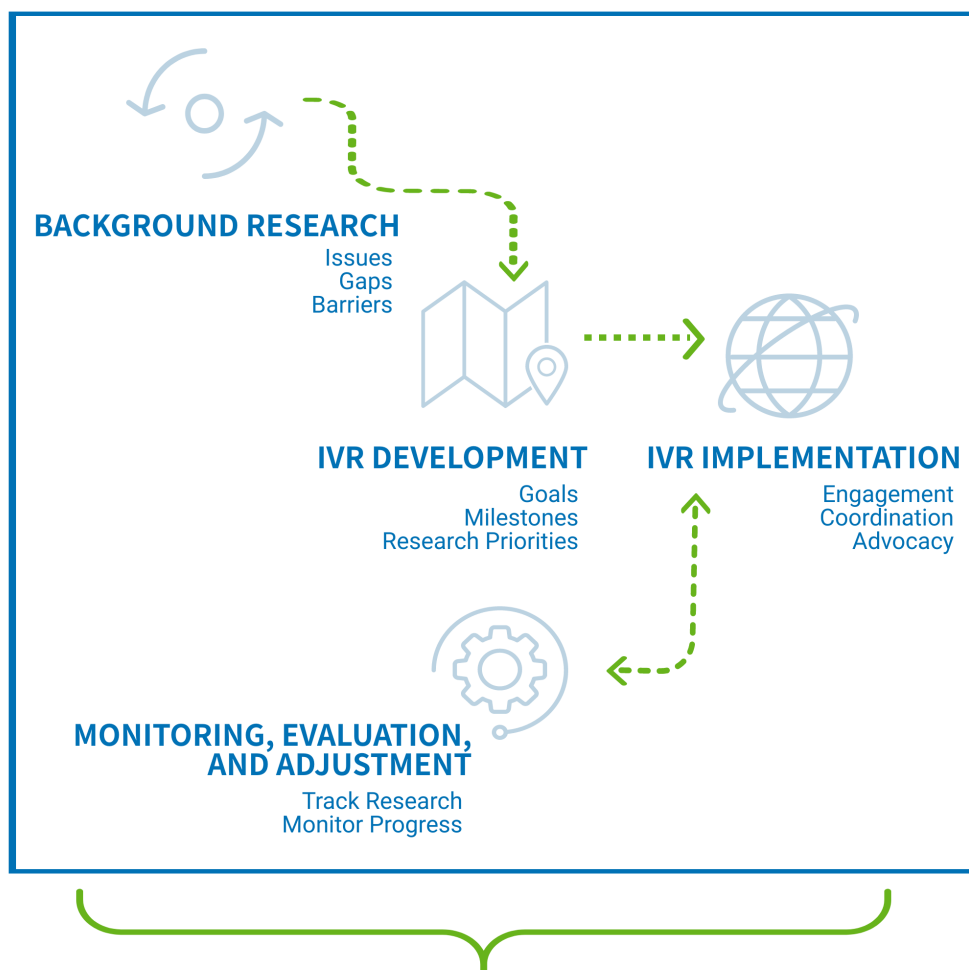
POLICY, FINANCING, AND REGULATION

In addition to influenza vaccine development, other interventions are critical for effective influenza prevention and control. These include the development of influenza vaccines for use in domestic animals, the promotion of technology-transfer for vaccine production in LMICs, and the development and delivery of effective antiviral drugs, monoclonal antibody therapies, and vaccines to prevent other lower respiratory tract infections. Increased availability of influenza vaccines, especially



in LMICs, enhanced uptake among high-risk or underserved populations, and broader acceptance of influenza vaccines are also critical ongoing activities, but all these issues are beyond the scope of this roadmap.

## IVR Development and Outcomes



### IMPROVED INFLUENZA VACCINES



Improved  
Vaccine  
Effectiveness



Increased  
Immune  
Durability



Improved  
Breadth  
of Protection



Improved  
Usability in  
LMICs



## Topic 1: Virology Applicable to Vaccine Development

This section addresses issues around continuous evolution of seasonal influenza viruses (antigenic shift) and the potential emergence of pandemic influenza viruses (antigenic drift), particularly at the human-animal interface. It also examines spread of influenza viruses in relation to population dynamics.

**Issue: Continuous evolution of influenza viruses (genetic changes that confer antigenic drift)**

### Barriers

- Antigenic drift results in influenza virus variants that are no longer neutralized by immune responses generated through prior natural infection or strain-specific vaccinations, placing people at continuous risk of infection (Bouvier 2018).
- The antigenic variability of influenza viruses necessitates frequent changes in vaccine seed

strains and limits the potential for seasonal vaccines to generate long-term humoral immunity (Estrada 2019).

- Antigenic drift can contribute to mismatches between seasonal influenza vaccines and the predominant circulating viruses (Gouma 2020a).
- Improved understanding of changes in circulating subtypes of influenza virus has driven the need from bivalent A/B, to trivalent A/B, to now quadrivalent A/B vaccines, which demonstrates the complexity of providing vaccine coverage as strains change over time.



## Gaps

- Although the WHO Global Influenza Surveillance and Response System (GISRS) and the Global Initiative on Sharing Avian Influenza Data (GISAID) have successfully fostered international sharing of influenza virus isolates and gene sequences for years, global surveillance for influenza is not uniformly distributed, with limited data for large populations, including global hot spots for influenza virus diversity. Expanding the geographic range of influenza sequence data, with increased metadata collection and virus sample sharing for phenotypic analysis, could provide important information about global virus evolution, including the impact of travel and host genetics. 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 (Polack 2020).
- Improved computational methods, including shared databases and modeling approaches, could facilitate better understating of the emergence of viral variants, the relative capacity of acquired viral receptor mutations to interact with the host cells, and the possibility to infer effectiveness of vaccines via simulation.
- Efforts by the WHO Collaborating Centers and others to improve methods for antigenic characterization of H3N2 viruses have been underway for many years. Progress has been made (including development of moderate throughput plaque reduction assays and the high content imaging-based neutralization test [HINT]), although further improvements are needed for ongoing antigenic characterization of H3N2 viruses to enhance understanding of the public health implications regarding co-circulation of different antigenic variants of this viral subtype (Allen 2018, Harding 2018, Zost 2017).
- Additional research is needed to determine:
  - ◇ How viral changes (e.g., changes in HA-head glycosylation, NA modification, interior protein changes) affect vaccine efficacy and immunogenicity (Allen 2018, Medina 2013, Wille 2020).
  - ◇ How antigenic drift might help predict the impact of selective pressure on conserved epitopes targeted by vaccines (Saad-Roy 2019).
  - ◇ How best to predict the direction and speed of antigenic drift for influenza viruses to improve forecasting ability (Ali 2021, Dadonaite 2019).
  - ◇ The role of new tools (such as computational analysis and systems biology) to facilitate understanding of influenza virus evolution (Erbelding 2018, Viboud 2020).
  - ◇ Reasons for antigenic mismatches between vaccine strains and circulating strains and how they could be avoided.

## Issue: Emergence of novel influenza viruses with pandemic potential (antigenic shift)

### Barriers

- Within the range of different HA and NA influenza A virus subtypes found in nature, only three HAs (H1, H2, H3) and two NAs (N1, N2) have been identified in pandemic viruses. It is possible, however, that influenza A viruses of other HA and NA subtypes could generate a pandemic strain

through antigenic shift, and this uncertainty is an important barrier to predicting the emergence of pandemic viruses (Morens 2019).

- Numerous influenza A viruses are enzootic in animal reservoirs (e.g., wild and domestic birds, swine, horses, dogs), and humans are largely immunologically naive to these viruses. Some have the potential to cross the species barrier and infect humans following exposure at the human-animal interface (Long 2019). The inability to predict which strains will spill over to immunologically naive populations is an important challenge in understanding the risks.
- Novel or unanticipated viral strains are not targeted by current seasonal vaccine technology. Although strain-specific vaccines are being produced for certain H5 and H7 viruses, vaccines against other subtypes with pandemic potential need to be addressed. For example, previously endemic (1957 to 1968) human H2N2 viruses could re-emerge, or novel avian influenza A viruses could spill over into humans and become more easily transmissible from person to person (Reneer 2019, Trucchi 2019).

### Gaps

- Important needs include:
  - ◇ Renewed commitments for ongoing influenza virus surveillance programs in wild and domestic animals living near people, particularly for swine and poultry (Erbelding 2018, Neumann 2019).
  - ◇ Improved surveillance and rapid characterization to identify and monitor emergent influenza viruses for changes in person-to-person transmissibility and increased virulence (Neumann 2019).

- ◇ Additional information to clarify how and where influenza viruses cross species barriers (Schrauwen 2014).
- ◇ More research to (1) identify mutations in the viral genome that confer binding to human-type receptors (Neumann 2019), (2) identify the sialic acid receptors present in human airways, (3) assess which of those are preferential for influenza viruses, (4) identify amino acid changes in animal HAs that confer efficient binding to these preferred receptors (Neumann 2019), and (5) better understand the phenotypes that promote cross-species transmission and emergence of zoonotic viruses.

Issue: Influenza virus transmissibility and spread, particularly with regard to population dynamics and the impact of vaccination

### Barriers

- Influenza virus transmission has been historically difficult to study, and the impact of vaccination on interrupting transmission in humans is unknown (Erbelding 2018, Leung 2021).
- Capacity to conduct surveillance for influenza is limited in some areas of the world, particularly in tropical and subtropical countries (WHO 2016a).
- Resources to conduct comprehensive influenza virus transmission studies in animals are limited, and further efforts are needed to optimize animal models for studying transmission dynamics (Neumann 2019). (Also see [Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model](#).)

Gaps

- Efforts are needed in several other areas:
  - ◇ Ongoing assessment of transmissibility of mutant and reassortant viruses to predict the pandemic potential of novel influenza viruses (Neumann 2019).
  - ◇ Enhanced understanding of factors associated with transmissibility to allow better modeling of population dynamics and mechanisms to interrupt viral transmission cycles (Crank 2019, Erbeling 2018).
  - ◇ Better definition of the level and type of herd immunity required in a given human population to prevent viral transmission (Erbeling 2018).
  - ◇ Clarification of the impact of vaccination on spread of influenza.
  - ◇ Further study of the role of viral interference (i.e., where one respiratory virus can block infection with another through stimulation of antiviral defenses in the airway mucosa) on transmission dynamics (Anchi 2020).
  - ◇ The inclusion of aerobiologists, engineers, and other experts not generally involved in influenza research to improve transmission knowledge.

Strategic Goals and Aligned Milestones for Topic 1: Virology Applicable to Vaccine Development

Strategic Goal 1.1: Improve understanding of human and animal influenza virus evolution (Wille 2020).	
Beginning in 2022, and then every 2 years thereafter	<b>Milestone 1.1.a:</b> Assess and evaluate sampling strategies for obtaining isolates of circulating influenza viruses in geographically diverse areas, with the aim of developing an adequately resourced, enduring, globally comprehensive, and geographically diverse system, as well as to increase, refine, and standardize the types of metadata collected. As part of this effort, public health officials should consider initiating a demonstration project to obtain data over several years at sites in both hemispheres and the tropics to assess differences among regions over time.
By 2023	<b>Milestone 1.1.b:</b> Convene a group of stakeholders to determine how best to use new tools, such as computational approaches, machine learning, and systems biology, to enhance understanding of influenza virus evolution and to improve capabilities to predict circulating influenza virus strains, including emergence of novel viruses (Erbeling 2018, Neumann 2019, Viboud 2020).





By 2025	<b>Milestone 1.1.c:</b> Develop and implement a plan to improve genetic and antigenic characterization of emerging and circulating influenza viruses (including epitopes beyond HA and NA, such as T cell epitopes), using techniques such as deep-sequencing technology, computational biology, and phylogenetic analysis (Agor 2018, Crank 2019). This plan should outline specific goals for how analytic characterization can be used to predict antigenic drift. Ongoing screening of emerging strains with a standardized, regularly updated panel of monoclonal antibodies (mAbs) binding key epitopes could also be considered as part of this effort.
By 2025	<b>Milestone 1.1.d:</b> Conduct population-based studies (or analyze data from studies currently in progress) that examine age-stratified groups and at-risk populations in different geographic regions (e.g., the Northern Hemisphere, the Southern Hemisphere, and the tropics) to determine levels of immunity against influenza that lead to antigenic drift and that mediate escape neutralization from a polyclonal antibody response in people (Yamayoshi 2019). Such studies should also consider viral fitness characteristics to improve predictive modeling (Morris 2018).
<b>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 vaccine production.</b>	
By 2022	<b>Milestone 1.2.a:</b> Review available data on antigenic mismatches between vaccine strains and circulating strains over past years to identify causes and determine steps that could have minimized or avoided them. Information obtained may be useful in developing contingency response plans in advance for when antigenic mismatches occur in the future.
By 2023	<b>Milestone 1.2.b:</b> Review current and new technologies for forecasting and modeling the emergence of drifted seasonal strains (such as use of machine learning and systems biology) and determine how best to apply them to improve forecasting. (Also see Milestone 1.1.b of this section).
By 2025	<b>Milestone 1.2.c:</b> Based on this review in Milestones 1.2.a and 1.2.b, develop methods to improve forecasting of circulating viruses.
By 2025	<b>Milestone 1.2.d:</b> If Milestones 1.2.a, 1.2.b, and 1.2.c are completed, reconvene the WHO expert group on improving influenza vaccine virus selection to review activities for improving the antigenic match between circulating viruses and annual vaccine seed strains, as outlined in 2015 by the WHO (WHO 2016a), develop consensus on new strategies to improve forecasting, and update the 2015 consensus report as needed to reflect new developments and strategies.



By 2025

**Milestone 1.2.e (High Priority):** Develop, standardize, and implement methods to improve antigenic characterization of H1N1 and H3N2 viruses (Allen 2018, Harding 2018, Zost 2017).

### Strategic Goal 1.3: Improve the ability to detect and understand the emergence of novel influenza viruses with pandemic potential (Neumann 2019).

By 2022

**Milestone 1.3.a:** Develop a plan to continue surveillance of influenza viruses at the human-animal interface and expand global influenza surveillance in poultry and swine, particularly in Africa, Asia, and South America. The plan should highlight the need for coordination among international groups, stress the importance of understanding the emergence of novel and potentially pandemic viruses in animal reservoirs, and promote data sharing and integration across different surveillance systems.

By 2023

**Milestone 1.3.b:** Identify funding and implement the expanded surveillance plan (to be funded for at least 5 years). One option is to create a coordinated network of centers around the world with the capability to sample domestic animals for influenza viruses.

By 2024

**Milestone 1.3.c:** Develop a strategy for improving the ability to detect the frequency with which animal influenza viruses infect humans.

### Strategic Goal 1.4: Enhance understanding of factors associated with viral transmissibility (Crank 2019).

By 2024

**Milestone 1.4.a:** Determine the feasibility of conducting a transmission study using a controlled human influenza virus infection model (CHIVIM). (Also see [Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model](#).)

By 2024

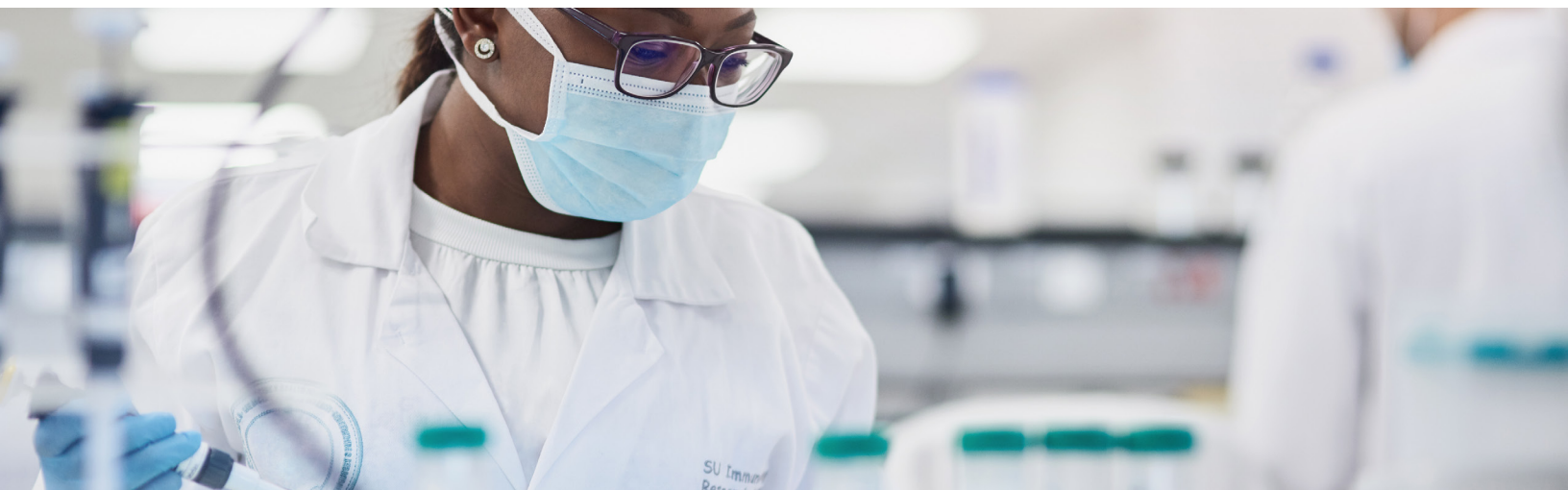
**Milestone 1.4.b:** Conduct at least two comprehensive influenza virus transmission studies in animals (to include naive and infected or vaccinated animals) (Neumann 2019). (Also see [Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model](#).)

