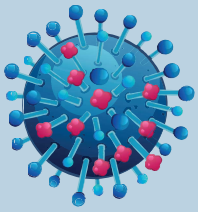
# Influenza Vaccines R&D Roadmap



First Annual Monitoring, Evaluation, and Adjustment (ME&A) Progress Report
March 2023

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# Report Purpose

CIDRAP launched the IVR Initiative on the CIDRAP website in September 2021. The IVR Initiative includes a research and development (R&D) roadmap for developing improved seasonal influenza vaccines and generating broadly protective influenza vaccines. It also information and resources for the influenza vaccine research community and other interested parties. The Initiative is now tracking progress on meeting the IVR goals and milestones through the IVR Monitoring, Evaluation, and Adjustment (ME&A) Program. This is the first annual report from the IVR ME&A program; the report focuses primarily on what progress has been made to date for high-priority milestones or milestones with a 2021/2022 date for completion. Future annual reports will provide additional information on funding allocations, gaps in progress, and ways to mitigate such gaps.

# Introduction

## Limitations with current influenza vaccines

Even though influenza virus vaccines are the cornerstone of public-health efforts to reduce the burden of seasonal influenza and to respond to the unpredictable emergence of pandemic influenza, the current vaccines and vaccine-development approaches are not optimal. For example, seasonal influenza vaccines are strain-specific and not designed to provide broad protection against the continual evolution of influenza viruses; therefore, they need to be reformulated annually (CDC 2020). Even quadrivalent influenza vaccines provide protection against only four influenza strains (two A and two B) and are formulated annually based on what strains are likely to circulate that season. Vaccine-induced immunity is short-lived and researchers have yet to identify determinants of durable protective immunity (i.e., lasting 5 to 10 years). The lag time between annual vaccine strain selection and vaccine production (up to 6 months for egg-based technologies, which include the majority of vaccines currently being produced) leaves ample time for changes to occur in the circulation of different virus strains and lineages, which can lead to antigenic distinctions between the vaccine and circulating viruses. Finally, the need for annual vaccinations is a barrier to implementing influenza vaccination programs in many low- and middle-income countries (LMICs), leading to variable vaccine uptake around the globe and vulnerabilities in global influenza pandemic preparedness (Ortiz 2019). Development of durable, universal vaccines that protect against all current and future strains of influenza and that are suitable for use in LMICs would be a game-changing public-health breakthrough. This advancement would have a dramatic impact on the entire influenza vaccination enterprise by improving vaccine effectiveness, eliminating the need and cost for developing annual reformulations and annual vaccination campaigns, and simplifying the entire vaccine delivery system to allow broader global implementation and access.

In addition, the occurrence of a severe influenza pandemic remains widely recognized as a critical global biological threat. Our current strategy of waiting until the next pandemic is detected and then formulating a strain-specific vaccine, primarily using reliable but time-consuming egg-based production methods, could result in a delay in roll-out and production of effective vaccines. During the 2009-10 H1N1 pandemic, for example, vaccine arrived after the pandemic peak in many areas, limiting the utility of vaccines during the first year of the

pandemic (Broadbent 2011, Ropero-Alvarez 2012). As the COVID-19 pandemic demonstrated, delays in vaccine availability during a severe pandemic can have dire consequences.

## The Influenza Vaccines R&D Roadmap

To address the needs for improved seasonal influenza vaccines and development of broadly protective, or even universal influenza vaccines, in 2017 the Global Funders Consortium for Universal Influenza Vaccine Development (GFC) called for the creation of a global influenza vaccines research and development (R&D) roadmap (hereafter referred to as the IVR) to advance the development of broadly protective influenza vaccines (Bresee 2019). According to Bresee and colleagues, the roadmap "could guide and coordinate research and development, and be a tool for advocacy." Additionally the roadmap can serve as a framework to monitor progress over time and to identify gaps, redundancies, and areas where additional resources are needed.


In response to this request from the GFC, in 2019 the Wellcome Trust provided funding to the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota to coordinate development of the R&D roadmap. Over 2 years (2019 to 2021), CIDRAP developed the roadmap in partnership with a steering group comprised of representatives from CIDRAP, the World Health Organization (WHO), the Bill & Melinda Gates Foundation, the Sabin Vaccine Institute, the Wellcome Trust, the US Centers for Disease Control and Prevention (US CDC), and the Task Force for Global Health (TFGH). The IVR development process also included a diverse 17-member IVR taskforce of global subject-matter experts (SMEs) and leaders in the field, who contributed valuable guidance, information, and insights throughout the roadmap development process. Including current and past members of the IVR taskforce, members represent 17 countries in the Global North and South. Additionally, in fall 2020, CIDRAP convened four online consultations for invited international subject matter experts (SMEs) to review and discuss different sections of the IVR; 147 SMEs, representing nearly 100 different organizations and 20 countries, participated in one or more of the sessions. The last phase of stakeholder engagement was a public comment period, which involved posting the draft IVR online during January and February 2021 and inviting comments, via email and social media, from a broad group of global stakeholders. CIDRAP received 109 sets of comments from stakeholders in 26 countries. The roadmap builds on and complements various organizational

strategic plans, such as the WHO Global Influenza Strategy 2019-2030 (WHO 2019) and the US National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) strategic plan for universal influenza vaccines (Erbelding 2018). Roadmap goals are intended to be relatively broad, whereas the milestones are intended to be actionable and relatively specific, using SMART criteria to the degree possible (specific, measurable, achievable, realistic/relevant, and time-sensitive).

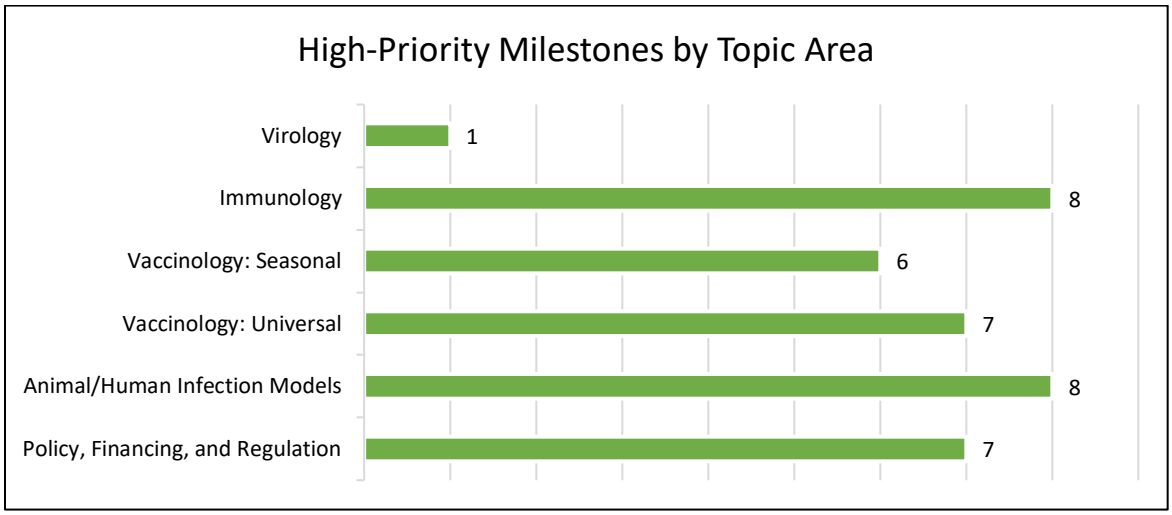
In September 2021, CIDRAP launched the IVR Initiative on the CIDRAP website (CIDRAP 2023). The IVR is intended to serve as a strategic planning tool to facilitate R&D, coordinate funding, and promote stakeholder engagement in R&D aimed at improving seasonal influenza vaccines and generating broadly protective or universal influenza vaccines. It covers a 10-year timeframe (that began in 2021 while the roadmap was under development) and identifies goals and milestones across six different topic areas: virology; immunology; vaccinology for seasonal vaccines; vaccinology for universal vaccines; animal and human infection models; and policy, financing, and regulation.

The original version of the roadmap included 113 milestones across the six topic areas. Using a consensus process involving IVR steering group and taskforce members, 37 milestones were ranked as high priority. The consensus process required that 75% of voting participants agree that a milestone was high priority. The table below outlines the milestones included in the original version of the IVR by topic area and target date for completion.