By 2025

**Milestone 1.4.c:** Conduct at least one modeling study to predict influenza virus transmission across geographic regions (Erbelding 2018).

## Additional R&D Priorities for Topic 1: Virology Applicable to Vaccine Development

- **Identify** mechanisms to maximize the use of existing tools (such as the Influenza Risk Assessment Tool [IRAT] from the US CDC and the Tool for Influenza Pandemic Risk Assessment [TIPRA] from the WHO) for tracking novel influenza viruses and assessing their risk to humans. This may include taking steps to standardize and share risk assessments and risk assessment protocols across the two systems.
- **Increase collaboration** with experts in environmental sciences (e.g., aerobiologists, engineers, ventilation experts) for influenza virus transmission research.
- **Encourage collaborations** among influenza virologists, surveillance teams, immunologists, and epidemiologic mathematical modelers to generate insights on population dynamics of immunity, transmission dynamics, burden of disease (especially in under-surveilled LMICs), and seasonality of disease under changing climate conditions.
- **Consider expanding** the US CDC's H5N1 Genetic Changes Inventory to include other influenza viruses of concern (e.g., H7N9, H5N6, H5N8, H3N2v) and to capture new mutations.
- **Implement** efforts to characterize epitopes on emerging viruses by generating panels of mAbs against the HA and NA glycoproteins (and perhaps other epitopes) as new variants arise.
- **Further study** the impact of viral interference on transmission dynamics, which may be important for clinical research into new vaccines (Anchi 2020).
- **Research** the impact of vaccination on the spread of influenza in diverse communities.
- **Develop** mechanisms to assess influenza viral shedding during infection, such as measuring viral load in expired air over the course of an infection.
- **Enhance** understanding of viral and host factors associated with virus transmission.
- **Continue to identify and monitor** emergent influenza viruses for changes in human-to-human transmissibility and enhancement of virulence (Neumann 2019).
- **Continue to determine** mechanisms by which influenza viruses cross species barriers (Schrauwen 2014).
- **Consider the utility** of developing a vaccine for H2N2 and creating a stockpile, as is being done for H5 and H7 strains.
- **Provide** in-country training for new participants in influenza surveillance or clinical research, to include regulators, to expedite reviews of protocols. This should also involve agreements regarding host-nation clinical samples leaving the country for centralized testing.



## Topic 2: Immunology and Immune Correlates of Protection

This section addresses critical immunologic issues for improving influenza vaccines, such as overcoming immunodominance the HA globular head, defining the mechanisms for inducing durable B cell immune memory, developing an improved understanding of the T cell immune response to influenza, clarifying issues around immune imprinting, determining the role of mucosal immunity, and generating new correlates of protection for assessing next-generation influenza vaccines.

**Issue: Fundamental understanding of human immunology relevant to improving influenza vaccines**

### Barriers

- Much of the immunologic research needed for improving influenza vaccines depends on access to clinical samples, which may not be readily available, particularly from commercial entities.

- Research efforts may be complicated by genetic differences among populations and environmental conditions, such as potential for exposure to other pathogens.

### Gaps

- To develop improved influenza vaccines, a better understanding of the following is needed regarding:
  - ◇ Human immunology (Morens 2019), including the role of host factors in immune responses



to vaccines and correlates of protection by immune compartment.

- ◇ Differences between immune responses to influenza virus infection and influenza vaccination (Clemens 2018, Krammer 2019a, Lopez 2020).
- ◇ Cooperation across the immune system, including the polyclonal antibody response cooperation—synergistic, additive, or interfering—and immune homeostasis.
- ◇ Characterization of innate and adaptive immune responses to influenza, including the critical immune factors required for inducing broad, durable protection (Erbelding 2018, Topham 2019) and the mechanisms of vaccine-induced immunity (Cortese 2020).
- ◇ Mechanisms of non-neutralizing immune effectors and their potential for immune protection, immune interference, or disease enhancement (Bouvier 2018, Crowe 2019, Erbelding 2018).
- ◇ The processes by which immune dysregulation may contribute to severe influenza (Bouvier 2018, Erbelding 2018).

## Issue: The humoral response to influenza virus infection and vaccination

### Barriers

- Variable antigens on the HA globular head exhibit immunodominance over the more conserved viral antigens (Krammer 2019a). This creates obstacles for developing new vaccine constructs that are targeted to more conserved domains of the virus (Zost 2019).

- Manufacturing and price constraints limit the number of antigens that can be included in new vaccine constructs.

### Gaps

- Further knowledge is needed regarding:
  - ◇ The dynamics among B cell subsets following influenza infection and how to influence those dynamics to induce durable memory driven by long-lived plasma cells in the bone marrow (Krammer 2019a).
  - ◇ What level of B cell response to conserved antigens is sufficient to provide protection, either independently or in combination with T cell responses.
  - ◇ The role of NA antibodies in contributing to protection from infection (Eichelberger 2019, Eichelberger 2018, Krammer 2018b, Yamayoshi 2019). (Also see [Topic 3: Vaccinology for Seasonal Influenza Vaccines.](#))
  - ◇ Immunodominance hierarchies in antibody response (Angeletti 2018, Krammer 2019a).
  - ◇ The differences in mechanisms of humoral immunity between protection against infection (sterilizing immunity) and protection from symptomatic or severe disease (Krammer 2019b, Yamayoshi 2019).
  - ◇ The role of stem-specific antibodies in viral fitness and immune escape.
  - ◇ Which neutralizing and non-neutralizing B cell responses enable long-lasting immunologic protection post-infection or vaccination (Coughlan 2018, Krammer 2019a).



## Issue: The cell-mediated response to influenza virus infection and vaccination

### Barriers

- A robust memory CD8 T cell response to influenza infection can protect against severe disease; however, strong CD8 T cell responses may lead to excessive pro-inflammatory reactions and enhanced immunopathology. This creates a challenge for optimizing vaccine-induced memory CD8 T cell responses without causing adverse clinical outcomes (Souquette 2018).

### Gaps

- The influenza-specific CD4 T cell repertoire in humans is highly diverse with regard to abundance, specificity, and functionality, making it difficult to define an optimal strategy for vaccine-induced T cell-mediated immunity (Sant 2018, Sant 2019).
- Improved, more affordable, and standardized T cell assays or markers of T cell function are needed to better assess T cell immunity.
- More information is need regarding:
  - ◇ The T cell response in protecting against severe influenza, both directly and in potentiating the response of other lymphoid cells (Jansen 2019, Sant 2019).
  - ◇ The determinants of beneficial versus detrimental T cell responses.

## Issue: Immune response to influenza virus infection in different anatomic compartments

### Gaps

- The immune response to influenza viruses may vary by anatomic or cellular compartments (particularly in regard to reassortment/vaccine strain interference) and the types of immune responses that an effective vaccine must elicit in the various compartments are not fully elucidated (Morens 2019).
- The route of vaccine administration (e.g., intranasal, other mucosal route, intramuscular, transdermal) affects key aspects of the protective immune response in the various immunologic compartments, but feasible-to-use biomarkers of the different responses for influenza protection are not sufficiently established to guide vaccine development strategies (Calzas 2019, Morens 2019).
- Better understanding of the following is needed:
  - ◇ Age-associated changes in lung immune cells in response to influenza virus infection to inform the development of improved vaccines for the elderly (Nguyen 2021).
  - ◇ The role of mucosal immunity in the protective response to influenza infection, including the potential magnitude and scope of mucosal immunity elicited by influenza infection or vaccines and identification of factors affecting the degree of protection following intranasal vaccination or mucosal vaccination by other routes (Calzas 2019, Epstein 2018, Krammer 2019a).





## Issue: The role of immune imprinting and prior exposure to influenza infection or vaccine on influencing the immune response to future influenza vaccination and viral infection over time

### Barriers

- The immune response to influenza may be significantly influenced by early childhood exposure to specific strains of influenza viruses (referred to as immune imprinting) through natural infection or vaccination, leading to different risks of disease from various influenza subtypes (Gostic 2019, Nayak 2019, Valkenburg 2017). The development of universal vaccines will require a better understanding of the influence of immune imprinting and exposure history on vaccine effectiveness (Knight 2020).

### Gaps

- More information is needed regarding:
  - ◇ The underlying mechanisms of immune imprinting and the host and virologic factors that influence its outcome (Cobey 2017, Guthmiller 2018, Yewdell 2020, Zhang 2019).
  - ◇ The role of immune imprinting from early childhood exposure on subsequent immune responses to influenza infection or vaccines (Dugan 2020, Worobey 2020).
  - ◇ The role of immune imprinting on B cell responses to non-HA head antigens (e.g., NA- and HA-stalk antigens) and on T cell responses to internal proteins (Zhang 2019).
  - ◇ How immune imprinting may protect or blunt responses to vaccination and its effect on

vaccine innovation (Meade 2020, Coughlan 2018, Henry 2018).

- ◇ The role that annual vaccination plays in determining subsequent vaccine effectiveness (Belongia 2017, Kim 2020) such as potential alterations in B cell and CD4 T cell responses following repeated seasonal influenza vaccinations (Richards 2020), which may have implications for vaccine design (such as inducing immune responses more similar to those of natural infection or modifying antigenic structures and vaccine-adjuvant combinations).

## Issue: New immune correlates of protection for influenza vaccines

### Barriers

- Identifying a single correlate of protection responsible to guide selection of target antigens and measuring protective efficacy of influenza vaccines may not be possible. Instead, multiple or complex correlates of protection may be needed, since several different antigens stimulate protective responses and the responses interact synergistically (Lim 2020, Plotkin 2020).
- The most commonly used marker for immune response to influenza infection or vaccination is the serum HA antibody inhibition (HAI) titer; however, measurement of this titer has limitations in predicting vaccine effectiveness, particularly for non-HA strain-specific vaccines, and does not provide a comprehensive assessment of immunity (Reber 2013, Wraith 2020).
- Immune markers that may correlate with protection but are not yet validated and require further assessment include: interferon gamma-



secreting cells, cross-reactive CD8 and CD4 T cells in peripheral blood, serum NA inhibition (NAI) antibodies, nasal IgA, and anti-HA stalk antibodies (Krammer 2020).

- A correlate of protection for assessing mucosal immunity (e.g., through measurement of mucosal antibodies) has not yet been established.
- Immune correlates of protection may differ quantitatively and qualitatively by type of vaccine, various host characteristics (e.g., age, gender, major histocompatibility complex [MHC] group) and intended outcome of vaccination (e.g., prevention of mucosal or respiratory tract infection vs. prevention of severe disease), which complicates assessment approaches (Plotkin 2010).

### Gaps

- The lack of qualified and harmonized methods to measure antibody indicators other than HAI remains an important gap to assessing immunity generated by natural infection or more broadly protective vaccines (FLUCOP, Krammer 2020, Lim 2020, Madsen 2020, Ng 2019, Reber 2013).
- Additional priority needs include the following:
  - ◇ Sensitive and standardized methods to collect and measure antibodies at mucosal sites and identify correlates of protection for mucosal immunity (Reber 2013). This is particularly important for live-attenuated influenza vaccines (LAIVs), for which a correlate of protection has yet to be defined (Reber 2013, Shannon 2019).
  - ◇ Reagents and standardized assays for non-HA head immune responses (such as HA-stem antibodies, NA antibodies, and cell-mediated immunity) to assess different types of humoral immunity and to allow comparison of data across studies (Coughlan 2018, Reber 2013).
  - ◇ One or more standardized quantitative influenza-specific CD4 and CD8 assays to identify CD4 and functional cytolytic CD8 T cells elicited by natural infection and novel influenza vaccines that are correlated with protection from defined clinical end points (e.g., serious complications from influenza in older adults as well as potential vaccine-enhanced disease in relation to CD8 T cell stimulation).
  - ◇ In vitro high-throughput assays to measure protective responses other than virus neutralization and T cell-mediated immune responses to understand the level of protective immunity contributed by these other responses (such as influenza virus-specific antibody-dependent cellular cytotoxicity [ADCC], antibody-dependent cellular phagocytosis, and complement dependent cytotoxicity) (Gianchecchi 2019, Plotkin 2018).





## Strategic Goals and Aligned Milestones for Topic 2: Immunology and Immune Correlates of Protection

**Strategic Goal 2.1: Ensure that critical tools are available for conducting research on human immunology that is needed to inform development of next-generation influenza vaccines.**

By 2022	<b>Milestone 2.1.a:</b> Complete the following: (1) develop a comprehensive list of clinical studies that are ongoing or planned (such as ongoing cohort studies); (2) create a coordinating mechanism to ensure that relevant clinical samples, such as from mucosal sites, from such studies (potentially including samples from commercial entities) are provided to investigators for immunologic research relevant to improved influenza vaccines; and (3) develop guidance to support the management, storage, and distribution of the clinical samples.
By 2023	<b>Milestone 2.1.b:</b> Develop and ensure availability of standardized reference reagents and harmonized assay protocols for studying immunoglobulin responses to influenza infection and vaccination, such as qualified assays for detecting mucosal antibodies.
By 2025	<b>Milestone 2.1.c:</b> Develop standardized and lower cost assays (e.g., simplified high-throughput testing) for measuring T cell responses to facilitate research on vaccines targeting T cell responses, which may be critical for providing protection against severe influenza (Gianchecchi 2019).

**Strategic Goal 2.2: Gain better understanding of human immunology to inform influenza vaccine development through basic research focused on new tools and technologies.**

Beginning in 2023	<b>Milestone 2.2.a:</b> Convene an annual international workshop to identify advances in understanding immune responses to influenza infection and vaccination that can be applied to improving seasonal vaccines and to developing durable, broadly protective or universal vaccines; disseminate a summary report of key findings from each workshop.
By 2026	<b>Milestone 2.2.b:</b> Investigate the interrelated roles of T and B lymphocytes in adaptive immune responses to influenza vaccination to enhance understanding of immune homeostasis and cooperation across the immune system (Bouvier 2018, Crank 2019, Gostic 2016, Ranjeva 2019).



By 2027	<b>Milestone 2.2.c (High Priority):</b> Determine key mechanisms of long-term protection following influenza virus 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.
By 2028	<b>Milestone 2.2.d:</b> Identify distinctions between immune responses to influenza infection and vaccination in different age-groups and birth-year cohorts (Erbelding 2018).
By 2028	<b>Milestone 2.2.e:</b> Characterize human immune responses to influenza vaccines in diverse populations, according to a range of host factors, including age, sex, pregnancy, obesity, presence of coinfections or other comorbidities, concurrent use of immunotherapies, geographic region, and socioeconomic factors (Dhakal 2019, Erbelding 2018).
<b>Strategic Goal 2.3: Improve understanding of aspects of the B cell immune response to influenza infection that are important for developing better vaccines and optimal strategies for vaccination, particularly in the context of partial preexisting immunity from continual exposure to influenza viruses (Linderman 2020).</b>	
By 2025	<b>Milestone 2.3.a:</b> Determine the mechanisms underlying the production of durable, broadly protective B cell immunity driven by long-lived plasma cells in the bone marrow (Davis 2020, Krammer 2019a, Turner 2020).
By 2026	<b>Milestone 2.3.b:</b> Identify the factors that determine immunodominance hierarchies of B cell responses to surface glycoproteins and identify methods to circumvent immunodominance to inform the development of influenza vaccine approaches that effectively target subdominant, functionally conserved antigenic sites (Angeletti 2018, Angeletti 2019, Bajic 2019, Zost 2019).
By 2026	<b>Milestone 2.3.c:</b> Explore the reshaping of the B cell repertoire following infection and vaccination to clarify differences between the responses to natural infection compared with vaccination, which are relevant to inform broadly protective vaccination strategies (Coughlan 2018).



## Strategic Goal 2.4: Determine the impact of prior influenza virus infection or vaccination on future immune responses to influenza viruses or vaccines (Cobey 2017, Guthmiller 2018, Henry 2018, Worobey 2020, Zhang 2019).