**IVR Milestones by Topic Area and Target Year for Completion**

| Topic Area | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Virology | -- | 3 | 3 | 3 | 6 | -- | -- | -- | -- | -- | 15 |
| Immunology | -- | 2 | 4 | 3 | 2 | 5 | 1 | 6 | 1 | 2 | 26 |
| Vaccinology: Seasonal | -- | 6 | 3 | 4 | 5 | 4 | 2 | 1 | -- | -- | 25 |
| Vaccinology: Universal | -- | 5 | 4 | 3 | 1 | -- | 1 | -- | -- | -- | 14 |
| Animal/Human Infection Models | -- | 4 | 3 | 2 | 2 | 2 | -- | -- | -- | -- | 13 |
| Policy, Financing, and Regulation | 1 | 8 | 8 | 2 | 1 | -- | -- | -- | -- | -- | 20 |
| Total | 1 | 28 | 25 | 17 | 17 | 11 | 4 | 7 | 1 | 2 | 113 |

The breakdown by topic area for the 37 high-priority milestones is as follows:




## Monitoring, Evaluation, and Adjustment Program for the IVR

Following launch of the IVR Initiative on the CIDRAP website in September 2021 (CIDRAP 2023), the Wellcome Trust provided additional funding to CIDRAP to create a monitoring, evaluation, and adjustment (ME&A) program to track international progress on the goals and milestones outlined in the IVR. The IVR ME&A program was initiated in spring 2022 and will continue for at least 3 years into early 2025. The aims of the IVR ME&A program are to: (1) monitor progress in achieving the IVR goals and milestones and changes in the status of knowledge gaps and barriers to influenza vaccine R&D, (2) track funding for influenza vaccine R&D and display funding through a publically available online dashboard, (3) evaluate research outcomes and funding allocations over time to identify gaps and barriers to progress, and (4) revise and update the roadmap annually, with a major revision in the third year of the project (autumn 2024) to reflect overall progress toward meeting IVR goals and milestones.

This is the first IVR ME&A Annual Progress Report; it covers progress in meeting IVR goals and milestones identified from the time of launching the IVR in September 2021 through the first year following release of the roadmap (September 2022). Given availability of time and resources, this report focuses on milestones that are considered high priority and those milestones with a 2021/2022 target date for completion. Progress on all IVR milestones will be included in one or more future annual reports. In addition, while one of the aims of the IVR ME&A program is to track funding allocations, this activity was initiated later during the first year of the project and program staff were still developing that part of the project during Year 1. Therefore, only very limited funding information is provided in this initial report. Future annual reports will include more detailed influenza vaccine funding information. Additionally, CIDRAP plans to launch the online funding tracker dashboard on the CIDRAP IVR Initiative in late spring 2023.

# Methods

## Overview

CIDRAP's current approach to ME&A for the IVR involves collecting information in two broad areas: (1) identifying research outcomes, such as published literature and meeting presentations, to capture "downstream" progress and (2) identifying major funding allocations, to assess where research is headed from a further "upstream" perspective. The high-level methods for both are similar and are outlined below. As noted above, this report focuses primarily on research outcomes, since the tracking of funding allocations was initiated later in Year 1 of the project. More detailed information about tracking funding allocations will be presented in future IVR ME&A annual reports.

Information collection for ME&A can be grouped into the following broad methodologic categories:

- Bibliometrics and online resources
- Conference presentations
- Technology development tracking
- Expert consultation and input

## Bibliometrics and online resources

A major focus for information collection is review of publications in the scientific literature. Primary sources include peer-reviewed papers located via PubMed and Google Scholar, and preprint (non-peer-reviewed) servers such as medRxiv, bioRxiv, and Research Square. Search strategies include keywords relevant to influenza vaccine R&D topics, author names, and specific vaccine technologies. Searches are conducted on an ongoing basis. Information obtained is organized and stored in CIDRAP's online reference manager.

CIDRAP also regularly reviews other sources of online information, including the following:

- Clinical trial registries, including ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register.
- Websites for government agencies (e.g., the NIH RePORTER and BARDA. Medicalcountermeasures.gov) and nongovernmental organizations (e.g., the Bill & Melinda Gates Foundation Global Grand Challenges, the Sabin Vaccine Institute Influenzer Initiative, Flu Lab, and WHO).
- Pharmaceutical and biotech company websites, including pipelines and press releases.
- Industry news (e.g., Precision Vaccinations, Linksbridge).

## Conference and meeting presentations

During the timeframe for this report and later into the fall of 2022, CIDRAP staff attended and obtained information from several conferences and meetings, including the following:

- The annual meeting for the Collaborative Influenza Vaccine Innovation Centers (CIVICs), held in July 2022. The CIVICs network is supported and funded by NIAID.
- The annual meeting of the Centers of Excellence for Influenza Research and Response (CEIRR), held in July 2022. The CEIRR network is also supported and funded by NIAID.

- Options XI for the Control of Influenza, which is sponsored by the International Society for Influenza and Other Respiratory Virus Diseases (ISIRV).
- The annual meeting of the Global Funders Consortium for Universal Influenza Vaccine Development (GFC), which was held in early November 2022. (Although this meeting was technically outside the timeframe for this initial annual report, information gleaned from this meeting informed this summary.)

## Technology development tracking

In 2019, CIDRAP created the Universal Influenza Vaccine Technology Landscape, which is housed on the CIDRAP website and is a database of novel influenza vaccine candidates designed to provide broader and more durable protection against seasonally circulating influenza viruses and pandemic influenza viruses, compared with current strain-specific seasonal influenza vaccines. The scope of investigational vaccine technologies in the Landscape includes potentially universal, broadly protective, and next-generation influenza vaccines, which are defined as follows:

- *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 hemagglutinin (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.

The Universal Influenza Vaccine Technology Landscape is an important resource for tracking global technology development for broadly protective, universal, and next-generation influenza vaccines. CIDRAP researchers continually update the Landscape using publicly available sources of information, including clinical trial registries, the scientific literature, industry websites and news sources, and websites for research funders, such as NIAID and the US Biomedical Advanced Research and Development Authority (BARDA).

## Expert consultation and input

Additional important information related to monitoring progress on influenza vaccine R&D is not available in the published literature or online; therefore, peer review and expert input are critical

to monitoring such progress and identifying changes in the R&D ecosystem that affect the direction and pace of new influenza vaccine development.

CIDRAP holds approximately quarterly meetings with the IVR steering group to assess and discuss key issues related to the program, including strategies for assessing progress. In addition, in September 2022 CIDRAP convened a one-day hybrid (in-person and virtual participation) meeting of the IVR steering group, IVR taskforce, and selected additional experts (including industry representatives) to review and discuss progress on the IVR goals and milestones (referred to herein collectively as IVR SMEs). This IVR SME meeting focused on milestones with a 2021/2022 target date for completion and milestones that are designated high priority.

In preparation for the meeting, CIDRAP summarized progress to date based on available information sources for each of the milestones under evaluation. Milestones were organized into tables according to the topic area (i.e., virology, immunology, vaccinology for seasonal vaccines, vaccinology for universal vaccines, animal and human infection models, and policy, financing, and regulation). These tables were then reviewed and discussed in the meeting and any additional pertinent information was captured and recorded as part of the meeting summary. In addition, CIDRAP sent out a follow-up survey on the milestones to IVR steering group and taskforce members to ascertain any additional information that was not captured during the September IVR SME meeting.

During the September 2022 meeting, participants were asked to review status of progress for the milestones according to the definitions outlined in the table below.

| **Definitions for status of progress on IVR milestones** | |
|---|---|
| **Status** | **Definition** |
| Target date met | Milestone fully met by the target date. |
| Target partially met | Milestone partially but not fully met by the target date; this applies when more than one activity is included in the milestone AND where the target date has been met for some but not all of the activities. |
| In progress | Ongoing milestone-related activities, but outcomes not yet available. |
| No progress | No progress toward the milestone identified yet. |

Additionally, participants made recommendations for revising some of the milestones, such as changing milestone wording, changing target dates for completion, or in a few instances, deleting a milestone. IVR SMEs also recommended adding one new milestone. These additional changes are reflected in the Appendix and in a revision of the IVR; the updated version and the original version of the roadmap are available on the IVR Initiative website.

## Summary of Progress

This section summarizes progress during the first year of the IVR ME&A program (September 2021 to September 2022) toward achieving the high-priority milestones (N=37) and milestones with a 2021/2022 target date for completion (N=29, nine of which are also high priority). This summary is organized by the six main topic areas and includes the status of progress for each

of the milestones that were assessed during the September 2022 taskforce meeting discussions. The information below summarizes overall progress for the 57 milestones that were assessed as part of this review.

## Overall progress

A review of progress across all six IVR topic areas, using the original IVR as the benchmark, demonstrates the following:

- High-priority milestones with a 2021/2022 target date for completion (N=9)
  - One milestone (11%) met the date for completion.
  - Eight milestones (89%) are in progress.
- Non-high-priority milestones with a 2021/2022 target date for completion (total: N=20, tracked: N=18, and deleted: N=2):
  - Four milestones (20%) met (N=2) or partially met (N=2) the target date for completion.
  - Eleven milestones (55%) are in progress.
  - No progress was identified for three milestones (15%).
  - Two milestones (10%; 4.1.c and 6.3.b) were deleted from the next version of the roadmap, per recommendations from IVR SMEs, because they were not considered to be important enough to be tracked as a milestone. These two were not assessed for progress.
- High-priority milestones with a 2023 or later target date for completion (total: N=28, tracked: N=27, and deleted: N=1):
  - None have been completed to date.
  - Twenty-one milestones (75%) are in progress.
  - No progress was identified for six milestones (21%).
  - One milestone (4%, 6.2.b) was deleted from the next version of the roadmap, per recommendations from IVR SMEs, because it was not considered to be important enough to be tracked as a milestone. Again, this milestone was not assessed for progress.

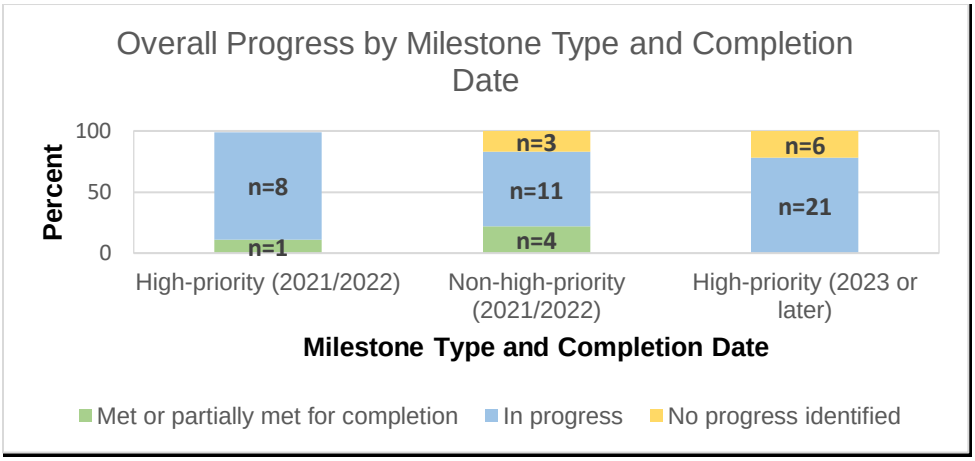
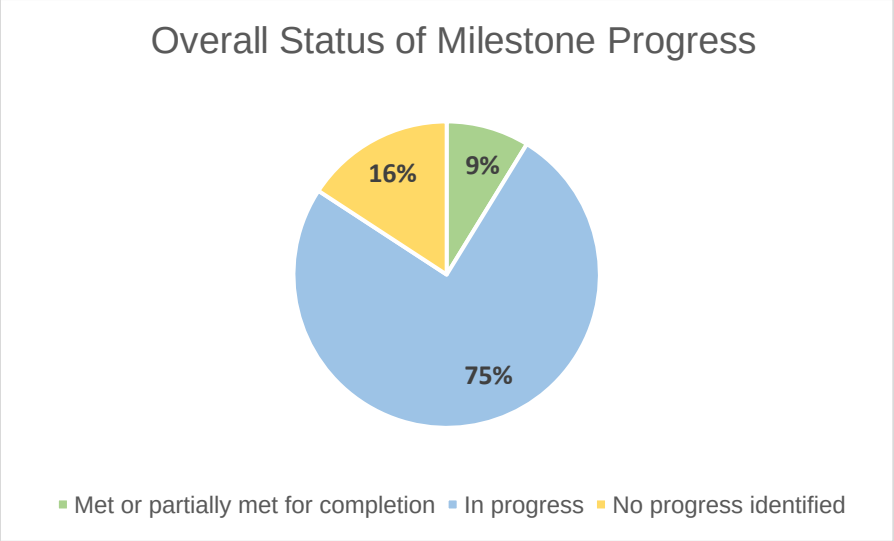



*Figure does not include deleted milestones.*

Although only five (9%) of the original 57 IVR milestones included in this report fully or partially met the target date for completion, most (75%) are in progress and a great deal of progress is being made across the six topic areas. Excluding the three milestones that were deleted from the next version of the roadmap (and therefore, progress status was not included) no progress was identified for only nine (16%) of the assessed milestones and six of those have target completion dates of 2023 or later.




During the review process, IVR SMEs recommended several changes to the IVR milestones. These changes were made and are reflected in the Appendix. An overall summary of the recommended changes includes the following:

- Date changes only: 12 milestones (21%). Most of these involved changing 2022 target dates for completion to later dates, usually 2023 or 2024.
- Word changes only: 14 milestones (26%).
- Word and date changes: 12 milestones (21%).
- Most of the word changes were minor, although substantive changes were made to five of the milestones (milestones 1.2.a, 3.2.a, 5.1.a, 6.3.d, and 6.4.a).
- Three milestones were deleted (4.1.c, 6.2.b, and 6.3.b).
- Two milestones (3.2.i and 6.3.h) were added and are included in the Appendix and in the tables of progress for each of the sections below.

## Topic-specific progress

Detailed information for all of the high-priority milestones and milestones with a 2021/2022 date for completion for each of the six main topic areas is provided in the topic-specific tables in the Appendix. Highlights of progress for each main topic area are provided below.

### *Virology*

| | High-Priority | | Non-High-Priority | |
|---|---|---|---|---|
| **Target completion date** | **2021 & 2022** | **2023 or later** | **2021 & 2022** | **Total** |
| Met or partially met completion date | - | - | - | - |
| In progress | - | 1 | 3 | 4 |
| No progress identified | - | - | - | - |
| **Total** | **-** | **1** | **3** | **4** |

The original IVR virology section includes three non-high priority milestones that had an initial target date of 2022. One (milestone 1.1.a) involves assessing and evaluating sampling strategies for obtaining sequences and isolates of influenza viruses, the second (milestone 1.2.a) involves determining how antigenic sequence data can be used to improve the antigenic match between vaccine strains and circulating influenza strains, and the third (milestone 2.2.a) deals with plans for continuing global surveillance of influenza viruses, with a particular focus on the animal/human interface. While none of these milestones have been completed, progress has been made on all three, particularly related to work being conducted by WHO and the US CDC. During the September 2022 consultation, IVR SMEs recommended changes to the completion dates for these milestones and changes to some of the milestone language; the changes are reflected in Appendix and in the revised version of the IVR.

The original IVR virology section also includes one high-priority milestone (milestone 1.2.e), which is focused on developing, standardizing, and implementing methods to improve antigenic characterization of H1N1 and H3N2 influenza viruses. The original target date for completing this milestone is 2025 and the milestone is currently in progress. For example, several reports were published in 2022 that demonstrate progress on this issue. Additionally, this milestone is being addressed through US CDC mapping efforts and the development of faster and more accurate methodologies to characterize viruses directly from clinical samples. IVR SMEs recommended minor word changes to this milestone to include the use of predictive artificial intelligence and other new technologies to improved antigenic characterization of H1N1 and H3N2 influenza viruses.

### *Immunology and Immune Correlates of Protection*

| | High-Priority | | Non-High-Priority | |
|---|---|---|---|---|
| **Target completion date** | **2021 & 2022** | **2023 or later** | **2021 & 2022** | **Total** |
| Met or partially met completion date | - | - | - | - |
| In progress | - | 8 | 2 | 10 |
| No progress identified | - | - | - | - |
| **Total** | **-** | **8** | **2** | **10** |

The original IVR immunology section does not include any high-priority milestones with a 2021/2022 target date for completion; however, it includes eight high-priority milestones with target dates of 2023 or later. Six of these milestones involve the following areas of research: (1) clarifying a number of issues related to improving understanding of human immunology to inform influenza vaccine development (milestones 2.2.c), (2) determining the impact of prior influenza infection and vaccination on future immune responses to influenza viruses or vaccines (milestones 2.4.b, 2.4.c, and 2.4.d), and (3) improving understanding of the role of mucosal immunity in protecting against influenza (2.6.a and 2.6.d). Because these issues are highly complex, these milestones require longer timelines for completion, with 2026 to 2029 target dates. However, progress is being made on all of them and critically relevant research is being led by a number of different organizations, including NIH (e.g., through the CEIRR and CIVICs networks), the European Commission, the Canadian Institutes of Health Research, the US CDC, BARDA, and the Bill & Melinda Gates Foundation.