By 2022	<b>Milestone 2.4.a:</b> Establish longitudinal clinical studies to follow cohorts of different age-groups in various geographic locations to enable characterization of immune responses to naturally occurring influenza infection and vaccination over time.
By 2026	<b>Milestone 2.4.b (High Priority):</b> Determine through prospective birth-year cohort studies how repeated influenza vaccinations affect the immune response to subsequent influenza vaccinations (Ranjeva 2019).
By 2028	<b>Milestone 2.4.c (High Priority):</b> Determine how the initial encounter with an influenza virus (i.e., immune imprinting) affects B and T cell responses (Arevalo 2020, Zhang 2019), including immunologic responses to subsequent influenza virus infection or vaccination.
By 2029	<b>Milestone 2.4.d (High Priority):</b> Determine if vaccination with inactivated influenza vaccine (IIV) versus LAIV of very young children before their first encounter with influenza virus has a significant impact on future influenza vaccine responses (Zhang 2019).

## Strategic Goal 2.5: Clarify the role of T cells in generating or supporting protective immunity to influenza virus infection and vaccination.

By 2024	<b>Milestone 2.5.a:</b> Prepare a catalogue of major influenza epitopes recognized by CD4 and CD8 T cells for a comprehensive range of human leukocyte antigen (HLA) types and define the epitopes that elicit broadly protective T cell immunity.
By 2030	<b>Milestone 2.5.b:</b> Determine CD4 or CD8 T cell effector function(s) that are most needed to enhance protective immunity or to modulate disease severity and determine whether T cells require localization in lymph nodes or mucosal tissue to be protective, and characterize the drivers and markers of T cell homing to the respiratory mucosa (Crank 2019, Sant 2019).
By 2030	<b>Milestone 2.5.c:</b> Define the role of heterologous infections (e.g., sequential infection with different influenza A virus strains) on the establishment and maintenance of CD4 and CD8 T cells, which might have both beneficial and detrimental effects on disease outcomes (Souquette 2018).



## Strategic Goal 2.6: Improve understanding of the role of mucosal immunity in protecting against influenza.

By 2023	<b>Milestone 2.6.a (High Priority):</b> Further determine the role of mucosal antibodies in protecting against influenza virus infection, disease, and transmission.
By 2024	<b>Milestone 2.6.b:</b> Develop improved and agreed-upon sample collection methods for detecting mucosal antibodies (de Silva 2017).
By 2026	<b>Milestone 2.6.c:</b> Clarify drivers of myeloid and lymphoid cell differentiation and migration to protect the upper and/or lower respiratory airway and determine how this information can be translated into vaccine R&D.
By 2026	<b>Milestone 2.6.d (High Priority):</b> Determine the role of mucosal T cells in protecting against influenza virus infection, disease, and transmission.
By 2028	<b>Milestone 2.6.e:</b> Identify how the route of vaccination (e.g., intranasal, oral, sublingual, or other mucosal route) affects the degree of mucosal immunity (Epstein 2018).

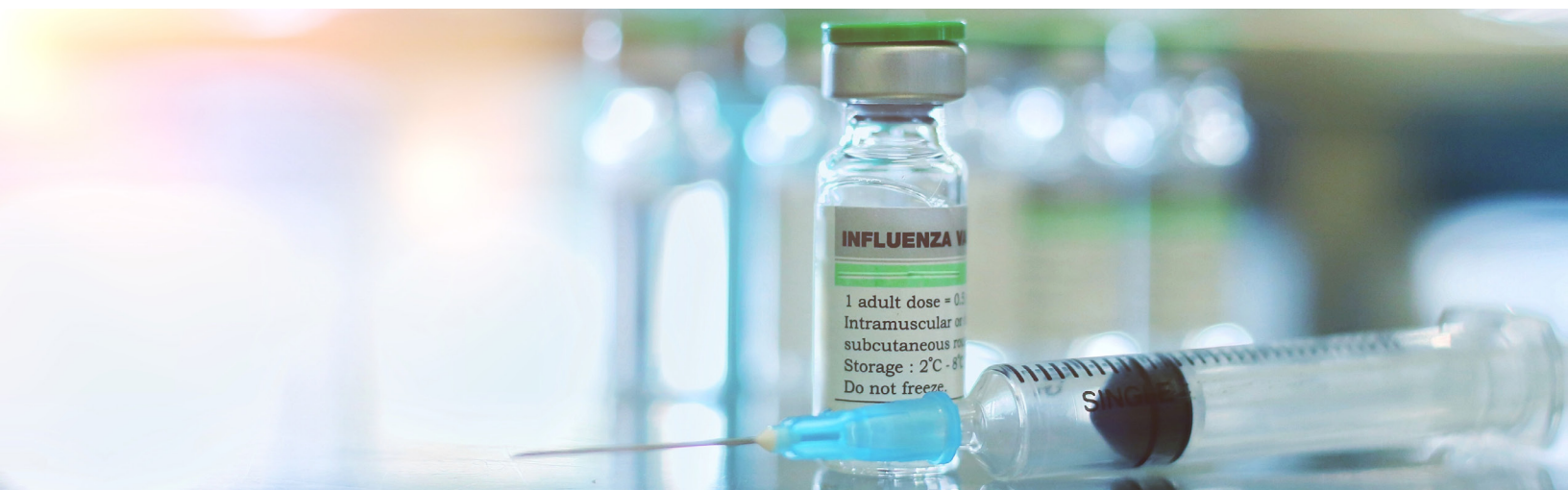
## Strategic Goal 2.7: Develop novel correlates of protection for assessing seasonal influenza vaccines and broadly protective or universal influenza vaccines, as part of clinical studies that demonstrate efficacy against a disease end point (Erbelding 2018, Krammer 2020, Lim 2019, Plotkin 2018).

By 2025	<b>Milestone 2.7.a (High Priority):</b> 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 (Coughlan 2018, Gianchecchi 2019, Krammer 2019).
By 2028	<b>Milestone 2.7.b (High Priority):</b> Develop new measurement tools, including qualified correlates of protection, for mucosal immunity, particularly for assessing LAIVs or other mucosal vaccines if developed (Reber 2013).
By 2028	<b>Milestone 2.7.c:</b> Conduct side-by-side standardized comparative studies of immune markers, including serum NA inhibition titers, as potential correlates of protection in vaccine efficacy/effectiveness studies or in studies that use a human infection model (Eichelberger 2019, Valkenburg 2017).



## Additional R&D Priorities for Topic 2: Immunology and Immune Correlates of Protection

- **Identify** how distinct types of B cell responses (e.g., neutralizing antibodies against the HA head and ADCC antibodies against non-neutralizing conserved epitopes) synergize or compete to result in a protective response (Boudreau 2019, Coughlan 2018, Jegaskanda 2018).
- **Expand** the use of new computational tools, such as multiplexing and systems immunology using innate signatures, to evaluate immunologic responses in various populations to identify vaccine-induced immunologic mechanisms and signatures predictive of protective immunologic responses (Nakaya 2016, Stacey 2018).
- **Enhance collaboration** with selected research consortia focusing on other pathogens (e.g., HIV, coronaviruses) to share information on key determinants of long-lived immunity, such as intrinsic host factors or antigen delivery strategies.
- **Develop and test** complex correlates of protection, potentially using the CHIVIM (Plotkin 2020).
- **Explore** methods to circumvent virus escape of T cell immunity, such as strategies to optimize peptide presentation and boost responses to subdominant epitopes (Clemens 2018).
- **Investigate** the role for influenza vaccination in priming hosts for adequate CD4 T cell support for neutralizing antibody production and for localized effector function in the lung to enhance vaccine protection against influenza.
- **Continue to research** additional influenza virus epitopes (such as non-structural proteins) as potential vaccine targets (Sautto 2018), including generation of mAbs with a wide breadth of activity to identify potential epitopes that can be targeted by novel vaccines.
- **Clarify** the role of CD4 T helper cells in the B cell response against influenza (Crank 2019).
- **Continue to determine** how immune dysregulation contributes to severe influenza disease (Bouvier 2018, Erbelding 2018, Crowe 2019).
- **Further explore** the potential mechanisms for viral interference or immune exclusion, such as ACE-2 receptor competition, interferon-mediated effects, or other mucosal defense mechanisms, which may provide information relevant to adjuvant design or immunization timing (Anchi 2020).
- **Assess** how the route of vaccine administration affects the protective immune response in the various immunologic compartments (Morens 2019).
- **Apply** mathematical modeling to explore the interplay of different immune system components.



## Topic 3: Vaccinology for Seasonal Influenza Vaccines

This section addresses strategies for improving effectiveness of seasonal influenza vaccines, such as shortening the lag time for seasonal vaccine development; generating influenza vaccines that prevent severe disease and are suitable for use in LMICs; exploring mechanisms that could enhance vaccine effectiveness, such as use of adjuvants or alternate routes of administration; assessing new vaccine platforms (such as mRNA-based); and determining the role of NA in optimizing seasonal vaccines.

**Issue: Suboptimal vaccine effectiveness and annual reformulation of current seasonal influenza vaccines**

### Barriers

- Currently available seasonal influenza vaccines do not provide a high level of protection against matched strains, particularly in the elderly, show
- diminished effect against drifted strains, and likely would not protect against antigenically shifted strains (Gouma 2020a).
- Because of the time needed to manufacture egg-based influenza vaccines each season, decisions on which strains to include need to be made months in advance, which allows the potential for later changes in circulating strains to result in antigenic mismatches between vaccine strains and circulating viruses, potentially reducing vaccine effectiveness (Zimmerman 2016). While





a good match between vaccine strains and circulating strains has occurred during many influenza seasons, antigenic mismatches also occur (Trucchi 2019).

- Because whole-virus influenza vaccines were noted to be reactogenic, current seasonal influenza vaccines are based on immune response to the HA head. Since this domain is constantly changing and evolving, vaccines that focus on HA head antigens may have limited vaccine effectiveness by the time they are available for clinical use.
- The H3N2 subtype, which has been circulating in humans since the 1968 H3N2 pandemic, continues to undergo extensive antigenic and genetic changes that often result in reduced seasonal vaccine effectiveness against H3N2 subtype strains (Gouma 2020b, Flannery 2019).
- Cell-mediated immune responses to current seasonal influenza vaccines, especially LAIVs, may be suboptimal because of a mismatch between T cell epitopes of cold-adapted master donor viruses isolated about 60 years ago and currently circulating viruses (Korenkov 2018). (Although influenza T cell epitopes are considered more conserved in comparison to B cell epitopes, some evolution can occur over time, which could lead to these mismatches.)
- Adjuvants licensed for use in influenza vaccines include alum, MF59, AS03, and AF03 (Wei 2020). Adding adjuvants to vaccine formulations may improve the potency and breadth of humoral immune responses to seasonal vaccines, particularly in the very young or the elderly, but key barriers exist for developing vaccines that use novel adjuvants. The manufacturing costs may be high, and it can take years to develop a new adjuvanted vaccine. In addition, unforeseen adverse effects may surface during post-marketing assessment, which increases risk to manufacturers (Tregoning 2018). Adjuvants with good safety profiles, however, may improve vaccine effectiveness in children and the elderly and enable dose-sparing, which may be important for pandemic response.
- Immunosenescence (a decline in immune function with aging) is a barrier to vaccine protection in the elderly (Castrucci 2018, Navarro-Torné 2019).
- Influenza viruses generally do not involve a viremic phase, so the primary encounter with the immune system is at the mucosal level. Creating effective vaccines to respiratory viruses that lack a viremic phase may limit options for inducing durable protective immunity.
- Success in implementing the clinical research needed to improve seasonal influenza vaccines may require enhanced cooperation and transparency, particularly sharing of data and clinical samples from industry and more rapid responsiveness from regulatory authorities.
- NA-inhibiting antibodies may play an important role in vaccine effectiveness by reducing disease severity and providing cross-protection, but the NA antigen content in current seasonal influenza vaccines is unstandardized and generally low or unknown, or nonexistent (in recombinant influenza vaccines) (Eichelberger 2018, Eichelberger 2019, Giurgea 2020, Krammer 2018b, Yamayoshi 2019, Zheng 2020). In addition, current production processes may denature or destroy much of the NA that may be present in the formulations.



## Gaps

- Research is needed to:
  - ◇ Assess whether vaccine combinations (e.g., LAIV and IIVs) are synergistic in enhancing protection against influenza viruses (Yan 2018).
  - ◇ Determine the utility of adjusting antigen doses for different populations and age-groups to enhance immunogenicity and vaccine effectiveness.
  - ◇ Assess the level of NA-specific antibody titers necessary to induce protection against disease and to establish the dose of NA that reliably elicits a protective titer for use in seasonal vaccines (Chen 2018).
  - ◇ Identify production processes that retain NA in vaccine formulations.
  - ◇ Confirm and standardize the NA content in seasonal vaccines (Giurgea 2020).
  - ◇ Determine whether NA-standardized products provide greater protective efficacy than current HA-based vaccines.

## Issue: The need to shorten the lag time for seasonal influenza vaccine development

### Barriers

- The production time for seasonal vaccines using egg-based and recombinant cell-culture methods is at least 6 months from strain selection to vaccine production (Harding 2018, Paules 2019a).
- Most of the world's influenza vaccines are produced in eggs, which creates a major

disincentive for manufacturers to change to other technologies that require building and validating new production facilities, unless such technologies substantially enhance efficacy or lower costs. Furthermore, egg-based methods don't currently provide sufficient capacity to produce pandemic vaccines on a global scale.

- Many influenza viruses do not grow well in eggs, which can result in egg-adapted mutations that alter antigenicity and reduce vaccine effectiveness (Allen 2018, Skowronski 2014, Zost 2017). Similar growth problems may also occur with cell-culture and recombinant methods.
- Variant influenza viruses can emerge late in the vaccine production cycle, when it's too late to change the vaccine composition for that season, increasing the likelihood of mismatches (WHO 2016a). Shortening the lag time will improve this issue but may not eliminate it.

### Gaps

- Several needs are evident:
  - ◇ Data over time to determine whether vaccines generated through egg-independent processes may be significantly more effective, result in high yields, be cost-effective to produce, and not lead to other significant challenges as more experience is gained regarding their use.
  - ◇ Research to develop mRNA-based technologies, similar to those used in several of the new COVID-19 vaccines, as an alternative platform (Bahl 2017, Bartley 2021, Feldman 2019, Pardi 2018, Scorza 2018).
  - ◇ Studies to compare efficacy, safety, and effectiveness of new egg-independent production methods with each other and with traditional egg-based methods (Trombetta 2019).





- ◇ A coordinated global effort to expand production capacity for egg-independent vaccine production technologies, including identifying creative funding strategies—provided these methods offer significant advantages.

needed to facilitate seasonal vaccination and pandemic response globally.

### Gaps

- Important needs include:
  - ◇ Data on vaccine effectiveness when influenza vaccines and COVID-19 vaccines are co-administered, as well as on vaccines that combine antigens for the two diseases.
  - ◇ Improved seasonal vaccines that offer better protection against or attenuation of severe influenza disease and more durable protection (WHO 2017).
  - ◇ Data to demonstrate the public health burden of influenza—especially severe influenza—in LMICs. (Also see [Topic 6: Policy, Financing, and Regulation](#).)
  - ◇ Information on whether influenza vaccines prevent severe acute respiratory infection (SARI) and, if so, what viral, host, or seasonal factors contribute to better clinical outcomes (Bouvier 2018), as well as information on better ways to assess SARI.
  - ◇ Methods to reliably assess vaccine protection against severe disease including standardized criteria and measurements of disease severity.
  - ◇ Determining whether or not certain genes are correlated with severity of influenza (Allen 2017, Randolph 2017) and how this information may relate to vaccine response versus natural infection.
  - ◇ Determining if expanding use of new vaccines in young children can reduce influenza transmission and thereby lower the overall burden of the disease.