The other two high-priority milestones in the IVR immunology section involve developing correlates of protection for assessing influenza vaccines and both are in progress. One milestone (milestone 2.7.a), which has a 2025 target date for completion, involves developing functional assays to accurately capture the breadth of protective immune responses. Several reports published in 2022 describe new assays to assess antibody-dependent cellular cytotoxicity (ADCC) antibodies, new enzyme-linked immunoassay (ELISA)-based potency assays, or harmonization/qualification of the influenza-specific interferon-gamma ELISpot assay to assess cellular immune responses. Additional projects from the US CDC and the European Commission are also addressing this milestone. The other milestone (milestone 2.7.b), which has a 2028 target date for completion, involves developing new measurement tools for assessing mucosal immunity. One published report was identified that addresses this issue and the European Commission is also funding a project that will contribute to the milestone.

The immunology section also includes two non-high-priority milestones with a 2022 target date for completion. One of these (milestone 2.1.a) deals with developing a list of clinical studies that are ongoing and creating a mechanism and guidance for sharing clinical samples with investigators. To address this milestone (at least in part), the NIH is developing a list of NIH-funded studies, and NIH is planning workshops on cohort studies that will address this milestone. The other 2022 milestone (milestone 2.4.a) deals with establishing longitudinal clinical studies to follow cohorts of different age groups to characterize immune responses. A number of such studies have been or are being initiated. The date for this milestone was changed to 2023, even though a great deal of progress has already been made in this area.

### *Vaccinology for Seasonal Influenza Vaccines*

| | High-Priority | | Non-High-Priority | |
|---|---|---|---|---|
| **Target completion date** | **2021 & 2022** | **2023 or later** | **2021 & 2022** | **Total** |
| Met or partially met completion date | - | - | 3 | 3 |
| In progress | 1 | 4 | 1 | 6 |
| No progress identified | - | 1 | 1 | 1 |
| **Total** | **1** | **5** | **5** | **10** |

The original IVR section on vaccinology for seasonal influenza vaccines includes six milestones with a 2022 target date for completion, one of which is also high priority. The 2022 high-priority milestone (milestone 3.2.b) involves convening a workshop to review the development of novel platforms (e.g., messenger ribonucleic acid [mRNA]) for COVID-19 vaccines to identify how best to apply them to influenza vaccines. The Bill & Melinda Gates Foundation is planning a workshop on this topic for 2023; therefore, this milestone is in progress. Since the workshop is planned for 2023, the target date for completion was changed to 2024. Furthermore, several mRNA-based vaccine candidates for influenza are already in clinical development.

For the other five non-high priority milestones with a 2022 target date for completion, the target date was met for two and partially met for one other. The first completed milestone (milestone 3.2.a) involved identifying preliminary lessons learned from coronavirus disease 2019 (COVID-19) vaccine development that are applicable to seasonal influenza vaccines. Two reviews have addressed this issue; one from the National Academies of Sciences, Engineering, and Medicine (NASEM) (NASEM 2022) and one from the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) (IFPMA 2022). Although this milestone has been met, additional work on this issue is ongoing. The second completed milestone (milestone 3.2.c) involved documenting that at least two combined COVID-19 and seasonal influenza vaccines are being evaluated in clinical trials. Several companies, including Moderna, Pfizer, and Novavax are conducting clinical trials of combined vaccines, so this milestone has been met. The milestone that was partially met (milestone 3.3.b) involves developing and validating a standard scale for assessing influenza disease severity. The US CDC has developed a disease-severity scale, but further validation is needed to consider this milestone fully met (Chow 2021). For the two remaining milestones with a 2022 date for completion, progress is being made on one (milestone 3.5.a), which involves generating standardized, harmonized, and validated assays for measuring neuraminidase (NA) content in seasonal influenza vaccines. For the other milestone (milestone 3.3.a), no progress was identified. That milestone involves developing standardized clinical endpoints for severe influenza disease.

The IVR section on vaccinology for seasonal influenza vaccines includes five high-priority milestones with completion dates of 2023 or later; four of the five are in progress. These milestones deal with the following issues: (1) evaluating effectiveness of alternate routes of vaccine delivery (milestone 3.2.h; target date of 2028), (2) determining if any promising new adjuvants improve the immune response to influenza vaccines in the elderly (milestone 3.4.b;

target date 2026) or in the very young (milestone 3.4.c; target date 2026), and (3) determining if the presence of NA improves new or next generation seasonal vaccines (milestone 3.5.d; target date of 2025). The last milestone (milestone 3.2.e; target date 2024), for which no progress was identified, involves conducting a workshop to determine optimum methods for assessing the effectiveness of egg-based and cell culture-based vaccines in comparison with new vaccine technologies. IVR SMEs suggested revising this milestone to reflect conducting a workshop to address the challenges of assessing comparative effectiveness of the vaccine technologies, rather than determining optimum methods for assessing vaccine effectiveness.

One new milestone was added to this section, based on a discussion at the September 2022 meeting (milestone 3.2.i; target date of 2029). Because this new milestone does not have a 2021/2022 date of completion and is not high priority, progress on this milestone has not yet been tracked. However, it is added here, since it reflects a new milestone in the IVR. This new milestone addresses the potential for optimizing the effectiveness of seasonal influenza vaccines by targeting the use of next-generation influenza vaccines (e.g., novel multivalent vaccines including all known influenza subtypes and lineages) in very young children before their first exposure to influenza viruses. IVR SMEs indicated that this was an important concept that was missing from the original IVR.

### *Vaccinology for Universal Influenza Vaccines*

| | **High-Priority** | | **Non-High-Priority** | |
|---|---|---|---|---|
| **Target completion date** | **2021 & 2022** | **2023 or later** | **2021 & 2022** | **Total** |
| Met or partially met completion date | - | - | - | - |
| In progress | 1 | 5 | 3 | 9 |
| No progress identified | - | 1 | - | 1 |
| **Total** | **1** | **6** | **3** | **10*** |
| *One original milestone in this section (4.1.c) was removed from the next version of the roadmap, so that milestone was not included in this summary as progress was not assessed. The original roadmap contained 11 milestones in this section. | | | | |

The original version of the IVR section on vaccinology for universal influenza vaccines included five milestones with a 2022 target date for completion (one of these milestones has been deleted, as noted below, giving only four milestones with a 2022 target date in the table above). Of these, one is considered high priority (milestone 4.1.d) and involves convening a workshop to review novel platforms (e.g., mRNA-based vaccines) for COVID-19 to identify how best to apply them to broadly protective influenza vaccines; this is similar to a milestone under the section on vaccinology for seasonal vaccines. The Bill & Melinda Gates Foundation is planning a workshop on this topic, so this milestone is in progress and the date was changed to 2024.

Key points for the original four non-high-priority milestones with a 2022 target date for completion include the following. One of these milestones (milestone 4.1.a) involves developing a set of preferred product characteristics (PPCs) for broadly protective vaccines. This milestone is in progress and is currently being addressed by WHO and the London School of Hygiene and

Tropical Medicine (LSHTM). Another milestone (milestone 4.1.b) deals with developing a summary analysis of influenza vaccine approaches for broadly protective influenza vaccines. This milestone is also in progress since several reports on this topic have recently been published. Additionally, the Universal Influenza Vaccine Technology Landscape informs this effort. The third 2022 milestone (milestone 4.2.a) involves developing use cases for broadly protective vaccines; this milestone is also in progress and is being addressed by WHO and LSTMH. The final 2022 milestone (milestone 4.1.c) involved identifying a transparent process for identifying the most promising vaccine candidates that warrant investigation. IVR SMEs suggested that this milestone be removed from the roadmap, since such an effort is not likely to happen because of challenges with coming to any kind of consensus between scientists, regulators, and industry representatives; therefore, this milestone is not included in the revised version of the IVR and is not included in the summary table at the beginning of this section.

This section of the IVR also includes six additional high-priority milestones with target dates of completion ranging from 2023 to 2027. Five of the six are in progress. Four of these in-progress, high-priority milestones involve identifying promising broadly protective vaccine candidates and moving them through the vaccine development pipeline (milestones 4.1.e, 4.2.f, 4.2.h, and 4.2.i). Another in-progress high-priority milestone (milestone 4.2.g), which has a 2024 target date for completion, involves determining correlates of protection for assessing broadly protective vaccines. An ISIRV-sponsored conference on this topic was held in early March 2023 (ISIRV 2023) and a great deal of effort is being devoted to this issue. No progress was identified for one high-priority milestone (milestone 4.2.e) that involves developing consensus on streamlining clinical research for evaluating broadly protective influenza vaccines (2023 target date for completion). IVR SMEs noted that this effort could potentially be included within other activities related to clinical trial design; this will be reassessed in future IVR ME&A annual reports.

### *Animal Models and the Controlled Human Influenza Virus Infection Model (CHIVIM)*

| | High-Priority | | Non-High-Priority | |
|---|---|---|---|---|
| **Target completion date** | **2021 & 2022** | **2023 or later** | **2021 & 2022** | **Total** |
| Met or partially met completion date | - | - | - | - |
| In progress | 2 | 3 | 1 | 6 |
| No progress identified | - | 3 | 1 | 4 |
| **Total** | **2** | **6** | **2** | **10** |

This section of the IVR contains two goals: one for advancing animal models and one for optimizing the CHIVIM for influenza vaccine research. For animal models, the original version of the IVR included three milestones that had a 2022 target date for completion; two are in progress. The first (milestone 5.1.b), which is also designated as high priority, addresses the need for validated reagents, updated viral stocks, and harmonized assays; several NIH-funded projects are working on this issue. The second in-progress milestone (milestone 5.1.c) deals with developing best practices for conducting influenza virus transmission studies in ferrets;

several studies have recently been published that address this issue. No progress was identified for the third 2022 milestone (milestone 5.1.a), which called for a strategic plan for standardizing and harmonizing animal models. IVR SMEs suggested a substantive revision of this milestone to focus on developing a plan for broad sharing of animal-model resources rather than on standardization/harmonization of animal models. The target completion dates for these three milestones were all moved forward to 2023.

The IVR contains three additional high-priority milestones for advancing animal models; one is in progress and no progress was identified for the other two. The in-progress, high-priority milestone (milestone 5.1.g; 2026 completion date) deals with developing and validating novel animal models for evaluating immune responses; a number of ongoing projects are addressing this issue. The two high-priority milestones for which no progress was identified include convening a workshop on pre-exposure animal models (5.1.d; 2024 completion date) and completing a comprehensive analysis of the predictive value of different animal models (5.1.f; 2025 completion date).

This section of the IVR also includes four high-priority milestones for optimizing the CHIVIM for influenza vaccine research, one of which had a 2022 target date for completion. Three are in progress: determining use cases for the CHIVIM (milestone 5.2.a; original target date of 2022 but revised to 2024), ensuring that viral strains for CHIVIM research are broadly available (milestone 5.2.b; original target date of 2023 but revised to 2024), and further developing the CHIVIM for broader use (milestone 5.2.d; target date of 2024). The remaining high-priority milestone, for which no progress was identified, involves creating a viral repository of viral challenge stocks for CHIVIM research (milestone 5.2.c) original target date of 2023 but revised to 2024).

### *Policy, Financing, and Regulation*

| | **High-Priority** | | **Non-High-Priority** | |
|---|---|---|---|---|
| **Target completion date** | **2021 & 2022** | **2023 or later** | **2021 & 2022** | **Total** |
| Met or partially met completion date | 1 | - | 1 | 2 |
| In progress | 4 | 1* | 1 | 6 |
| No progress identified | - | 1 | 1 | 2 |
| **Total** | **5** | **2** | **3** | **10†** |

*One additional high-priority milestone that has a 2025 target date for completion was added by IVR SMEs (milestone 6.3.h). This milestone is included in the Appendix and is included in this table, as progress on this milestone has been assessed, even though it represents a new milestone.

†Two of the original milestones in this section (milestones 6.2.b and 6.3.b) were removed from the next version of the roadmap, so those two milestone are not included in this summary as progress was not assessed. The original roadmap contained 11 milestones in this section; the roadmap now has 10, since 2 were removed and one new milestone was added.

The original IVR section on policy, financing, and regulation included nine milestones with a 2021/2022 target date for completion; five of which were considered high-priority. For the five 2021/2022 high-priority milestones, the first (milestone 6.1.a) deals with developing a full value of vaccine assessment (FVVA; also referred to as the full value of influenza vaccine assessment [FVIVA]); this work is being conducted by WHO and other partners (including LSTMH and US CDC) and will likely be completed in 2024. The second (milestone 6.1.b) deals with developing communication strategies that build on the FVIVA; this is also part of the WHO project and is in progress. The third milestone (milestone 6.2.a) involves distilling lessons learned from COVID-19 pandemic and has been completed (NASEM 2022). The fourth (milestone 6.3.c) involves assessing the impact of the Nagoya protocol on sharing influenza isolates. While no formal assessment has been conducted, WHO and US CDC are actively working on this issue. The fifth high-priority milestone (milestone 6.4.a) involves conducting one or more workshops on regulatory issues related to broadly protective influenza vaccines. The WHO FVIVA project will address this need to some degree (so the milestone is in progress), but it is likely that multiple different workshops on regulatory issues will be needed over time (perhaps woven into workshops on other topics.

For the other four non-high priority milestones with a 2021/2022 date, key points are the following. The first (milestone 6.3.a) involves creating by 2021 a comprehensive landscape of universal influenza vaccine technologies in preclinical and clinical development and developing a mechanism to update and analyze the landscape. This landscape has been created by CIDRAP (The Universal Influenza Vaccine Technology Landscape); however, a mechanism to analyze the data is still needed. This milestone, therefore, has been partially completed. The second milestone (milestone 6.3.b) dealt with implementing a plan to reuse vaccine study data (i.e., secondary mining of study data). IVR SMEs recommended removing this milestone from the roadmap and incorporating this concept into a different milestone; therefore, progress is not being tracked for this milestone and it is not included in the summary table at the beginning of this section. The concept of secondary mining of study data was added to the third milestone (milestone 6.3.d) in this group, which deals with implementing a plan to improve existing data management and sharing among influenza vaccine R&D researchers. No evidence of progress was identified for this milestone. The fourth milestone (milestone 6.3.e) deals with mapping of intellectual property and is being addressed as part of WHO's FVIVA effort.

In addition to the five high-priority milestones with 2021/2022 dates for completion, the original IVR included two other high-priority milestones. The first (milestone 6.2.b; target date 2023) involved identifying a set of strategies for accelerating development of universal influenza vaccines. Owing to the vagueness of this milestone, IVR SMEs recommended removing this milestone from the roadmap; therefore, this milestone is not being tracked and it is not included in the summary table at the beginning of this section. The other milestone (milestone 6.4.b) involves identifying a framework to address post-marketing assessment of new broadly protective vaccines (original target date 2023). No evidence of progress was identified for this milestone and IVR SMEs recommended that the target date be moved to 2024.

IVR SMEs also recommended that a new high-priority milestone be added to this topic area (Milestone 6.3.h): By 2025, develop strategies for international data sharing that take into account the impact of the Nagoya protocol and other limitations on data sharing. This milestone

is in progress and is included in the table above. US CDC is supporting this work through WHO working groups and input to the WHO World Health Assembly. Additionally, WHO has published several reports on the public health implications of the Nagoya protocol; these are outlined in the Appendix.

## Conclusions

This summary report demonstrates that a great deal of progress has been made on meeting the milestones outlined in the IVR. One important lesson learned from this program during the past year is that the IVR serves as a valid framework for assessing progress on moving influenza vaccine R&D forward. During this ME&A assessment process, IVR SMEs did not identify important areas of R&D that are not being addressed by the existing IVR milestones. To this point, IVR SMEs recommended adding only two milestones. The first one involves reviewing available data to determine if next-generation influenza vaccines should be targeted to very young children before their first exposure to influenza viruses. The second added milestone involves developing strategies for international data sharing that take into account the impact of the Nagoya protocol and other limitations on data sharing. The IVR already included a milestone on assessing the impact of the Nagoya protocol, but this new milestone takes that one step further.

This assessment demonstrates that most of the IVR milestones are in progress; no progress was identified for only nine (16%) of all the assessed milestones. Despite this progress, many of the in-progress milestones with a target date of 2021/2022 were not completed by the end of 2022. One consideration is that completing the work required to meet certain milestones is taking longer than anticipated, even though resources are being allocated. An example is WHO's FVIVA effort (under Policy, Financing, and Regulation), which is well underway but is requiring more time than originally anticipated, owing to the complexities of the project and the need to assess multiple different topic areas separately. Another reason for not completing milestones is the fact that resources are inadequate to meet the requirements of the milestone; this issue will be more fully assessed during future years of the program. Additionally, some milestones are simply not of high enough importance to move forward and are not necessarily critical for enhancing influenza vaccine R&D. For example, during this review process, IVR SMEs recommended deleting three milestones because they did not meet the SMART criteria (specific, measurable, achievable, realistic/relevant, and time-sensitive). One milestone (4.1.c) was deleted because IVR SMEs did not believe the milestone was achievable or realistic. Another (6.2.b) was deleted because the wording was considered too vague to be meaningful and the milestone didn't really meet the SMART criterion of being specific. The third milestone (6.2.c) was deleted as a separate concept and rolled into another milestone because IVR SMEs determined it fit better as part of another effort and was not completely relevant on its own.