## Issue: Seasonal influenza vaccines that prevent severe disease and are suitable for use in LMICs

### Barriers

- Many LMICs do not have national influenza vaccine programs because of challenges with current seasonal vaccine delivery approaches, competing public health priorities, the need for annual revaccination, lack of information indicating that influenza is an important public health problem, and the moderate effectiveness of current vaccines in preventing infection and disease (WHO 2017).
- Many LMICs are located in tropical and subtropical areas of the world, where influenza occurs year round, including times when there are gaps in vaccine availability owing to the need to reformulate vaccines each year (WHO 2017).
- Production facilities are geared to cope with the annual demands for seasonal vaccine—largely in high- and upper-middle-income countries—and are inadequate to cope with the enhanced worldwide demand that would be created by a pandemic; the development of mobile manufacturing centers may help to address this barrier in LMICs.
- More appropriate vaccine delivery methods, such as microarray patches or other needle-free injection approaches, suitable for LMICs, are



## Strategic Goals and Aligned Milestones for Topic 3: Vaccinology for Seasonal Influenza Vaccines

**Strategic Goal 3.1: Promote strategies that shorten the lag time from identification of candidate vaccine viruses through the process of annual vaccine production and release.**

By 2023	<b>Milestone 3.1.a:</b> Assess the advantages and tradeoffs of new seasonal influenza vaccine technologies, including recombinant, cell-culture, and mRNA technologies, over current egg-based IIVs for their potential to enhance effectiveness and shorten production time while maintaining capabilities for reliable annual delivery of vaccines (Bartley 2021, Kis 2020, Rajaram 2020, Rosa 2021).
By 2023	<b>Milestone 3.1.b:</b> Streamline the production of new potency assays to ensure timely release of annual vaccine preparations (Weir 2016).
By 2024	<b>Milestone 3.1.c:</b> Provide funding (such as through private-public partnerships) to further develop the most promising egg-independent vaccine production methods over at least a 5-year period (Barr 2018).
By 2025	<b>Milestone 3.1.d:</b> Further develop reverse genetic systems and make them available to improve the ability to quickly generate reassortant viruses (Nogales 2016).
By 2026	<b>Milestone 3.1.e:</b> Conduct studies to compare efficacy, safety, effectiveness, and cost-effectiveness of new egg-independent production methods to each other and to egg-based methods to determine any advantages (Trombetta 2019).

**Strategic Goal 3.2: Identify strategies and policies to optimize seasonal influenza vaccines and improve vaccine effectiveness.**

By 2022	<b>Milestone 3.2.a:</b> Identify lessons learned from COVID-19 vaccine development for improving seasonal influenza vaccines, ensuring reliable delivery of products, and sharing the costs of establishing new technologies or production strategies.
By 2022	<b>Milestone 3.2.b (High Priority):</b> 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 developing improved seasonal influenza vaccines.
By 2022	<b>Milestone 3.2.c:</b> Ensure that at least two combined COVID-19 and seasonal influenza vaccines are being evaluated in clinical trials.



By 2024	<b>Milestone 3.2.d:</b> Establish partnerships for designing, funding, and conducting multi-season, product-specific comparative efficacy trials of seasonal influenza vaccines in, and suitable for, LMIC populations and different age-groups.
By 2024	<b>Milestone 3.2.e (High Priority):</b> Determine optimum methods for assessing the effectiveness of conventional egg-based and cell culture-based vaccines with new vaccine technologies, in coordination with regulatory agencies and using consistent end points, to allow data to be combined (WHO 2016a) as appropriate over multiple seasons and to allow better comparability of data across studies.
By 2026	<b>Milestone 3.2.f:</b> Determine the utility of further adjusting antigen doses in existing seasonal influenza vaccines for different populations and age-groups.
By 2027	<b>Milestone 3.2.g:</b> Incentivize manufacturers to collaborate in clinical trials to assess vaccine combinations of licensed products (e.g., LAIV and IIV in a prime-boost strategy) and vaccine components (e.g., adjuvants) to identify strategies that offer improved effectiveness against influenza (Yan 2018).
By 2028	<b>Milestone 3.2.h (High Priority):</b> Evaluate the effectiveness of alternate routes of vaccine delivery (e.g., intranasal, oral, intradermal needle-free administration, topical) in preclinical and clinical studies, to identify new mechanisms of immune protection, such as enhancement of mucosal immunity (Calzas 2019, Erbeling 2018).

**Strategic Goal 3.3:** Improve the ability to assess the impact of seasonal influenza vaccines on preventing severe disease to support the development of vaccines that protect against severe disease as a primary goal, which is particularly important in LMICs.

By 2022	<b>Milestone 3.3.a:</b> Develop standardized clinical end points for severe influenza disease that can be used in clinical vaccine efficacy studies (WHO 2017).
By 2022	<b>Milestone 3.3.b:</b> Develop and validate a standard scale for assessing influenza disease severity.
By 2025	<b>Milestone 3.3.c:</b> Develop and validate a correlate of protection for severe influenza disease that can be used in clinical studies as a surrogate end point (WHO 2017).
By 2025	<b>Milestone 3.3.d:</b> Based on outcomes of milestones 3.3.a, 3.3.b, and 3.3.c, develop a consensus approach on clinical trial methodologies for demonstrating vaccine effectiveness in preventing severe influenza disease in different geographical settings.



**Strategic Goal 3.4: Further assess the role of existing and new adjuvants in creating next-generation seasonal influenza vaccines, informed by recent R&D with adjuvants in new COVID-19 vaccines (Li 2021, Tregoning 2018, Zhu 2021).**

By 2025	<b>Milestone 3.4.a:</b> Determine the value of expanding the use of currently licensed adjuvants with current seasonal influenza vaccines (for dose-sparing and to lower costs).
By 2026	<b>Milestone 3.4.b (High Priority):</b> 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.
By 2026	<b>Milestone 3.4.c (High Priority):</b> 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.
By 2027	<b>Milestone 3.4.d:</b> Conduct head-to-head studies comparing the safety and efficacy of different adjuvants in different age-groups.

**Strategic Goal 3.5: Determine the role of NA as a vaccine antigen for improving the effectiveness and immunogenicity of seasonal influenza vaccines (Eichelberger 2019, Giurgea 2020, Krammer 2018b, Morens 2019). (Also see [Topic 2: Immunology and Immune Correlates of Protection](#).)**

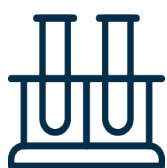
By 2022	<b>Milestone 3.5.a:</b> Generate standardized, harmonized, and validated assays for measuring NA content in seasonal influenza vaccines.
By 2023	<b>Milestone 3.5.b:</b> Measure and compare the antigenic variation of NA in seasonal influenza vaccines.
By 2024	<b>Milestone 3.5.c:</b> Investigate options for altering manufacturing processes to retain or add NA to inactivated or recombinant influenza vaccines, and establish methods to confirm, measure, and standardize NA content during development and manufacture.
By 2025	<b>Milestone 3.5.d (High Priority):</b> Determine if the presence of NA improves seasonal influenza vaccines, and, if so, establish the optimal dose of NA that improves immunogenicity and effectiveness.



## Additional R&D Priorities for Topic 3: Vaccinology for Seasonal Influenza Vaccines

- **Develop** stable cold chain-independent vaccine technologies suitable for stockpiling and deployment in low-resource settings.
- **Continue to develop and implement** methods for growing influenza viruses (particularly H3N2 strains) in eggs that reduce the likelihood of egg-adaptive mutations during production (Wu 2019).
- **Continue to conduct** clinical studies to enhance the use of existing seasonal influenza vaccines, including improvements in production, duration, and breadth of protection; safety and immunogenicity profiles; and dose-sparing formulations, especially for high-risk groups such as pregnant women, immunosuppressed patients, obese people, the very young, and the very old.
- **Determine** the optimal frequency of seasonal influenza vaccination, given both scientific and logistical constraints, and clarify if this is similar for LMICs and other countries.
- **Enhance understanding** of viral pathogenicity, host factors, and progression to severe disease, which may guide novel strategies for improved seasonal vaccines (Erbelding 2018, Mettelman 2020).
- **Develop** protocols to standardize the timing, specimen collection, and methods of data analysis used in large-scale studies of seasonal vaccine responses (Stacey 2018).
- **Continue to research** the role that certain genes play in disease severity for influenza, which has important implications for developing and evaluating new vaccine candidates.
- **Consider formalizing** a plan for prospective meta-analysis of vaccine effectiveness studies, with a focus on test-negative designs as a commonly used approach.
- **Replicate** the preliminary UK study of direct and indirect effects of LAIV in children under 12 years of age (Pebody 2018).
- **Conduct** vaccine probe studies to ascertain the contribution of influenza to particular clinical syndromes or the overall disease burden in children.
- **Promote development** of new vaccines that are stable at 4°C (39°F) or warmer for a considerable period so they can be used in low-resource settings.





## Topic 4: Vaccinology for Broadly Protective or Universal Influenza Vaccines

This section focuses on generating and assessing new constructs for broadly protective and durable influenza vaccines and ensuring that promising vaccine candidates move through the vaccine development pipeline.

### Issue: New constructs for broadly protective and durable influenza vaccines

#### Barriers

- There are many possible vaccine platforms and candidates for broadly protective or universal influenza vaccines, but resources for conducting clinical trials are limited, necessitating the selection of promising candidates for advanced trials (Epstein 2018, Madsen 2020).
- Inter-laboratory variability in assay techniques and determination of assay end points limit comparisons among measurements of immunogenicity of broadly protective or universal influenza vaccines in clinical trials (Reber 2013, Stacey 2018).
- The heterogeneity of HLA types within populations may complicate the development of new vaccine technologies involving T cell-directed approaches (Clemens 2018, Wen 2021).
- Global strategies for producing pandemic influenza vaccines and ancillary supplies to mitigate an emerging pandemic are based on



using the commercial seasonal influenza vaccine manufacturing infrastructure. In the absence of a truly universal influenza vaccine that is used globally to mitigate pandemic threats, development of broadly protective vaccines should, whenever possible, select manufacturing platforms that can be quickly adapted to respond to pandemics.

### Gaps

- Novel influenza vaccines based on mechanisms of protection other than neutralizing antibody may not prevent all infections (and allow some degree of transmission), but may decrease disease severity. Public health officials and regulators need to address the benefits of preventing severe disease versus reducing transmission of infection (Epstein 2018).
- Universal influenza vaccine constructs may need to include multiple antigenic targets to enable broadly protective and durable immunity against a wide range of influenza viruses (Jang 2020, Lopez 2020), including conserved antigens targeted by T cells, given clinical trial findings that broad T cell responses are associated with asymptomatic or mild disease.
- Other needs include:
  - ◇ Additional correlates of protection to assess novel influenza vaccine technologies (Madsen 2020). (Also see [Topic 2: Immunology and Immune Correlates of Protection.](#))
  - ◇ Guidance on the use of correlates of protection and clinical end points in assessing broadly protective or universal influenza vaccines at different stages of development.
  - ◇ New approaches for vaccine/immunogen design to achieve robust immune responses to conserved regions of the influenza virus (Kanekiyo 2019, Kanekiyo 2020, Krammer 2016, Nachbagauer 2018, Ross 2019, Yamayoshi 2019), which may require identifying successful strategies for overcoming the immunodominance of the HA globular head domain (Amitai 2020, De Jong 2020).
  - ◇ More clarity about potential safety issues, such as enhancement of infection or enhanced lung pathology, with next-generation influenza vaccines that do not protect against receptor binding (e.g., that elicit antibodies to stem immunogens).
  - ◇ Better understanding of the role of stem-specific antibodies in viral fitness and immune escape.
  - ◇ Mechanisms for evaluating and comparing data obtained from preclinical and clinical studies—including data from commercial entities—to refine and optimize platforms and strategies for durable, broadly protective or universal vaccines.
  - ◇ Research to better understand how influenza viruses will respond to new selective pressures created by broadly protective or universal influenza vaccines.
  - ◇ More research to evaluate the potential role of vaccine mechanisms other than those that achieve sterilizing immunity (e.g., induction of non-neutralizing antibodies and cell-mediated immunity) in promoting clinical outcomes such as cross-protection against future variant strains.
  - ◇ More research to assess the potential for T cell-based or non-neutralizing-antibody-based vaccines to exacerbate influenza immunopathology and allow considerable

influenza viral replication or promote vaccine-associated enhancement of respiratory disease (VAERD).

(Also see section on regulatory challenges for development of broadly protective or universal influenza vaccines in [Topic 6: Policy, Financing, and Regulation](#).)

## Strategic Goals and Aligned Milestones for Topic 4: 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 (Kanekiyo 2019, Krammer 2019b, Yamayoshi 2019).

By 2022	<b>Milestone 4.1.a:</b> Develop a set of preferred product characteristics (PPCs) for broadly protective and universal influenza vaccines, in collaboration with the WHO's efforts to revise its 2017 guidance on PPCs for next-generation influenza vaccines (WHO 2017).
By 2022	<b>Milestone 4.1.b:</b> Develop a summary analysis of influenza vaccine approaches for broadly protective or universal influenza vaccines, including intellectual property data, and create a mechanism to update this summary at least annually.
By 2022	<b>Milestone 4.1.c:</b> Develop a transparent process, such as an international consortium, for identifying the most promising influenza vaccine candidates that warrant further investigation (Epstein 2018).
By 2022	<b>Milestone 4.1.d (High Priority):</b> 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 developing broadly protective or universal influenza vaccines. (See similar milestone under Topic 3: Vaccinology for Seasonal Influenza Vaccines).
By 2024	<b>Milestone 4.1.e (High Priority):</b> 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 COVID-19 vaccine trials.

By 2022	<b>Milestone 4.2.a:</b> Develop use cases for broadly protective vaccines, defining how, where, and under what circumstances such vaccines would be used.
---------	---



By 2023	<b>Milestone 4.2.b:</b> Convene a workshop among government, industry, and academic influenza vaccine developers to review sector-specific needs for product development and identify gaps (e.g., in expertise and resources) that need to be addressed to facilitate early-stage development of universal influenza vaccine candidates.
By 2023	<b>Milestone 4.2.c:</b> Given the importance of age and preexisting partial immunity in vaccine-induced immune responses, develop strategies for evaluating universal influenza vaccine candidates in subjects by age and birth year to inform vaccine development and vaccination strategies.
By 2023	<b>Milestone 4.2.d:</b> Develop an approach for harmonizing clinical protocols (including defining clinical or immunologic end points) that deal with key issues, such as assessment of durability of broadly protective influenza vaccines over several years and assessment of broadly protective vaccines in special populations (e.g., pregnant women, young children, HIV-infected people). These efforts should focus on approaches that prioritize efficacy as a clinical trial end point as feasible.
By 2023	<b>Milestone 4.2.e (High Priority):</b> Develop consensus on streamlining clinical research for evaluating broadly protective influenza vaccines, drawing on COVID-19 vaccine experience.
By 2024	<b>Milestone 4.2.f (High Priority):</b> 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.
By 2024	<b>Milestone 4.2.g (High Priority):</b> Determine correlates of protection for assessing broadly protective or universal influenza vaccines that are appropriate for different stages of vaccine development.
By 2025	<b>Milestone 4.2.h (High Priority):</b> 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.
By 2027	<b>Milestone 4.2.i (High Priority):</b> 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.



## Additional R&D Priorities for Topic 4: Vaccinology for Broadly Protective or Universal Influenza Vaccines

- **Continue to research** novel mechanisms, antigens, and platforms to develop new influenza vaccine candidates.
- **Expand options** for multidisciplinary research for influenza vaccine R&D, including collaboration with computational biologists and veterinary researchers.
- **Investigate** how influenza viruses will respond to new selective pressures created by broadly protective influenza vaccines, particularly as promising candidates advance to clinical trials.
- **Conduct** ongoing research to evaluate the potential role of vaccine mechanisms other than those that achieve sterilizing immunity to promote clinical outcomes, such as cross-protection against variant influenza virus strains.
- **Explore** the potential for combination antigen vaccines to achieve broad immunologic protection (Epstein 2018, Estrada 2019).
- **Continue to monitor and track** universal influenza vaccine candidates in clinical and preclinical development, including technologies such as existing and novel adjuvants and alternative delivery methods such as oral formulations and microneedle patches (Ostrowsky 2020).



## Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model (CHIVIM)

This section addresses strategies for optimizing animal models for use in influenza vaccine research and for refining the CHIVIM to maximize its effectiveness.

### Issue: Optimization of animal models used for influenza vaccine R&D

#### Barriers

- The use of animal models that accurately reflect disease and immune responses in humans is an important element of influenza vaccine R&D (D'Alessio 2018, Lane 2020). A number of animal models exist for studying influenza, such as mice, ferrets, guinea pigs, rats, hamsters, swine, and nonhuman primates (NHPs). While these animals can provide extremely valuable information, they also have important limitations.
- NHPs may be useful for studying specific aspects of vaccine protection, but ethical considerations and cost constrain their use.
- Duration of protection is difficult to study in animals, particularly if protection is due to broadly protective antibodies or other immune mechanisms.

For example, influenza disease in certain animal models does not accurately mimic influenza disease in humans. Also, important immunologic differences exist between humans and certain animals (Bouvier 2010, D'Alessio 2018, Lane 2020).