Although some milestones have been ranked as high priority, more effort is needed to determine which milestones are truly most important for realizing the end goals of improving seasonal influenza vaccines and generating broadly protective or universal influenza vaccines. One way to conceptualize this is to focus more on what milestones are on the "critical path" for achieving improved influenza vaccines and determining if there is a stepwise approach to the

process. This issue will continue to be explored during future annual reviews of the IVR ME&A program.

In general, this initial review was focused on examining progress in meeting IVR milestones. IVR SMEs did not have extensive opportunities to delve into reasons why progress was not being made on certain important milestones. However, over the year of review, when progress on an issue was not noted, several key funders indicated that they would consider moving certain issues forward by holding workshops to "jump start" the process. For example, workshops were suggested (and in some instances planned) for correlates of protection, developing standardized clinical end points for severe influenza disease, reviewing novel platforms (e.g. mRNA) for applicability to influenza vaccines, and developing consensus on streamlining the clinical trial process. Progress in these areas will be reviewed during the next year of the program. Additionally, during 2023, CIDRAP will work with IVR SMEs to better identify and understand gaps in progress or funding and steps toward addressing those gaps.

While extensive efforts were made to identify progress on specific milestones, limitations to this assessment are as follows. First, although appropriate search terms were used for the literature review, the review was not meant to be comprehensive and certainly did not capture all pertinent published literature, particularly literature in related fields that may be important to these efforts. Second, while CIDRAP consulted a number of experts for this review to identify work that is not yet published but is in progress, the IVR SMEs are likely not aware of all important progress being made globally, particularly in countries such as Russia and China. Third, limited information was available for this report from industry representatives regarding what types of influenza vaccine R&D different companies are conducting toward meeting the IVR milestones. CIDRAP plans to more effectively engage industry in the future and to better understand the barriers to R&D progress from an industry perspective. Finally, while CIDRAP has initiated an effort to identify funding streams for influenza vaccine R&D, to more fully understand what progress is being made and how resources are being allocated, that effort was under development in 2022 and is not included in this review. Funding information, however, will be included in future progress reports.

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## Acknowledgements

The CIDRAP IVR Initiative team would like to thank the IVR steering group, taskforce, and other subject matter experts who provided critical information used to help identify progress towards meeting the goals and milestones outlined in the roadmap. IVR steering group and taskforce members are listed on the IVR Initiative website.

The September 2022 IVR SME meeting was successful largely due to the involvement of Joseph Bresee, Christopher Chadwick, Josie Golding, Ros Hollingsworth, Ann Moen, Michael Osterholm, and Diane Post, who gave presentations and facilitated discussions during the meeting. Additionally, a number of experts who are not IVR steering group or taskforce members participated in this meeting, and their participation was invaluable towards assessing progress towards IVR goals and milestones.

The CIDRAP team would also like to thank IVR steering group members Christopher Chadwick, Ann Moen, and Diane Post, who provided countless hours of help to ensure that the CIDRAP IVR Initiative team had a clear understanding of progress towards IVR goals and milestones made by WHO, CDC, and NIAID, respectively.

## Abbreviations

| | |
|---|---|
| ADCC | Antibody-dependent cellular cytotoxicity |
| BARDA | Biomedical Advanced Research and Development Authority |
| CDC | Centers for Disease Control and Prevention |
| CEIRR | Centers of Excellence for Influenza Research and Response |
| CHIVIM | Controlled human influenza virus infection model |
| CIDRAP | Center for Infectious Disease Research and Policy (University of Minnesota) |
| CIVICs | Collaborative Influenza Vaccine Innovation Centers |
| COVID-19 | Coronavirus disease 2019 |
| ELISA | Enzyme-linked immunoassay |
| EU | European Union |
| FVIVA | Full value of influenza vaccine assessment |
| FVVA | Full value of vaccine assessment |
| GFC | Global Funders Consortium for Universal Influenza Vaccine Development |
| HA | Hemagglutinin |
| ICTRP | International Clinical Trials Registry Platform (WHO) |
| IFPMA | International Federation of Pharmaceutical Manufacturers and Associations |
| ISIRV | International Society for Influenza and other Respiratory Virus Diseases |
| IVR | Influenza Vaccines Research & Development Roadmap |
| LSHTM | London School of Hygiene & Tropical Medicine |
| ME&A | Monitoring, evaluation, and adjustment |
| mRNA | Messenger ribonucleic acid |
| NA | Neuraminidase |
| NASEM | National Academies of Sciences, Engineering, and Medicine |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| PPCs | Preferred product characteristics |
| R&D | Research and development |
| SME | Subject matter expert |
| TFGH | Task Force for Global Health |
| US | United States |
| WHO | World Health Organization |

# Appendix: Research Progress by Strategic Goal and Milestone

The appendix details progress made towards meeting IVR milestones that are considered high priority and those milestones with a 2021/2022 target date for completion.

The appendix is organized into tables according to the six topic areas of the roadmap:

- Virology Applicable to Vaccine Development
- Immunology and Immune Correlates of Protection
- Vaccinology for Seasonal Influenza Vaccines
- Vaccinology for Universal Influenza Vaccines
- Animal Models and the Controlled Human Influenza Virus Infection Model (CHIVIM)
- Policy, Financing, and Regulation

An **acronym** list is included at the end of the appendix.

If the milestone wording and/or target date were changed based on IVR SME recommendations, this change is noted in the **milestone column**. (Original milestone language can be found on the IVR Initiative website by reviewing the original version of the roadmap that was published in September 2021.)

The **status column** defines milestone progress as one of the following:

- Target date met (the milestone was fully met by the target date)
- Target partially met (milestone partially but not fully met by the target date; this applies when more than one activity is included in the milestone AND where the target date has been met for some but not all of the activities)
- In progress (ongoing milestone-related activities, but outcomes not yet available)
- No evidence identified (no progress towards this milestone identified yet)

Progress identified toward meeting each milestone is detailed in the **IVR SME input, published reports, ongoing projects, and related work column** of the tables.

## VIROLOGY APPLICABLE TO VACCINE DEVELOPMENT

| ***Strategic Goal 1.1:*** Improve understanding of human and animal influenza virus evolution. | | |
|---|---|---|
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 1.1.a***:* Beginning in 2022, and then every 2 years thereafter, assess and evaluate sampling strategies for obtaining sequences and 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. [*Wording changed based on IVR SME recommendation*.] | In progress | *IVR SME Input:*<br>• Significant data relevant to this milestone will be available from WHO through multiple channels. As an extension of ongoing of sampling strategies and their assessment, evidence will be derived primarily from the WHO Global Influenza Surveillance and Response System (GISRS); additional sources include the WHO Global Influenza Programme, the Global Influenza Hospital Surveillance Network (GIHSN), and the WHO Collaborating Centers.<br>• Additional sources of data relevant to progress toward this milestone may include Africa CDC Institute for Pathogen Genomics (IPG) and PAHO collaborations on surveillance for influenza and other respiratory diseases.<br>• The US CDC provides funding and technical support to WHO GISRS for surveillance, global guidance, research on transmission zones, and regional network activities. |
| ***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** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 1.2.a***:* By 2024, determine how the use of genetic sequence data, modeling, and forecasting can be used to improve the antigenic match between vaccine strains and circulating strains. [*Date changed from 2022 to 2024 and wording changed based on IVR SME recommendation*.] | In progress | An overarching review evaluating global data has not been conducted.<br><br>*Published Reports:*<br>• Costa 2022 assessed influenza B vaccine mismatches and clinical aspects of Victoria and Yamagata infections in Brazil, 2010-2020; found mismatches between circulating viruses and the trivalent vaccine strains in 5 of the 11 seasons; recommended substituting QIV for TIV in the Brazilian National Immunization Program to minimize potential negative impact on VE. |
| *High-Priority Milestone* | In progress | *IVR SME Input*: |