- Because influenza viruses are constantly changing and evolving, up-to-date and representative viral stocks must be readily available for influenza vaccine research in animal models.
- Humans have pre-existing immunity to influenza viruses, which can be difficult to mimic in animals, so pre-exposure animal models are needed to address this issue, but they are expensive to maintain and reinfection can be challenging (D'Alessio 2018).
- Different vaccine platforms may require evaluation in different animal models, which adds complexity to determining preclinical vaccine research approaches (Lane 2020).
- Head-to-head studies with multiple vaccine candidates could help to better understand vaccine-induced immunity, but securing needed study materials can be challenging.
- ◇ Additional research to optimize animal models for examining: (1) specific issues such as cell-mediated immunity and enhanced respiratory disease; (2) novel vaccine platforms for broadly protective or universal vaccines; and (3) additional factors that may be important for experimental vaccine design, such as tissue tropism and patterns of receptor distribution (D'Alessio 2018, Margine 2014).
- ◇ Further refinement of animal models to mimic different human conditions such as underlying morbidities, advanced age, immunocompromised status, and pregnancy.
- ◇ Efforts to ensure ongoing back-translation of data from humans to animal models.
- ◇ More data on the role of the microbiome in animal research for influenza vaccines.
- ◇ Efforts to characterize the MHC epitopes in animal models, particularly ferrets, to better allow assessment of T cell-based vaccines.

## Gaps

- Needs related to animal models include:
  - ◇ Standardized and harmonized animal models to evaluate and compare vaccine-related research studies. Parameters to consider include the challenge virus strain, dose, route, and volume; the animal test species and appropriate clinical end point for that species; and the specific pathogen-free status of animals under study (D'Alessio 2018).
  - ◇ Ongoing efforts to ensure that validated, reliable reagents, updated viral strains and stocks, and harmonized assays are available to the research community to improve understanding of the innate and adaptive immune responses in ferrets and other small mammals, such as hamsters and guinea pigs (Albrecht 2018).
  - ◇ Efforts to advance emerging technologies to reduce reliance on animal models.
  - ◇ Better understanding of protection-relevant antibody subclasses and how they compare between animals and humans.

## Issue: Development and refinement of the CHIVIM

### Barriers

- Human infection studies are limited to healthy adults without comorbidities and thus do not reflect potential outcomes in special populations (Sherman 2019).



- These studies can assess only mild disease and viral shedding but not severe disease (Sherman 2019).
- Human infection studies may not necessarily mimic community-acquired infections because of artificialities in the model (i.e., studies are conducted under controlled situations) (Innis 2019a).
- Human infection studies have limited statistical power because of relatively few subjects.
- Ethical and safety concerns have constrained the use of such studies (Sherman 2019).
- Challenge viruses must be updated frequently, which can be expensive and time consuming, since people can become immune to such viruses through exposure to seasonal influenza viruses in the community.
- Current models do not use novel or non-seasonal influenza strains, owing to safety considerations. It may be possible to reassess this approach.
- Longer-term human infection studies that may be needed for examining long-term immunity are more difficult to fund and require longer-term retention of participants.

## Gaps

- Key issues regarding the CHIVIM need to be addressed, such as lack of standardization for certain elements of the model; limited access to challenge viruses; lack of harmonized protocols; better definition of end points, particularly for determining mucosal immunity; the need for agreed-upon criteria for selection of challenge strains; regulatory challenges; environmental

considerations such as heating, ventilation, and air conditioning (HVAC); concerns about dual use for published sequences; and concerns regarding risk to study participants and the community (Innis 2019a). It is also important to capture and standardize metadata to enable cross-study analysis and to address a greater diversity of research questions.

- Other needs include:
  - ◇ Efforts to include subjects of diverse age ranges and past experience with influenza to better study impacts of immunity induced by vaccine and natural infection.
  - ◇ Resources to expand human infection studies to additional research sites to ensure greater global diversity in the research (Erbelding 2018).
  - ◇ Steps to tie research in CHIVIM studies to research in animal models and vice versa.
  - ◇ Human challenge models that assess breadth of protection for broadly protective vaccines.
  - ◇ Further research to explore how best to apply systems biology approaches to influenza vaccine studies involving human infection models (Sherman 2019).



## Strategic Goals and Aligned Milestones for Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model

### Strategic Goal 5.1: Optimize animal models for influenza vaccine research.

By 2022	<b>Milestone 5.1.a:</b> Develop a strategic plan for standardizing and harmonizing current animal models for influenza vaccine research, which is particularly important for head-to-head comparisons of vaccines and other products (D'Alessio 2018).
By 2022	<b>Milestone 5.1.b (High Priority):</b> 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 comparison of studies across laboratories.
By 2022	<b>Milestone 5.1.c:</b> Develop best practices for conducting influenza virus transmission studies in ferrets, to include naive and infected or vaccinated animals (Belser 2018, Neumann 2019). (Also see <a href="#">Topic 1: Virology Applicable to Vaccine Development</a> .)
By 2023	<b>Milestone 5.1.d (High Priority):</b> Convene a workshop on the development of pre-exposure animal models to address the fact that humans generally have pre-existing immunity to influenza (D'Alessio 2018).
By 2025	<b>Milestone 5.1.e:</b> Define the ferret model for studying vaccine responses that mimic different types of human populations (e.g., children [using naive animals], pregnant women, people with morbidities such as obesity and diabetes, the elderly).
By 2025	<b>Milestone 5.1.f (High Priority):</b> 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).
By 2026	<b>Milestone 5.1.g (High Priority):</b> Develop and validate novel animal models, as needed, for evaluating immune responses—including durability—to broadly protective influenza vaccines (D'Alessio 2018).
By 2026	<b>Milestone 5.1.h:</b> Characterize the MHC epitopes in the ferret model to better allow assessment of T cell–based vaccines.





## Strategic Goal 5.2: Address steps needed to further develop and refine the CHIVIM (Innis 2019a, Innis 2019b).

By 2022	<b>Milestone 5.2.a (High Priority):</b> Determine the use cases for the CHIVIM and generate guidance, including ethical and safety considerations, for using the model.
By 2023	<b>Milestone 5.2.b (High Priority):</b> Ensure that reagents for the CHIVIM are broadly available.
By 2023	<b>Milestone 5.2.c (High Priority):</b> Ensure that a biorepository of diverse, accessible, and well-characterized challenge stocks is generated and made available to investigators.
By 2024	<b>Milestone 5.2.d (High Priority):</b> Further develop the CHIVIM to ensure that it can be widely used by different investigators.
By 2024	<b>Milestone 5.2.e:</b> Develop standardized protocols to allow CHIVIM vaccine studies to run concurrently across multiple centers with appropriate sharing of data and information to maximize benefit.

## Additional R&D Priorities for Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model

- **Determine** additional factors that may be important considerations for preclinical research, such as tissue tropism and patterns of receptor distribution (D'Alessio 2018, Margine 2014).
- **Identify** appropriate animal models for studying specific research topics, such as virus transmission, cell-mediated immunity, and enhanced disease (D'Alessio 2018, Margine 2014).
- **Continue to assess animal models to ensure** genotypic and phenotypic diversity to better mimic human conditions.
- **Conduct** further research to determine the role of NHP models for influenza vaccine R&D (Davis 2015).
- **Conduct** further research on the role of the microbiome in animals for influenza vaccine R&D.
- **Explore** ways to leverage emerging technologies to reduce reliance on animal models.
- **Ensure** that veterinary specialists who are certified in laboratory animal medicine are included in research and strategic discussions involving the development of new animal models.
- **Ensure** ongoing availability of appropriate and standardized influenza viruses for animal model research and for the CHIVIM, using current and representative viruses.
- **Develop** ongoing mechanisms to ensure back-translation of research findings from humans



to animal models, in both CHIVIM studies and clinical studies.

- **Explore** development of human infection models that use novel viruses to better assess breadth of protection for broadly protective influenza vaccines.
- **Encourage** collaboration between groups developing viruses for human infection models and those developing the models.
- **Continue to develop** ways to integrate systems biology approaches with human infection studies to promote understanding of influenza pathogenesis and immunology (Sherman 2019).



## Topic 6: Policy, Financing, and Regulation

This section addresses strategies for enhancing influenza vaccine investment, promoting innovation in influenza vaccine R&D, improving coordination of research and information sharing, and addressing regulatory challenges for assessing broadly protective or universal influenza vaccines.

### Issue: Influenza vaccine investment strategies

#### Barriers

- Substantial financial risks and inadequate incentives create significant barriers to bringing new broadly protective influenza vaccines to market (Osterholm 2012).
- Definitive human efficacy data from large comparative trials are needed to determine noninferiority or superiority of next-generation influenza vaccines; such trials are difficult to conduct because of high costs and organizational barriers.
- Bringing vaccines to market requires crossing what is referred to as the “valley of death” for vaccine development. This period encompasses early clinical trials through phase 3 clinical trials to the point of regulatory approval and early commercialization. During this time, substantial research, development, and licensure costs are incurred while outcomes are uncertain and no revenue is generated (Osterholm 2012). A root cause of the “valley of death” for new vaccines is that an asymmetry of risk exists, as manufacturers take on most of the risks but the public sector does not balance the risk with commitments and funding.
- Transformative changes in influenza vaccines will require changing the basic manufacturing



infrastructure—currently dominated by a few large companies—that drives influenza vaccine production in the private sector, which is currently based on the assurance of an ongoing annual seasonal vaccine market (Osterholm 2012).

- Development and deployment of improved influenza vaccines are occurring within the context of an existing standard of care in high-income countries (e.g., 30% to 40% of the US population is immunized against influenza annually) and lack of access to influenza vaccines in areas of the world, including those with a high burden of influenza.

### Gaps

- A coordinated commitment to sustained (i.e., 10 years) funding of R&D for universal influenza vaccines is lacking, leaving the world vulnerable to the next influenza pandemic (Hayes 2020). Efforts are needed to consider the feasibility of a “mission-driven” approach to R&D for universal influenza vaccines through a new public-private partnership, akin to COVID-19 vaccine development (Sabin 2021). Plans are also needed for ongoing funding of basic science research into influenza virology and immunology.
- Leveraging public investment to share the risk with vaccine developers will be critical for implementing clinical trials, completing advanced development, and manufacturing of all meritorious universal influenza vaccine candidates.
- The predominant commercial model for global influenza vaccine production is based on annual reformulation of influenza vaccines and on reliance of egg-based technology for production, and the companies that profit from this model may resist change. To overcome this, innovative strategies need to be considered for financing

development of new influenza vaccines. Such strategies should also address the interests and financial constraints of LMICs (Sabin 2019).

- Additional efforts are needed to articulate for policy makers and funders the global value of developing improved influenza vaccines and the risk of not doing so (Bartsch 2020, Bloom 2018, Global Funders Consortium 2018). These efforts should consider issues such as which types of vaccines are most suitable to which populations and the different use cases for vaccines.
- A coordinated communication strategy must advocate for the need to improve influenza vaccines and to stimulate investment in innovative R&D strategies. One issue is that influenza is often seen as nothing more than a mild illness, and key messages need to balance the threat of annual influenza epidemics with the danger of pandemic influenza.
- A comprehensive picture that details influenza vaccine funding trends is not available, which creates challenges in identifying research gaps and ensuring coordination of funding (Global Funders Consortium 2017).
- A number of influenza vaccine technologies are under development, and efforts to track their progress are under way (Ostrowsky 2020). Additional efforts, however, must analyze the vaccine landscape and identify the paths that vaccine developers in industry, academia, and government laboratories can take—as well as to identify the potential pitfalls—to stimulate and maintain productive vaccine R&D.
- The COVID-19 pandemic can help reframe expectations regarding the global impact of a pandemic respiratory virus and the value of vaccines in preventing the potentially devastating effects. A value proposition for influenza vaccines



should capitalize on the importance of pandemic preparedness, which may stimulate the necessary support.

- Efforts are needed to enlist scientists who are not currently focused on influenza to enhance innovation and generate multiple pathways toward creating improved influenza vaccines (Sabin 2019), including potential synergies with COVID-19 vaccine R&D that involve similar vaccine technologies and manufacturing processes. Scientists in other relevant fields, such as mucosal immunology and experimental animal challenge, and those who work with non-influenza respiratory viruses should be engaged to provide “out of the box” thinking.

establishes a global system for sharing viruses with pandemic potential and ensuring access to vaccines and antivirals during a pandemic (WHO 2011), the GISRS and GISAID have successfully fostered international sharing of influenza virus isolates and gene sequences for years. However, restrictions on the use of influenza viruses could result under certain provisions of the Nagoya Protocol (United Nations Environmental Programme, Secretariat of the Convention on Biological Diversity 2011).

### Gaps

- Developing innovative vaccine approaches will require substantial additional investments in R&D and vaccine production infrastructure, particularly to overcome challenges encountered during the “valley of death” period. Coordinated partnerships involving national governments, the pharmaceutical industry, philanthropic organizations, and academia will be critical to advance such vaccines through clinical trials and licensure (Bresee 2019, Osterholm 2012).
- Improved coordination is needed to maximize the value of influenza vaccine research, such as exploring options for reuse of influenza vaccine study data.
- The need for developing, adopting, and establishing data standards for certain research areas and identifying public data repositories for housing and sharing data should be further assessed.
- The impact, if any, of the Nagoya Protocol on influenza vaccines R&D should be assessed on an ongoing basis, including the impact of national Access and Benefit Sharing (ABS) legislation.

## Issue: Enhanced coordination and information sharing

### Barriers

- Influenza vaccine R&D efforts to date, while substantial, have been relatively fragmented, with a lack of coordinated effort and shared vision among a diverse range of stakeholders (Sabin 2019).
- The lack of adequate data management and sharing among academic, industry, and government developers inhibits influenza vaccine development.
- Challenges with mapping and potentially sharing of intellectual property and proprietary technologies is a barrier to combining approaches that could better address the public health need for improved influenza vaccines.
- Under the WHO Pandemic Influenza Preparedness (PIP) Framework, which





## Issue: Regulatory challenges for development of broadly protective or universal influenza vaccines

### Barriers

- Issues around licensure of broadly protective or universal influenza vaccines are complex and will require development of new 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, protection against severe vs. mild disease, or practical approaches vs. the most efficacious approaches—may require different clinical trial designs, which poses additional challenges for clinical evaluation.
- While the general licensing approach is the same for all vaccines, specific regulatory issues for any new influenza vaccine will depend on the particular construct of the vaccine and will be unique to that situation; therefore, it is not possible to create a “one size fits all” regulatory pathway for next-generation influenza vaccines.
- New influenza vaccines may involve approaches for which safety is poorly characterized—such as use of new antigens, new delivery systems, or novel platform technologies—necessitating careful safety assessments throughout the R&D process.

### Gaps

- Needs in this area include:
  - ◇ Further clarification regarding what the regulatory requirements will be for licensure of new influenza vaccines that do not rely

on current standards (e.g., the HAI assay). Currently, there is no regulatory pathway for approval and deployment of universal influenza vaccines. Examples of key issues that need resolution include requirements for demonstrating efficacy (e.g., against future pandemic viruses), defining criteria for “universal” vaccines, identifying requirements for post-marketing studies, and determining a mechanistic correlate of protection.

- ◇ Regulatory guidance to clarify how data from human infection studies can be used to support licensure of next-generation influenza vaccines (Innis 2019a).
- ◇ A better understanding of the correlates of protection for new influenza vaccines, how they can be measured, and how they will be used for licensure. (Also see [Topic 2: Immunology and Correlates of Protection](#).)
- ◇ Enhanced manufacturing capabilities, new methods of vaccine characterization, and regulatory issues related to these processes need to be identified and addressed.
- ◇ Improved infrastructure for post-licensure monitoring of new influenza vaccines, particularly if they are licensed under alternative regulatory pathways.
- ◇ Further guidance from regulatory authorities to establish robust measures of vaccine effectiveness that would enable comparisons among vaccines or combinations of vaccines.





## Strategic Goals and Aligned Milestones for Topic 6: Policy, Financing, 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.

By 2022	<b>Milestone 6.1.a (High Priority):</b> 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 (NASEM 2019).
By 2022	<b>Milestone 6.1.b (High Priority):</b> Develop targeted and creative communications and advocacy strategies and necessary communication tools that build on the FVVA and provide information on economic costs, the risk of future influenza pandemics, and the need for investment in influenza vaccine R&D (Navarro-Torné 2019, Sabin 2019).
By 2023	<b>Milestone 6.1.c:</b> Create and implement a mechanism to track influenza vaccine R&D funding trends to better assess where funding is being allocated and identify gaps in funding for priority research. (This may be similar to efforts for tuberculosis R&D funding [Treatment Action Group 2018].)
By 2023	<b>Milestone 6.1.d:</b> Explore the feasibility of creating a new public-private enterprise with robust and durable (i.e., 5 to 10 years) funding, aimed at “mission-driven” R&D for universal influenza vaccines, similar to efforts for development of vaccines against COVID-19, such as the US Operation Warp Speed or the WHO ACT Accelerator.

### Strategic Goal 6.2: Promote innovation for developing improved seasonal influenza vaccines and broadly protective or universal influenza vaccines.

By 2022	<b>Milestone 6.2.a (High Priority):</b> Distill lessons learned for influenza vaccines from experience with COVID-19 vaccine R&D, including clinical research and study designs, manufacturing, distribution, advocacy, financing, and global collaboration (Sabin 2021).
By 2023	<b>Milestone 6.2.b (High Priority):</b> Identify a set of strategies for accelerating the development of universal influenza vaccines through innovative approaches (Sabin 2019).



By 2023	<b>Milestone 6.2.c:</b> Develop an approach for working with industry partners that examines market challenges and evaluates potential solutions, including market incentives to help de-risk vaccine R&D and develop a market share for producing improved or universal influenza vaccines (Global Funders Consortium 2017).
By 2023	<b>Milestone 6.2.d:</b> Create a summary of critical evidence, as a basis for policy recommendations, relevant to the design of clinical trials for universal or broadly protective influenza vaccines and their outcomes, similar to the “evidence to recommendation” framework created by the WHO SAGE on Immunizations Working Group on COVID-19 Vaccines (WHO SAGE on Immunizations 2020).
By 2024	<b>Milestone 6.2.e:</b> Develop a global strategy that addresses health equity issues, encompasses the interests of LMICs—including the need for improved seasonal influenza vaccines—and is aimed at supporting country transitions from annual vaccination programs to use of more durable, broadly protective or universal vaccines.

### Strategic Goal 6.3: Promote information sharing aimed at moving influenza vaccine development forward.

By 2021	<b>Milestone 6.3.a:</b> Create a comprehensive landscape of universal influenza vaccine technologies in preclinical and clinical development and develop a mechanism to update and analyze the landscape, including identifying key factors underlying successful R&D efforts as well as persistent challenges and obstacles (Global Funders Consortium 2018).
By 2022	<b>Milestone 6.3.b:</b> Develop and implement an approach to reuse influenza vaccine study data (e.g., secondary mining of data sets) that may enhance influenza vaccine R&D (Erbelding 2018).
By 2022	<b>Milestone 6.3.c (High Priority):</b> 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.
By 2022	<b>Milestone 6.3.d:</b> Implement a plan that improves existing data management and sharing among influenza R&D researchers (Erbelding 2018).
By 2022	<b>Milestone 6.3.e:</b> Conduct mapping of intellectual property for improved influenza vaccines to identify synergies in approaches that may be used to develop new partnerships.



By 2023	<b>Milestone 6.3.f:</b> Develop a consensus vision for sharing intellectual property or proprietary technologies related to improved influenza vaccines that includes benefit sharing and equitable access for LMICs.
By 2023	<b>Milestone 6.3.g:</b> Convene a group of key R&D stakeholders to assess the need to develop and establish a set of harmonized data standards and explore mechanisms for broader data sharing.
<b>Strategic Goal 6.4: Further explore regulatory challenges associated with development and manufacturing of improved seasonal and broadly protective or universal influenza vaccines (Navarro-Torné 2019).</b>	
By 2022	<b>Milestone 6.4.a (High Priority):</b> 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.
By 2023	<b>Milestone 6.4.b (High Priority):</b> Identify a framework to address post-marketing assessment of safety and effectiveness of new broadly protective or universal influenza vaccines.
By 2024	<b>Milestone 6.4.c:</b> Develop consensus on best practices for using CHIVIM studies in supporting licensure of new influenza vaccine products (Bresee 2019, Erbeling 2018, Innis 2019a).
By 2025	<b>Milestone 6.4.d:</b> Identify regulatory challenges associated with developing influenza vaccines that prevent severe disease but do not necessarily prevent infection (Berlanda Scorza 2016), such as defining clinical end points.



## Additional R&D Priorities for Topic 6: Policy, Financing, and Regulation

- **Ensure** ongoing and substantial funding for basic science research into influenza virology, immunology, and vaccine R&D.
- **Explore** strategies for improving efficiencies of phase 3 clinical trials for universal influenza vaccines, such as harmonizing protocols on issues such as common end points and common validated assays, to allow data to either be combined or compared effectively.
- **Continue to promote** ongoing communications among international regulators regarding the development of universal influenza vaccines, including exploration of regulatory harmonization.



# References

Agor JK, Ozaltin OY. Models for predicting the evolution of influenza to inform vaccine strain selection. *Hum Vaccin Immunother* 2018 Mar 4;14(3):678-83 [[Full text](#)]

Albrecht RA, Liu WC, Sant AJ, et al. Moving forward: recent developments for the ferret biomedical research model. *mBio* 2018 Jul 17;9(4):e01113-8 [[Full text](#)]

Ali ST, Cowling BJ. Influenza virus: tracking, predicting, and forecasting. *Annu Rev Public Health* 2021 Apr 1;42:43-57 [[Full text](#)]

Allen EK, Randolph AG, T. Bhangale T, et al. SNP-mediated disruption of CTCF binding at the IFITM3 promoter is associated with risk of severe influenza in humans. *Nat Med* 2017;23:975-83 [[Full text](#)]

Allen JD, Ross TM. H3N2 influenza viruses in humans: viral mechanisms, evolution, and evaluation. *Hum Vaccin Immunother* 2018;14(8):1840-7 [[Full text](#)]

Amitai A, Sangesland M, Barnes RM, et al. Defining and manipulating B cell immunodominance hierarchies to elicit broadly neutralizing antibody responses against influenza virus. *Cell Syst* 2020 Dec 16;11(6):573-88.e9 [[Full text](#)]

Anchi W, Mihaylova VT, Landry MI, et al. Interference between rhinovirus and influenza A virus: a clinical data analysis and experimental infection study. *Lancet Microbe* 2020 Oct;1(6):e254-62 [[Full text](#)]

Angeletti D, Kosik I, Santos JJS, et al. Outflanking immunodominance to target subdominant broadly neutralizing epitopes. *Proc Natl Acad Sci USA* 2019 Jul 2;116(27):13474-9 [[Full text](#)]

Angeletti D, Yewdell JW. Is it possible to develop a “universal” influenza virus vaccine? Outflanking antibody immunodominance on the road to universal influenza vaccination. *Cold Spring Harb Perspect Biol* 2018 Jul 2;10(7):a028852 [[Full text](#)]

Arevalo CP, Le Sage V, Bolton MJ, et al. Original antigenic sin priming of influenza virus hemagglutinin stalk antibodies. *Proc Natl Acad Sci USA* 2020 Jul 21;117(29):17221-7 [[Full text](#)]

Bahl K, Senn JJ, Yuzhakov O, et al. Preclinical and clinical demonstration of immunogenicity by mRNA vaccines against H10N8 and H7N9 influenza viruses. *Mol Ther* 2017 Jun 7;25(6):1316-27 [[Full text](#)]

Bajic G, Maron MJ, Adachi Y, et al. Influenza antigen engineering focuses immune responses to a subdominant but broadly protective viral epitope. *Cell Host Microbe* 2019 Jun 12;25(6):827-835.e6. [[Full text](#)]

Barr IG, Donis RO, Katz JM, et al. Cell culture-derived influenza vaccines in the severe 2017-2018 epidemic season: a step towards improved influenza vaccine effectiveness. *NPJ Vaccines* 2018 Oct 9;3:44 [[Full text](#)]

Bartley JM, Cadar AN, Martin DE. Better, faster, stronger: mRNA vaccines show promise for influenza vaccination in older adults. *Immunol Invest* 2021 Apr 8:1-11 [[Abstract](#)]

Bartoszek J, Loeb M. The burden of influenza in older adults: meeting the challenge. *Aging Clin Exp Res* 2021 Mar;33(3):711-7 [[Full text](#)]

Bartsch SM, Mitgang EA, Geller G, et al. What if the influenza vaccine did not offer such variable protection? *J Infect Dis* 2020 Sep 1;222(7):1138-44 [[Full text](#)]

Baselga-Moreno V, Trushakova S, McNeil S, et al. Influenza epidemiology and influenza vaccine effectiveness during the 2016–2017 season in the Global Influenza Hospital Surveillance Network (GIHSN). *BMC Public Health* 2019 May 2;19(1):487 [[Full text](#)]

Belongia EA, Skowronski DM, McLean HQ, et al. Repeated annual influenza vaccination and vaccine effectiveness: review of evidence. *Expert Rev Vaccines* 2017 Jul;16(7):1-14 [[Full text](#)]



- Belser JA, Barclay W, Barr I, et al. Ferrets as models for influenza virus transmission studies and pandemic risk assessments. *Emerg Infect Dis* 2018 Jun;24(6):965-71 [[Full text](#)]
- Berlanda Scorza F, Tsvetnitsky V, Donnelly JJ. Universal influenza vaccines: shifting to better vaccines. *Vaccine* 2016 Jun 3;34(26):2926-33 [[Abstract](#)]
- Bill & Melinda Gates Foundation (BMGF). Ending the pandemic threat: a grand challenge for universal influenza vaccine development. 2018a [[Web page](#)]
- BMGF. Target product profile for universal Influenza vaccines. 2018b [[Full text](#)]
- Bloom DE, Fan VY, Sevilla JP. The broad socioeconomic benefits of vaccination. *Sci Transl Med* 2018 May 16;10(441):eaaj2345 [[Abstract](#)]
- Boudreau CM, Alter G. Extra-neutralizing FcR-mediated antibody functions for a universal influenza vaccine. *Front Immunol* 2019 Mar 18;10:440 [[Full text](#)]
- Bouvier NM. The future of influenza vaccines: a historical and clinical perspective. *Vaccines (Basel)* 2018 Aug 30;6(3):58 [[Full text](#)]
- Bouvier NM, Lowen AC. Animal models for influenza virus pathogenesis and transmission. *Viruses* 2010;2(8):1530-63 [[Full text](#)]
- Bresee JS, McKinlay MA, Abramson J, et al. Global Funders Consortium for Universal Influenza Vaccine Development (Commentary). *Vaccine* 2019 Jan 7;37(2):211-3 [[Abstract](#)]
- Calzas C, Chevalier C. Innovative mucosal vaccine formulations against influenza A virus infections. *Front Immunol* 2019 Jul 17;10:1605 [[Full text](#)]
- Castrucci MR. Factors affecting immune responses to the influenza vaccine. *Hum Vaccin Immunother* 2018 Mar 4;14(3):637-46 [[Full text](#)]
- CDC. H5N1 Genetic Changes Inventory: A Tool for International Surveillance. March 18, 2015 [[Webpage](#)]
- CDC. Past seasons vaccine effectiveness estimates. Adjusted vaccine effectiveness estimates for influenza seasons from 2004-2018; Updated Jan 29, 2020 [[Webpage](#)]
- Chen YQ, Wohlbold TJ, Zheng NY, et al. Influenza infection in humans induces broadly cross-reactive and protective neuraminidase-reactive antibodies. *Cell* 2018 Apr 5;173(2):417-29.e10 [[Full text](#)]
- Chung JR, Rolfes MA, Flannery B, et al. Effects of influenza vaccination in the United States during the 2018-2019 influenza season. *Clin Infect Dis* 2020 Nov 5;71(8):e368-76 [[Full draft](#)]
- Clemens EB, van de Sandt C, Wong SS, et al. Harnessing the power of T cells: the promising hope for a universal influenza vaccine. *Vaccines (Basel)* 2018 Mar 26;6(2):18 [[Full text](#)]
- Cobey S, Hensley SE. Immune history and influenza virus susceptibility. *Curr Opin Virol* 2017 Feb;22:105-11 [[Abstract](#)]
- Cortese M, Sherman AC, Rouphael NG, et al. Systems biological analysis of immune response to influenza vaccination. *Cold Spring Harb Perspect Med* 2020 Mar 9:a038596 [[Full text](#)]
- Coughlan L, Palese P. Overcoming barriers in the path to a universal influenza virus vaccine. *Cell Host Microbe* 2018 Jul 11;24(1):18-24 [[Full text](#)]
- Crank MC, Mascola JR, Graham BS. Preparing for the next influenza pandemic: the development of a universal influenza vaccine. *J Infect Dis* 2019 Apr 8;219(suppl1):S107-9 [[Full text](#)]
- Crowe JE. Antibody determinants of influenza immunity. *J Infect Dis* 2019 Apr 8;219(suppl1):S21-9 [[Full text](#)]
- Dadonaite B, Gilbertson B, Knight ML, et al. The structure of the influenza A virus genome. *Nat Microbiol* 2019 Nov;4(11):1781-9 [[Full text](#)]
- D'Alessio F, Koopman G, Houard S, et al. Workshop report: experimental animal models for universal influenza vaccines. *Vaccine* 2018 Nov 12;36(46):6895-901 [[Abstract](#)]
- Davis AS, Taubenberger JK, Bray M. The use of nonhuman primates in research on seasonal, pandemic and avian influenza, 1893–2014. *Antiviral Res* 2015 May;117:75-98 [[Full text](#)]





Davis CW, Jackson KJL, McCausland MM, et al. Influenza vaccine-induced human bone marrow plasma cells decline within a year after vaccination. *Science* 2020 Oct 9;370(6513):237-41 [[Full text](#)]

De Jong NMC, Aartse A, Van Gils MJ, et al. Development of broadly reactive influenza vaccines by targeting the conserved regions of the hemagglutinin stem and head domains. *Expert Rev Vaccines* 2020 Jun;19(6):563-77 [[Full text](#)]

de Silva TI, Gould V, Mohammed NI, et al. Comparison of mucosal lining fluid sampling methods and influenza-specific IgA detection assays for use in human studies of influenza immunity. *J Immunol Methods* 2017 Oct;449:1-6 [[Abstract](#)]

Dhakal S, Klein SL. Host factors impact vaccine efficacy: implications for seasonal and universal influenza vaccine programs. *J Virol* 2019 Oct;93(21):e00797-819 [[Full text](#)]

Dugan HL, Guthmiller JJ, Arevalo P, et al. Preexisting immunity shapes distinct antibody landscapes after influenza virus infection and vaccination in humans. *Sci Transl Med* 2020 Dec 9;12(573):eabd3601 [[Abstract](#)]

European External Action Service (EEAS). EU-India joint call “towards a next generation influenza vaccine to protect citizens worldwide.” Brussels: European Union. Aug 1, 2018 [[Full text](#)]

Eichelberger MC, Monto AS. Neuraminidase, the forgotten surface antigen, emerges as an influenza vaccine target for broadened protection. *J Infect Dis* 2019 Apr 8;219(suppl1):S75-80 [[Full text](#)]

Eichelberger MC, Morens DM, Taubenberger JK. Neuraminidase as an influenza vaccine antigen: a low hanging fruit, ready for picking to improve vaccine effectiveness. *Curr Opin Immunol* 2018 Aug;53:38-44 [[Abstract](#)]

Epstein SL. Universal influenza vaccines: progress in achieving broad cross-protection in vivo. *Am J Epidemiol* 2018 Dec 1;187(12):2603-14 [[Full text](#)]

Erbelding EJ, Post DJ, Stemmy EJ, et al. A universal influenza vaccine: the strategic plan for the National Institute of Allergy and Infectious Diseases. *J Infect Dis* 2018 Jul 2;218(3):347-54 [[Full text](#)]

Estrada LD, Schultz-Cherry S. Development of a universal influenza vaccine. *J Immunol* 2019 Jan 15; 202:392-8 [[Abstract](#)]

Feldman RA, Fuhr R, Smolenov I, et al. mRNA vaccines against H10N8 and H7N9 influenza viruses of pandemic potential are immunogenic and well tolerated in healthy adults in phase 1 randomized clinical trials. *Vaccine* 2019 May 31;37(25):3326-34 [[Full text](#)]

Flannery B, Chung JR, Monto AS, et al. Influenza vaccine effectiveness in the United States during the 2016–2017 season. *Clin Infect Dis* 2019 May 17;68(11):1798-1806 [[Full text](#)]

FLUCOP. Standardization and Development of Assays for Assessment of Influenza Vaccines Correlates of Protection (FLUCOP) [[Website](#)]

Francis ME, King ML, Kelvin AA. Back to the future for influenza preimmunity—looking back at influenza virus history to infer the outcome of future infections. *Viruses* 2019 Jan 30;11(2):122 [[Full text](#)]

Giancchetti E, Torelli A, Montomoli E. The use of cell-mediated immunity for the evaluation of influenza vaccines: an upcoming necessity. *Hum Vaccines Immunother* 2019;15(5):1021-30 [[Full text](#)]