| | | |
|---|---|---|
| **Milestone 1.2.e:** 2025, develop, standardize, and implement methods (e.g., the use of predictive artificial intelligence and other new technologies) to improve antigenic characterization of H1N1 and H3N2 viruses. [*Wording changed based on IVR SME recommendation*.] | | • A US CDC project is underway to develop a human epitope map and identify escape variants. To date, researchers have screened hundreds of antibodies for their suitability for inclusion in a library of human mAbs that recognize antigenic sites of the A(H1N1)pdm09 HA molecule. Tens of these mAbs have been characterized and mapped to antigenic sites in the HA. Work continues to add to this panel of reagents to generate a comprehensive library of mAbs that map the antigenic sites of contemporary A(H1N1)pdm09 influenza viruses.<br>• The US CDC initiated work to characterize the NA antigenicity of A(H3N2) viruses, which includes optimizing methods for analysis and assessing contemporary A(H3N2) viruses as part of the WHO vaccine recommendation process.<br><br>*Published Reports:*<br>• Galli 2022 developed and described a high-throughput whole-genome sequencing protocol for A(H3N2) viruses, providing a fast and accurate method to characterize the complete genome of H3N2 viruses directly from clinical respiratory samples.<br>• Harvey 2022 developed a new approach using a Bayesian model for integrating genetic and antigenic data to identify genetic changes in H3N2 virus that underpin antigenic drift.<br>• Wang 2022 critically reviews: (1) capabilities of primary analytic methods for antigenic characterization of influenza viruses, and (2) current challenges with these methods that prevent efficient vaccine strain selection and accurate assessment of virus antigenicity. |
| ***Strategic Goal 1.3:*** Improve the ability to detect and understand the emergence of novel influenza viruses with pandemic potential (Neumann 2019). | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |

| | | |
|---|---|---|
| **Milestone 1.3.a***:* By 2023, 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 identify geographic surveillance gaps, 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. [*Date changed from 2022 to 2023 based on IVR SME recommendation*.] | In progress | Key organizations with active surveillance systems include OFFLU (Global Network of Expertise on Animal Influenza), the UK Flu-MAP project (monitoring HPAI in wildlife and domestic animals in the UK and Europe), FAO (tracking circulating animal viruses, One Health emphasis), the WHO, and/or the NIAID Centers of Excellence for Influenza Research and Response (CEIRR) network. |
| ***Strategic Goal 1.4:*** Enhance understanding of factors associated with viral transmissibility (Crank 2019). | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| No milestones for this goal were high-priority or had a 2022 target date for completion. | | |

## 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. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 2.1.a:** By 2022, 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 | In progress | *IVR SME Input*:<br>• NIH is developing a comprehensive list of NIH-funded influenza cohort studies, to be publicly available within a year.<br>• NIH is planning multiple workshops (primarily for academic researchers) on cohort studies that will address the establishment of a sample repository and issues regarding access to commercial samples from clinical trials (informed by Denmark's and Sweden's COVID sample repositories, which may serve as models). Additional workshops and meetings will focus on the CHIVIM, animal models, and an update to the NIAID strategic plan for universal influenza vaccine development. |

| | | |
|---|---|---|
| vaccines; and (3) develop guidance to support the collection, management, storage, and distribution of the clinical samples. [*Wording changed based on IVR SME recommendation.*] | | |
| ***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** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| *High-Priority Milestone*<br>**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. | In progress | *Ongoing Progress:*<br>• NIH-funded project to F. Lund: Identification and characterization of effector memory B cell populations that dominate memory responses to subsequent influenza infection and vaccination (Additional Information).<br>• The NIAID CIVICs network (Duke and UGA/St Jude centers) is working on biomarkers for durable immune responses to vaccines.<br>• The NIAID-funded researchers are working on longitudinal cohort studies in: (1) infants to determine how initial and repeated infections and/or vaccinations shape immunity to future influenza exposure (St Jude/DIVINCI; Cincinnati/PREVAIL IMPRINT); and (2) older adults to improve understanding of influenza immunity affecting influenza vaccine responses and vaccine effectiveness (S. Leng et al., U01).<br>• NIAID is working on evaluating mechanisms of response to influenza vaccines and infection in the elderly (e.g., J. Alcorn: Uncovering latent factors underlying weak and robust responses to influenza vaccine in healthy and obese older adults [R01] AI170108-01).<br>• US CDC is conducting an antibody landscape analysis of a longitudinal infant cohort, with sera collected from kids through 5 influenza seasons.<br>• US CDC is using longitudinal data for modeling to investigate the development of antibody immunity in young children over time.<br>• US CDC is conducting population immunity studies; participants will be enrolled longitudinally (multiple time points) to assess the dynamic change of population immunity over time.<br><br>*Related work*:<br>• Mount Sinai-Emory Multi-Institutional CIVIC study: Identifying immunologic mechanisms that contribute to persistence of humoral and cellular immunity induced by cHA and mRNA influenza vaccines, using a nonhuman primate model (R. Amara, R. Ahmed, NIAID-SEM-CIVIC network). |

| ***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. | | |
|---|---|---|
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| No milestones for this goal were high-priority or had a 2022 target date for completion | | |
| ***Strategic Goal 2.4:*** Determine the impact of prior influenza virus infection or vaccination on future immune responses to influenza viruses or vaccines. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 2.4.a***:* By 2023, 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. [*Date changed from 2022 to 2023 based on IVR SME recommendation.*] | In progress | *Ongoing Projects*:<br>• Open Philanthropy funded project to M. Staat: Cincinnati Children's Hospital Medical Center, Infant immunome and influenza studies (Additional Information).<br>• CIHR project to M. Miller: Defining the mechanisms of original antigenic sin to improve influenza vaccine effectiveness (Additional Information)**.**<br>• University of Pennsylvania sponsored clinical trial: Characterization of humoral and cellular immune responses elicited by influenza vaccination in healthy adults, 2021-2027 (Additional Information). This study will:<br>  ○ Assess how Ab responses to seasonal influenza vaccination differ in individuals across multiple age groups.<br>  ○ Compare baseline serum nAbs to post-vaccination serum nAb against the influenza A (H1N1 and H3N2) and influenza B viral strains included in the QIV.<br>  ○ Compare nAb titers between groups of individuals with different birth years.<br>• US CDC has ongoing population immunity studies, with sera collected in all 10 HHS regions, covering all age groups (0->70 years).<br><br>*Related Work*:<br>• Wellcome Trust funded project to S. Riley: The life course of human immune responses to influenza infection and vaccination.<br>• EC project to Helmholtz-Zentrum für Infektionsforschung GmbH: (Additional Information). |
| *High-Priority Milestone*<br>**Milestone 2.4.b***:* By 2026, determine through prospective birth-year cohort studies how repeated influenza vaccinations affect the | In progress | *Ongoing Projects*:<br>• University of Hong Kong sponsored clinical trial: The dynamics of the immune responses to repeat influenza vaccination exposures (DRIVE) Study - a randomized controlled trial, 2020-2025 (Additional Information). This study aims to: |

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| immune response to subsequent influenza vaccinations. | | ○ Measure humoral and selected cellular immune responses to repeated influenza vaccination with Flublok, and their associations with age, birth year, and prior vaccination history.<br>○ Identify characteristics of participants who are vaccinated but still become infected with influenza virus ("vaccine failures") and participants who have poor immune responses to vaccination.<br>○ Predict how influenza vaccinations and infections shape immunity.<br>• CIHR project to M. Loeb: Towards a better understanding of Influenza Vaccination: lessons from the Hutterite community (Additional Information).<br>• US CDC is assessing the dynamic change of population immunity and susceptibility to emerging influenza antigenic variants in the United States.<br><br>*Published Reports:*<br>• Jones-Gray 2022 found that vaccination in two consecutive years provides better protection than does no vaccination, even though vaccination in the previous year attenuates vaccine effectiveness.<br><br>*Related Work*:<br>• Wellcome Trust funded project to S. Riley: The life course of human immune responses to influenza infection and vaccination. |
| *High-Priority Milestone*<br>**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. | In progress | *Ongoing Projects:*<br>• Children's Hospital Medical Center, Cincinnati-sponsored clinical trial: Influenza IMPRINT cohort: Defining the impact of initial influenza exposure on immunity in infants, 2019 to 2028 (Additional Information). The study will:<br>○ Document the natural history of infection and immune response to influenza in study infants for at least 3 entire flu seasons; observational prospective cohort; 1,500 mother-infant pairs enrolled during pregnancy and followed up to age 4.<br>○ Define immune responses to the infants' initial influenza exposure (vaccine or infection) and how those responses affect the immune response to subsequent influenza exposures.<br>• St. Jude Children's Research Hospital, University of Michigan: Dissection of influenza vaccination and infection for childhood immunity (DIVINCI) research study, 2019 to 2023 (Additional Information), to explore how influenza affects the developing immune system and how influenza infection and vaccines change immune responses to influenza virus over time. |