Giurgea LT, Morens DM, Taubenberger JK, et al. Influenza neuraminidase: a neglected protein and its potential for a better influenza vaccine. *Vaccines (Basel)* 2020 Jul 23;8(3):409 [[Full text](#)]

Global Funders Consortium for Universal Influenza Vaccine Development. 2nd Annual Meeting Report, Nov 7-8, 2018. Atlanta, GA: The Task Force for Global Health [[Full text](#)]

Global Funders Consortium for Universal Influenza Vaccine Development. Shaping a path forward. Meeting Report, Nov 2-3, 2017. Atlanta, GA: The Task Force for Global Health [[Full text](#)]

Gostic KM, Bridge R, Brady S, et al. Childhood immune imprinting to influenza A shapes birth year-specific risk during seasonal H1N1 and H3N2 epidemics. *PLOS Pathog* 2019 Dec 19;15(12):e1008109 [[Full text](#)]



Gouma S, Anderson EM, Hensley SE. Challenges of making effective influenza vaccines. *Annu Rev Virol* 2020a Sep 29;7(1):495-512 [[Full text](#)]

Gouma S, Weirick M, Hensley SE. Antigenic assessment of the H3N2 component of the 2019-2020 Northern Hemisphere influenza vaccine. *Nat Commun* 2020b May 15;11(1):2445 [[Full text](#)]

Guthmiller JJ, Wilson PC. Harnessing immune history to combat influenza viruses. *Curr Opin Immunol* 2018 Aug;53:187-95 [[Abstract](#)]

Harding AT, Heaton NS. Efforts to improve the seasonal influenza vaccine. *Vaccines (Basel)* 2018 Mar 30;6(2):19 [[Full text](#)]

Hayes M. What can the United States do to prevent another pandemic? Commit to modernizing influenza vaccines. Washington DC: Center for Strategic and International Studies. Oct 12, 2020 [[Full text](#)]

Henry C, Palm AKE, Krammer F, et al. From original antigenic sin to the universal influenza virus vaccine. *Trends Immunol* 2018 Jan;39(1):70-9 [[Full text](#)]

Hensen L, Kedzierska K, Koutsakos M. Innate and adaptive immunity toward influenza B viruses. *Future Microbiol* 2020 Jul;15:1045-58 [[Full text](#)]

Innis BL, Berlanda Scorza F, Blum JS, et al. Meeting report: Convening on the influenza human viral challenge model for universal influenza vaccines, part 1: Value; challenge virus selection; regulatory, industry and ethical considerations; increasing standardization, access and capacity. *Vaccine* 2019a Aug 14;37(35):4823-9 [[Full text](#)]

Innis BL, Berlanda Scorza F, Blum JS, et al. Meeting report: Convening on the influenza human viral challenge model for universal influenza vaccines, part 2: Methodologic considerations. *Vaccine* 2019b Aug 14;37(35):4830-4 [[Full text](#)]

Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018 Mar 31;391(10127):1285-300 [[Full text](#)]

Jang YH, Seong BL. Call for a paradigm shift in the design of universal influenza vaccines by harnessing multiple correlates of protection. *Expert Opin Drug Discov* 2020 Dec;15(12):1441-55 [[Abstract](#)]

Jansen JM, Gerlach T, Elbahesh H, et al. Influenza virus-specific CD4+ and CD8+ T cell-mediated immunity induced by infection and vaccination. *J Clin Virol* 2019 Oct;119:44-52 [[Abstract](#)]

Jegaskanda S. The potential role of Fc-receptor functions in the development of a universal influenza vaccine. *Vaccines (Basel)* 2018 May 17;6(2):27 [[Full text](#)]

Kanekiyo M, Ellis D, King NP. New vaccine design and delivery technologies. *J Infect Dis* 2019 Apr 8;219 (suppl1):S88-96 [[Full text](#)]

Kanekiyo M, Graham BS. Next-generation influenza vaccines. *Cold Spring Harb Perspect Med* 2020 Mar 30;a038448 [[Full text](#)]

Kim SS, Flannery B, Foppa IM, et al. Effects of prior season vaccination on current season vaccine effectiveness in the US Flu VE Network, 2012-13 through 2017-18. *Clin Infect Dis* 2020 Jun 7;ciaa706 [[Full text](#)]

Kis Z, Kontoravdi C, Shattock R, et al. Resources, production scales and time required for producing RNA vaccines for the global pandemic demand. *Vaccines (Basel)* 2020 Dec 23;9(1):3 [[Full text](#)]

Knight M, Changrob S, Li L, Wilson PC. Imprinting, immunodominance, and other impediments to generating broad influenza immunity. *Immunol Rev* 2020 Jul;296(1):191-204 [[Full text](#)]

Korenkov D, Nguyen THO, Isakova-Sivak I, et al. Live attenuated influenza vaccines engineered to express the nucleoprotein of a recent isolate stimulate human influenza CD8+ T cells more relevant to current infections. *Human Vaccin Immunother* 2018 Apr 3;14(4):941-6 [[Full text](#)]

Krammer F. Novel universal influenza virus vaccine approaches. *Curr Opin Virol* 2016 Apr;17:95-103 [[Full text](#)]

Krammer F. The human antibody response to influenza A virus infection and vaccination. *Nat Rev Immunol* 2019a Jun;19:383-97 [[Abstract](#)]



Krammer F, Fouchier RAM, Eichelberger MC, et al. NAction! How can neuraminidase-based immunity contribute to better influenza virus vaccines? *mBio* 2018b Apr 3;9(2):e02332-17 [[Full text](#)]

Krammer F, Garcia-Sastré A, Palese P. Is it possible to develop a “universal” influenza virus vaccine? Potential target antigens and critical aspects for vaccine development. *Cold Spring Harb Perspect Biol* 2018a Jul 2;10(7):a028845 [[Full text](#)]

Krammer F, Palese P. Universal influenza virus vaccines that target the conserved hemagglutinin stalk and conserved sites in the head domain. *J Infect Dis* 2019b Apr 8;219(suppl1):S62-7 [[Abstract](#)]

Krammer F, Weir JP, Engelhardt O, et al. Meeting report and review: immunological assays and correlates of protection for next-generation influenza vaccines. *Influenza Other Respir Viruses* 2020 Mar;14(2):237-43 [[Full text](#)]

Lane MC, Gordon JL, Jiang C, et al. Workshop report: Optimization of animal models to better predict influenza vaccine efficacy. *Vaccine* 2020 Mar 17;38(13):2751-7 [[Full text](#)]

Leung NHL. Transmissibility and transmission of respiratory viruses. *Nat Rev Microbiol* 2021 Mar 22;1–18 [[Full text](#)]

Lewnard JA, Cobey S. Immune history and influenza vaccine effectiveness. *Vaccines (Basel)* 2018 May 21;6(2):28 [[Full text](#)]

Li Z, Zhao Y, Li Y, et al. Adjuvantation of influenza vaccines to induce cross-protective immunity. *Vaccines (Basel)* 2021 Jan 21;9(2):75 [[Full text](#)]

Lim WW, Leung NHL, Sullivan SG, et al. Distinguishing causation from correlation in the use of correlates of protection to evaluate and develop influenza vaccines. *Am J Epidemiol* 2020 Mar 2;189(3):185-92 [[Abstract](#)]

Linderman SL, Ellebedy AH, Davis C, et al. Influenza immunization in the context of preexisting immunity. *Cold Spring Harb Perspect Med* 2020 Sep 28:a040964 [[Full text](#)]

Long JS, Mistry B, Haslam SM, et al. Host and viral determinants of influenza A virus species specificity. *Nat Rev Microbiol* 2019 Jan;17(2):67-81 [[Abstract](#)]

Lopez CE, Legge KL. Influenza A virus vaccination: immunity, protection, and recent advances toward a universal vaccine. *Vaccines (Basel)* 2020 Aug 3;8(3):434 [[Full text](#)]

Madsen A, Cox RJ. Prospects and challenges in the development of universal influenza vaccines. *Vaccines (Basel)* 2020 Jul 6;8(3):361 [[Full text](#)]

Margine I, Krammer F. Animal models for influenza viruses: implications for universal vaccine development. *Pathogens* 2014 Oct 21;3(4):845-74 [[Full text](#)]

Mathew NR, Angeletti D. Recombinant influenza vaccines: saviors to overcome immunodominance. *Front Immunol* 2020 Jan 10;10:2997 [[Full text](#)]

McElhaney JE, Andrew MK, Haynes L, et al. Influenza vaccination: accelerating the process for new vaccine development in older adults. *Interdiscip Top Gerontol Geriatr* 2020a;43:98-112 [[Full text](#)]

McElhaney JE, Verschoor CP, Andrew MK, et al. The immune response to influenza in older humans: beyond immune senescence. *Immun Ageing* 2020b May 7;17:10 [[Full text](#)]

McLean HQ, Belongia EA. Influenza vaccine effectiveness: new insights and challenges. *Cold Spring Harb Perspect Med* 2020 Jan 27:a038315 [[Full text](#)]

Meade P, Kuan G, Strohmeier S, et al. Influenza virus infection induces a narrow antibody response in children but a broad recall response in adults. *mBio* 2020 Jan 21;11(1):e03243-19 [[Full text](#)]

Medina RA, Stertz S, Manicassamy B, et al. Glycosylations in the globular head of the hemagglutinin protein modulate the virulence and antigenic properties of the H1N1 influenza viruses. *Sci Transl Med* 2013 May 29;5(187):187ra70 [[Full text](#)]

Mettelman RC, Thomas PG. Human susceptibility to influenza infection and severe disease. *Cold Spring Harb Perspect Med* 2020 Jan 21:a038711 [[Full text](#)]

Morens DM, Taubenberger JK. Making universal influenza vaccines: lessons from the 1918 pandemic. *J Infect Dis* 2019 Apr 8;219(suppl1):S5-13 [[Full text](#)]



Morris DH, Gostic KM, Pompei S, et al. Predictive modeling of influenza shows the promise of applied evolutionary biology. *Trends Microbiol* 2018 Feb;26(2):102-18 [[Full text](#)]

Nachbagauer R, Palese P. Development of next generation hemagglutinin-based broadly protective influenza virus vaccines. *Curr Opin Immunol* 2018 Aug;53:51-7 [[Abstract](#)]

Nakaya HI, Clutterbuck E, Kazmin D, et al. Systems biology of immunity to MF59-adjuvanted versus nonadjuvanted trivalent seasonal influenza vaccines in early childhood. *Proc Natl Acad Sci* 2016 Feb 16;113(7):1853-8 [[Full text](#)]

National Academies of Sciences, Engineering, and Medicine (NASEM). Value proposition and innovative models for multi-sectoral engagement in global health: proceedings of a workshop. Washington, DC: The National Academies Press, 2019 [[Full text](#)]

National Institute of Allergy and Infectious Diseases. The Collaborative Influenza Vaccine Innovation Centers (CIVICs) Program [[Web page](#)]

Navarro-Torné A, Hanrahan F, Kerstiëns, K et al. Public health-driven research and innovation for next-generation influenza vaccines, European Union. *Emerg Infect Dis* 2019 Feb;25(2):e180359 [[Full text](#)]

Nayak J, Hoy G, Gordon A. Influenza in children. *Cold Spring Harb Perspect Med* 2019 Dec 30;a038430 [[Full text](#)]

Neumann G, Kawaoka Y. Predicting the next influenza pandemics. *J Infect Dis* 2019 Apr 8;219(suppl1):S14-20 [[Abstract](#)]

Ng S, Nachbagauer R, Balmaseda A, et al. Novel correlates of protection against pandemic H1N1 influenza A virus infection. *Nat Med* 2019 Jun;25(6):962-7 [[Full text](#)]

Nguyen TH, McAuley JL, Kim Y, et al. Influenza, but not SARS-CoV-2, infection induces a rapid interferon response that wanes with age and diminished tissue-resident memory CD8+ T cells. *Clin Transl Immunology* 2021 Jan 26;10(1):e1242 [[Full text](#)]

Nogales A, Martinez-Sobrido L. Reverse genetics approaches for the development of influenza vaccines. *Int J Mol Sci* 2016 Dec 22;18(1):20 [[Full text](#)]

Osterholm MT, Kelley NS, Manske JM, et al. The compelling need for game-changing influenza vaccines: an analysis of the influenza vaccine enterprise and recommendations for the future. Minneapolis: University of Minnesota, Center for Infectious Disease Research and Policy, Oct 2012 [[Full text](#)]

Ostrowsky J, Arpey M, Moore K, et al. Tracking progress in universal influenza vaccine development. *Curr Opin Virol* 2020 Feb;40:28-36 [[Abstract](#)]

Pardi N, Hogan MJ, Porter FW, et al. mRNA vaccines—a new era in vaccinology. *Nat Rev Drug Discov* 2018 Apr;17(4):261-79 [[Full text](#)]

Paules CI, Fauci AS. Influenza vaccines: good, but we can do better. *J Infect Dis* 2019a Apr 8;219(suppl1):S1-4 [[Full text](#)]

Paules CI, McDermott AB, Fauci AS. Immunity to influenza: catching a moving target to improve vaccine design. *J Immunol* 2019b Jan 15;202(2):327-31 [[Full text](#)]

Pebody RG, Sinnathamby MA, Warburton F, et al. Uptake and impact of vaccinating primary school-age children against influenza: experiences of a live attenuated influenza vaccine programme, England, 2015/16. *Euro Surveill* 2018 Jun;23(25):1700496 [[Full text](#)]

Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol* 2010 Jul;17(7):1055-65 [[Full text](#)]

Plotkin SA. The influenza vaccine mess. *J Ped Infect Dis Soc* 2018 Aug 17;7(3):178-80 [[Abstract](#)]

Plotkin SA. Updates on immunologic correlates of vaccine-induced protection. *Vaccine* 2020 Feb 24;38(9):2250-7 [[Abstract](#)]

Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603-15 [[Full text](#)]

Rajaram S, Boikos C, Gelone DK, et al. Influenza vaccines: the potential benefits of cell-culture isolation and manufacturing. *Ther Adv Vaccines Immunother* 2020 Feb 22;8:2515135520908121 [[Full text](#)]



- Randolph AG, Yip WK, Allen EK, et al. Evaluation of IFITM3 rs12252 association with severe pediatric influenza infection. *J Infect Dis* 2017;216:14-21 [[Full text](#)]
- Ranjeva S, Subramanian R, Fang VJ, et al. Age-specific differences in the dynamics of protective immunity to influenza. *Nat Commun* 2019 Apr 10;10(1):1660 [[Full text](#)]
- Reber A, Katz J. Immunological assessment of influenza vaccines and immune correlates of protection. *Expert Rev Vaccines* 2013 May;12(5):519-36 [[Abstract](#)]
- Reneer ZB, Ross TM. H2 influenza viruses: designing vaccines against future H2 pandemics. *Biochem Soc Trans* 2019 Feb 28;47(1):251-64 [[Abstract](#)]
- Richards KA, Shannon I, Treanor JJ, et al. Evidence that blunted CD4 T-cell responses underlie deficient protective antibody responses to influenza vaccines in repeatedly vaccinated human subjects. *J Infect Dis* 2020 Jun 29;222(2):273-7 [[Full text](#)]
- Rosa SS, Prazeres DMF, Azevedo AM, et al. mRNA vaccines manufacturing: challenges and bottlenecks. *Vaccine* 2021 Apr 15;39(16):2190-200 [[Full text](#)]
- Ross TM. Universal influenza vaccine approaches using full-length or head-only hemagglutinin proteins. *J Infect Dis* 2019 Apr 8;219(suppl1):S57-61 [[Abstract](#)]
- Saad-Roy CM, McDermott AB, Grenfell BT. Dynamic perspectives on the search for a universal influenza vaccine. *J Infect Dis* 2019 Apr 8;219(suppl1):S46-56 [[Abstract](#)]
- Sabin-Aspen Vaccine Science & Policy Group. Accelerating the development of a universal influenza vaccine. Washington DC: The Aspen Institute and Sabin Vaccine Institute. Jul 25, 2019 [[Full text](#)]
- Sabin-Aspen Vaccine Science & Policy Group. Powering vaccine R&D: opportunities for transformation. Washington DC: The Aspen Institute and Sabin Vaccine Institute. May 3, 2021 [[Full text](#)]
- Sah P, Alfaro-Murillo JA, Fitzpatrick MC, et al. Future epidemiological and economic impacts of universal influenza vaccines. *Proc Natl Acad Sci USA* 2019 Oct 8;116(41):20786-92 [[Full text](#)]
- Sant AJ. The way forward: potentiating protective immunity to novel and pandemic influenza through engagement of memory CD4 T cells. *J Infect Dis* 2019 Apr 8;219(suppl1):S30-7 [[Abstract](#)]
- Sant AJ, Richards KA, Nayak J. Distinct and complementary roles of CD4 T cells in protective immunity to influenza virus. *Curr Opin Immunol* 2018 Aug;53:13-21 [[Abstract](#)]
- Sautto GA, Kirchenbaum GA, Ross TM. Towards a universal influenza vaccine: different approaches for one goal. *Virology* 2018 Jan 19;15(1):17 [[Full text](#)]
- Schrauwen EJA, de Graaf M, Herfst S, et al. Determinants of virulence of influenza A virus. *Eur J Clin Microbiol Infect Dis* 2014 Apr;33(4):479-90 [[Full text](#)]
- Scorza FB, Pardi N. New kids on the block: RNA-based influenza virus vaccines. *Vaccines (Basel)* 2018 Apr 1;6(2):20 [[Full text](#)]
- Shannon I, White CL, Nayak JL. Understanding immunity in children vaccinated with live attenuated influenza vaccine. *J Pediatric Infect Dis Soc* 2020 Mar 19;9(suppl1):S10-14 [[Full text](#)]
- Sherman AC, Mehta A, Dickert NW, et al. The future of flu: a review of the human challenge model and systems biology for advancement of influenza vaccinology. *Front Cell Infect Microbiol* 2019 Apr 17;9:107 [[Full text](#)]
- Skowronski DM, Janjua N., De Serres G, et al. Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. *PLOS One* 2014 Mar 25;9(3):e92153 [[Full text](#)]
- Souquette A, Thomas PG. Past life and future effects—how heterologous infections alter immunity to influenza viruses. *Front Immunol* 2018 May 22;9:1071 [[Full text](#)]
- Sparrow E, Wood JG, Chadwick C, et al. Global production capacity of seasonal and pandemic influenza vaccines in 2019. *Vaccine* 2021 Jan 15;39(3):512-520 [[Full text](#)]
- Stacey HD, Barjesteh N, Mapletto JP, et al. “Gnothi Seauton”: leveraging the host response to improve influenza virus vaccine efficacy. *Vaccines (Basel)* 2018 Apr 12;6(2):23 [[Full text](#)]
- Topham DJ, DeDiego ML, Nogales A, et al. Immunity to influenza infection in humans. *Cold Spring Harb Perspect Med* 2019 Dec 30:a038729 [[Full text](#)]





- Treatment Action Group. Tuberculosis research funding trends, 2005-2017. New York: Treatment Action Group, Dec 2018 [\[Full text\]](#)
- Tregoning JS, Russell RF, and Kinnear E. Adjuvanted influenza vaccines. *Hum Vaccin Immunother* 2018 Mar 4;14(3):550–64 [\[Full text\]](#)
- Trombetta CM, Marchi S, Manini I, et al. Challenges in the development of egg-independent vaccines for influenza. *Exp Rev Vaccines* 2019 Jul;18(7):737-50 [\[Abstract\]](#)
- Trucchi C, Paganino C, Amicizia D, et al. Universal influenza virus vaccines: what needs to happen next? *Expert Opin Biol Ther* 2019 Jul;19(7):671-83 [\[Abstract\]](#)
- Turner JS, Zhou JQ, Han J, et al. Human germinal centres engage memory and naive B cells after influenza vaccination. *Nature* 2020 Oct;586(7827):127-32 [\[Full text\]](#)
- United Nations Environmental Programme, Secretariat of the Convention on Biological Diversity. Nagoya protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization to the convention on biological diversity: text and annex. Geneva, Switzerland: Secretariat of the Convention on Biological Diversity, 2011 [\[Full text\]](#)
- Valkenburg SA, Leung NHL, Bull MB, et al. The hurdles from bench to bedside in the realization and implementation of a universal influenza vaccine. *Front Immunol* 2018 Jul 2;9:1479 [\[Full text\]](#)
- Viboud C, Gostic K, Nelson MI, et al. Beyond clinical trials: evolutionary and epidemiological considerations for development of a universal influenza vaccine. *PLOS Pathog* 2020 Sep 24;16(9):e1008583 [\[Full text\]](#)
- Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob Health* 2020 Apr;8(4):e497-510 [\[Full text\]](#)
- Wei CJ, Crank MC, Shiver J, et al. Next-generation influenza vaccines: opportunities and challenges. *Nat Rev Drug Discov* 2020 Apr;19(4):239-52 [\[Full text\]](#)
- Weir JP, Gruber MF. An overview of the regulation of influenza vaccines in the United States. *Influenza Other Respir Viruses* 2016 Sep;10(5):354-60 [\[Full text\]](#)
- Wen S, Wu Z, Zhong S, et al. Factors influencing the immunogenicity of influenza vaccines. *Hum Vaccin Immunother* 2021 Mar 11:1-13 [\[Abstract\]](#)
- Wille M, Holmes EC. The Ecology and evolution of influenza viruses. *Cold Spring Harb Perspect Med* 2020 Jul 1;10(7):a038489 [\[Full text\]](#)
- World Health Organization (WHO). Global Influenza Strategy 2019-2030. Geneva: World Health Organization, 2019 [\[Full text\]](#)
- WHO. Immunization Agenda 2030: a global strategy to leave no one behind. Geneva: World Health Organization, 2020 [\[Full text\]](#)
- WHO. Improving influenza vaccine virus selection: report of the 4th WHO informal consultation, Hong Kong SAR, China, Nov 18-20, 2015. Geneva: World Health Organization, 2016a [\[Full text\]](#)
- WHO. Pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits. Geneva: World Health Organization, 2011 [\[Full text\]](#)
- WHO. R&D Blueprint Initiative. [\[Web page\]](#)
- WHO. WHO preferred product characteristics for next-generation influenza vaccines. Geneva: World Health Organization, 2017 [\[Full text\]](#)
- WHO Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines. Critical evidence questions for COVID-19 vaccines policy making. Geneva: World Health Organization, Oct 14, 2020 [\[Full text\]](#)
- Worobey M, Plotkin S, Hensley SE. Influenza vaccines delivered in early childhood could turn antigenic sin into antigenic blessings. *Cold Spring Harb Perspect Med* 2020 Oct 1;10(10):a038471 [\[Full text\]](#)
- Wraith S, Nachbagauer R, Balmaseda A, et al. Antibody responses to influenza A(H1N1)pdm infection. *Vaccine* 2020 Jun 2;38(27):4221-5 [\[Abstract\]](#)





Wu NC, Wilson IA. Influenza hemagglutinin structures and antibody recognition. Cold Spring Harb Perspect Med 2020 Aug 3;10(8):a038778 [[Full text](#)]

Yamayoshi S, Kawaoka Y. Current and future influenza vaccines. Nat Med 2019 Feb;25(2):212-20 [[Abstract](#)]

Yan LM, Li OTW, Poh CM, et al. Combined use of live-attenuated and inactivated influenza vaccines to enhance heterosubtypic protection. Virology 2018 Dec;525:73-82 [[Abstract](#)]

Yewdell JW, Santos JJS. Original antigenic sin: how original? How sinful? Cold Spring Harb Perspect Med 2020 Jan 21;a038786 [[Full text](#)]

Young BE, Chen M. Influenza in temperate and tropical Asia: a review of epidemiology and vaccinology. Hum Vaccin Immunother 2020 Jul 2;16(7):1659-67 [[Full text](#)]

Zhang A, Stacey HD, Mullarkey CE, et al. Original antigenic sin: how first exposure shapes lifelong anti-influenza virus immune responses. J Immunol 2019 Jan 15;202(2):335-40 [[Abstract](#)]

Zheng A, Sun W, Xiong X, et al. Enhancing neuraminidase immunogenicity of influenza A viruses by rewiring RNA packaging signals. J Virol 2020 Jul 30;94(16):e00742-20 [[Abstract](#)]

Zhu W, Dong C, Wei L, et al. Promising adjuvants and platforms for influenza vaccine development. Pharmaceutics 2021 Jan 7;13(1):68 [[Full text](#)]

Zimmerman RK, Nowalk MP, Chung J, et al. 2014-2015 influenza vaccine effectiveness in the United States by vaccine type. Clin Infect Dis 2016 Dec 15;63(12):1564-73 [[Full text](#)]

Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci USA 2017 Nov 21;114(47):12578-83 [[Full text](#)]

Zost SJ, Wu NC, Hensley SE, et al. Immunodominance and antigenic variation of influenza virus hemagglutinin: implications for design of universal vaccine immunogens. J Infect Dis 2019 Apr 8;219(suppl1):S38-45 [[Abstract](#)]



# Acronyms

ABS	Access and benefit sharing
ADCC	Antibody-dependent cellular cytotoxicity
BMGF	Bill & Melinda Gates Foundation
CDC	Centers for Disease Control and Prevention (US)
CHIVIM	Controlled human influenza virus infection model
CIDRAP	Center for Infectious Disease Research and Policy (University of Minnesota)
CIVICs	Collaborative Influenza Vaccine Innovation Centers (NIH)
FVVA	Full value of vaccine assessment
GISRS	Global Influenza Surveillance and Response System
HA	Hemagglutinin
HAI	Hemagglutination inhibition assay
HINT	High content imaging-based neutralization test
HLA	Human leukocyte antigen
HVAC	Heating, ventilation, and air-conditioning
IIV	Inactivated influenza vaccine
IRAT	Influenza Risk Assessment Tool
IVR	Influenza Vaccines R&D Roadmap
LAIV	Live-attenuated influenza vaccine
LMIC	Low- and middle-income countries
mAb	Monoclonal antibody
MHC	Major histocompatibility complex
mRNA	Messenger ribonucleic acid
NA	Neuraminidase
NAI	NA inhibition
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases (US)
PIP	Pandemic Influenza Preparedness Framework (WHO)
PPC	Preferred product characteristics
R&D	Research and development
SARI	Severe acute respiratory infection
SMART	Specific, Measureable, Achievable, Realistic/Relevant, and Time-sensitive
SME	Subject-matter expert
TIPRA	Tool for Influenza Pandemic Risk Assessment (WHO Global Influenza Program)
VAERD	Vaccine-associated enhancement of respiratory disease
WHO	World Health Organization



# Appendix 1

## Influenza Vaccines R&D Roadmap: Steering Group

**Joseph Bresee, MD**

US Centers for Disease Control & Prevention, Task Force for Global Health, USA

**Martin Friede, PhD**

World Health Organization, Switzerland

**Bruce Gellin, MD, MPH**

Sabin Vaccine Institute, USA

**Josie Golding, PhD**

Wellcome Trust, UK

**Peter Hart, PhD**

Wellcome Trust, UK

**Rosalind Hollingsworth, PhD<sup>1</sup>**

Bill & Melinda Gates Foundation, USA

**Ann Moen, MPA**

World Health Organization, Switzerland

**Michael Osterholm, PhD, MPH**

Center for Infectious Disease Research and Policy (CIDRAP), University of Minnesota, USA

## Influenza Vaccines R&D Roadmap: CIDRAP Core Project Staff

**Alison Kraigsley, PhD**

Research Associate

**Angela Mehr, MPH**

Research Specialist

**Kristine Moore, MD, MPH**

Project Director

**Julie Ostrowsky, MSc**

Research Associate

**Maya Peters, MPH**

Program Manager

**Angela Ulrich, PhD, MPH**

Assistant Professor

**Jim Wappes**

Editorial Director

<sup>1</sup>Since March 2021; previous Bill & Melinda Gates Foundation representatives were Padmini Srikantiah, MD, MPH; Francesco Berlando Scorza, PhD; and Janet White, MBA



## Influenza Vaccines R&D Roadmap: Taskforce Members<sup>1</sup>

**William Ampofo, PhD**

University of Ghana, Ghana

**Wendy Barclay, PhD**

Imperial College London, UK

**Marco Cavaleri, PhD**

European Medicines Agency, The Netherlands

**Cheryl Cohen, PhD**

University of the Witwatersrand, South Africa

**Benjamin Cowling, PhD**

University of Hong Kong, Hong Kong SAR, China

**Rebecca Cox, PhD**

University of Bergen, Norway

**Ian Gust, AO, MD**

University of Melbourne, Australia

**Bruce Innis, MD**

PATH Center for Vaccine Innovation & Access, USA

**Gagandeep (Cherry) Kang, MBBS, MD, PhD**

Christian Medical College, India

**Jacqueline Katz, PhD**

US Centers for Disease Control & Prevention (Retired), USA

**Yoshihiro Kawaoka, DVM, PhD**

University of Wisconsin–Madison, USA

**Florian Krammer, PhD**

Icahn School of Medicine at Mount Sinai, USA

**Punnee Pitisuttithum, MD**

Mahidol University, Thailand

**Diane Post, PhD**

National Institutes of Health, USA

**Larisa Rudenko, MD, PhD, DSc**

Institute of Experimental Medicine, Russia

**Marilda Siqueira, PhD**

Oswaldo Cruz Foundation (FIOCRUZ), Brazil

**Jerry Weir, PhD**

Food and Drug Administration, USA

<sup>1</sup>Taskforce members from May 2019 to June 2021, during the roadmap development process. The taskforce was expanded in June 2021 to add new members and some of the previous members retired at that time.



# Appendix 2

## Definitions and Key Features of Universal Influenza Vaccines

Source	Definitions	Target Viruses	Duration of Protection	Target Population
<b>Bill &amp; Melinda Gates Foundation (BMGF)</b> Grand Challenges Initiative (BMGF 2018a; BMGF 2018b)	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 and influenza B viruses	Minimum of 3-5 years	All age-groups, especially in developing countries
<b>European Commission</b> European Union–India Collaboration for Next Generation Influenza Vaccines (EU 2017)	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 low- and middle-income countries (LMICs).	Increased breadth of influenza strains	Improved duration of immunity	Different populations and LMICs
<b>Global Funders Consortium for Universal Influenza Vaccine Development</b> (Bresee 2019)	Universal influenza vaccine: high efficacy; induces immunity to a broad array of influenza A viruses (and perhaps influenza B viruses); prevents severe disease; confer 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



<b>National Institute of Allergy &amp; Infectious Diseases (NIAID)</b> A Universal Influenza Vaccine: The Strategic Plan for the NIAID (Erbelding 2018)	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
<b>Sabin-Aspen Vaccine Science &amp; Policy Group</b> Accelerating the Development of Universal Influenza Vaccine (Sabin 2019)	Universal influenza vaccine: safe and highly effective in all age-groups, against any strain; confers lifelong immunity.	All influenza viruses	Lifelong	All age-groups
<b>World Health Organization (WHO)</b> Preferred Product Characteristics for Next-Generation Influenza Vaccines (WHO 2017)	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:** Bill & Melinda Gates Foundation (BMGF); low- and middle-income countries (LMICs); National Institute of Allergy and Infectious Diseases (NIAID); World Health Organization (WHO).





# Appendix 3

## Summary of Influenza Vaccines R&D Roadmap High-Priority Milestones by Topic and Strategic Goal

### Topic 1: Virology Applicable to Vaccine Development

**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 vaccine production.

**Milestone 1.2.e:** By 2025, develop, standardize, and implement methods to improve antigenic characterization of H1N1 and H3N2 influenza viruses.

### Topic 2: 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 new tools and technologies.

**Milestone 2.2.c:** By 2027, determine key mechanisms of long-term protection following influenza virus 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 inactivated influenza vaccine (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.a:** 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 end point.

**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.

### Topic 3: 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 developing improved seasonal influenza vaccines.

**Milestone 3.2.e:** By 2024, determine optimum methods for assessing the effectiveness of conventional egg-based and cell culture-based vaccines with new vaccine technologies, in coordination with regulatory agencies and using consistent end points, 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) 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 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 the 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.

## Topic 4: 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 developing broadly protective or universal influenza vaccines. (See similar milestone under Topic 3: 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 COVID-19 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.

	<p><b>Milestone 4.2.g:</b> By 2024, determine correlates of protection for assessing broadly protective or universal influenza vaccines that are appropriate for different stages of vaccine development.</p> <p><b>Milestone 4.2.h:</b> 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.</p> <p><b>Milestone 4.2.i:</b> 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.</p>
--	---

Topic 5: Animal Models and the Controlled Human Influenza Virus Infection Model (CHIVIM)

<p><b>Strategic Goal 5.1:</b> Optimize animal models for influenza vaccine research.</p>	<p><b>Milestone 5.1.b:</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 studies across laboratories.</p> <p><b>Milestone 5.1.d:</b> 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.</p> <p><b>Milestone 5.1.f:</b> 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).</p> <p><b>Milestone 5.1.g:</b> By 2026, develop and validate novel animal models, as needed, for evaluating immune responses—including durability—to broadly protective influenza vaccines.</p>
--	---



**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 used by different investigators.

## Topic 6: 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 communication tools that build on the FVVA and provide information on economic costs, the risk 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 for influenza vaccines 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.