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| | | • CIHR project to M. Miller: Defining the mechanisms of original antigenic sin to improve influenza virus vaccine effectiveness (Additional Information).<br>• NIH-funded project to P. Arevalo: Identifying determinants of human immunity against influenza: a multiscale approach (Additional Information).<br><br>*Related work:*<br>• Auladell 2022 found that: (1) recent H3N2 infection can overcome early life HA imprinting, leading to updated responses to more recent strains and (2) immune memory elicited by influenza infection can induce broader subtype-specific protection. Results are derived from a longitudinal household cohort study of the effect of prior H3N2 infection on HAI responses induced by seasonal vaccine in a vaccine-naïve population in Vietnam.<br>• Brouwer 2022 found that: (1) Ab responses to a virus depends on one's age when a related virus from the same antigenic cluster first circulated, not when that specific virus circulated; and (2) that young children may have Abs that cross-react with virus strains that have not yet circulated, possibly indicating that their immune systems are creating a wide array of Abs, which could inform possible mechanisms of antigenic seniority.<br>• Wraith 2022 examined the effects of influenza infection on subsequent infection with the same influenza virus subtype/lineage across multiple seasons, and found that protection wanes as time or antigenic distance increases.<br>• BMGF-funded project to the University of Arizona, to understand the molecular and cellular basis of how antigenic imprinting may have shaped the inadequate immune responses in victims of the 1918 influenza pandemic and to use those insights to improve influenza vaccination.<br>• EC funded project to the University of Oxford: Tracing the inFLUenza vaccine imPRINT on immune system to identify cellular signature of protection (Additional Information). |
| *High-Priority Milestone*<br>**Milestone 2.4.d:** By 2029, 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. | In progress | *Published Reports:*<br>• Yegorov 2022 evaluated the impact of repeated influenza vaccination across 3 seasons and the vaccine-elicited induction of group 1 influenza virus HA stalk bNAbs in children (median age 9 years), comparing the impact of IIV vs LAIV. The study found:<br>  ○ Repeated vaccination results in significant boosting of a durable bNAb response. |

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| | | ○ IIV and LAIV formulations elicit comparable boosting of serological bNAb titers (anti-stalk IgG and IgA).<br><br>*Related work*:<br>• US CDC is evaluating the effects of LAIV versus inactivated influenza vaccine on adaptive immunity, measuring T cell and B cell responses, as well as lymphocyte receptor repertoire diversity.<br>• MRC-Gambia/Imperial College London research on mucosal and systemic immunogenicity of LAIV in Gambian children, T. de Silva (Additional Information). |
| ***Strategic Goal 2.5:*** Clarify the role of T cells in generating or supporting protective immunity to influenza virus infection and vaccination. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| No milestones for this goal were high-priority or had a 2022 target date for completion. | | |
| ***Strategic Goal 2.6:*** Improve understanding of the role of mucosal immunity in protecting against influenza. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| *High-Priority Milestone*<br>**Milestone 2.6.a***:* By 2023, further determine the role of mucosal antibodies in protecting against influenza virus infection, disease, and transmission. | In progress | *Ongoing Projects:*<br>• EC funded project to INSERM: Induction of B-cell immunity in the lung mucosa (Additional Information).<br><br>*Published Reports:*<br>• Oh 2021 evaluated the phenotype, residency, and role of IgA-secreting B cells in the lung, and found that tissue-resident IgA-secreting B cells are the source of luminal IgA in the lung that confers sterilizing protection against challenge with homologous influenza virus and quicker recovery from heterologous challenge (preclinical study in mice).<br><br>*Related work:*<br>• Xu 2021 reviewed current approved intranasal influenza vaccines and candidates in development and analyzed factors unique to intranasal vaccines that are relevant to the development of new intranasal influenza vaccines.<br>• CIHR funded project to E. Wasan, et al.: Intranasal vaccines for pertussis and influenza using novel formulations of a triple adjuvant (Additional Information). |
| *High-Priority Milestone*<br>**Milestone 2.6.d***:* By 2026, determine the role of mucosal T cells in protecting against | In progress | *Ongoing Projects*:<br>• NIH-funded project to A. Sant (PI): Potentiating broadly protective local immunity to influenza virus (Additional Information). |

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| influenza virus infection, disease, and transmission. | | *Related Work*:<br>• Wellcome Trust funded project to A. Amini: Effector functions of MAIT [mucosal-associated invariant T] cells in response to viral infection and vaccines. |
| ***Strategic Goal 2.7:*** Develop novel correlates of protection for assessing seasonal influenza vaccines and broadly protective or universal influenza vaccines, as part of clinical studies that demonstrate efficacy against a disease endpoint. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| *High-Priority Milestone*<br>**Milestone 2.7.a***:* By 2025, develop functional assays that are fit for clinical trial purpose 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. [*Wording changed based on IVR SME recommendation.*] | In progress | *Ongoing Projects:*<br>• EC funded project to P. Londono-Hayes: Standardization and development of assays for assessment of influenza vaccines correlates of protection (Additional Information).<br>• US CDC is developing immunological assays to measure correlates of protection for the next-generation influenza vaccines.<br><br>*Published Reports:*<br>• Chen 2022 developed 4 novel cell-based assays to assess ADCC antibodies against HA or NA proteins to assess the contribution of ADCC antibody to vaccine immunogenicity.<br>• Cheung 2022 developed two ELISA-based potency assays for group 1 influenza A viruses using cross-reactive nanobodies.<br>• Waerlop 2022 described the harmonization and qualification of the influenza-specific interferon-gamma ELISpot assay to detect and qualify vaccine-induced cellular immune responses.<br><br>*Related work:*<br>• Janssens 2022 reviewed current assays for evaluating cell-mediated immune responses to influenza. |
| *High-Priority Milestone*<br>**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. | In progress | *Published Reports:*<br>• McIlwain 2021 identified new single and multi-variable cellular correlates of protection following oral vaccination with an Ad5-based influenza vaccine candidate (Vaxart VXA-A1.1); outcomes included prevention of virus shedding post-challenge (phase 2 study).<br><br>*Related Work*: |

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| | | • EC funded project to the University of Oxford: Tracing the inFLUenza vaccine imPRINT on immune system to identify cellular signature of protection (Additional Information). |

## 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. | | |
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| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| No milestones for this goal were high-priority or had a 2022 target date for completion. | | |
| ***Strategic Goal 3.2:*** Identify strategies and policies to optimize seasonal influenza vaccines and improve vaccine effectiveness. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 3.2.a:** By 2022, identify preliminary lessons learned from COVID-19 vaccine development that are applicable to seasonal influenza vaccines. Include a summary of the current landscape of next-generation influenza vaccine candidates based on mRNA, nanoparticles, recombinant proteins, and other new technologies applied to COVID-19 vaccine development. [*Wording changed based on IVR SME recommendation.*] | Target date met | • NASEM 2022 [consensus study report] provided recommendations for basic and translational research, clinical evaluation, manufacturing, and regulatory science for seasonal and pandemic influenza vaccines, based on an expert committee's review of the rapid development, evaluation, licensing, and deployment of effective COVID-19 vaccines.<br>• IFPMA 2022 summarized lessons learned for vaccine manufacturing during a pandemic, e.g., regarding pathogen surveillance and data sharing, equitable distribution, and pharmaceutical partnerships to accelerate R&D and manufacturing.<br>• WHO and LSHTM, with funding from US CDC as part of a 5-year cooperative agreement ending in 2024, are engaged in a full value of influenza vaccine assessment (FVIVA) project aimed at identifying critical success factors that would enable the development, approval, and introduction of next-generation influenza vaccines (WHO FVVA webpage). This project will also include additional lessons learned from the COVID-19 experience.<br><br>*IVR SME Input*: Additional lessons learned from the experience with SARS-CoV-2 omicron booster vaccine development include:<br>• The potential exists to speed production of influenza vaccines and eliminate the need for candidate strains.<br>• The FDA's approach to rapid approval of COVID-19 omicron boosters could be applied to influenza vaccines to speed access to updated vaccines for seasonal or pandemic influenza. |

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| *High-Priority Milestone*<br>**Milestone 3.2.b***:* By 2024, 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. (See similar milestone under Vaccinology for Universal Influenza Vaccines.) [*Date changed from 2022 to 2024 based on IVR SME recommendation.*] | In progress | *IVR SME Input*: BMGF is planning a workshop to be held in 2023 that will address novel platforms for both seasonal and broadly protective or universal vaccines (see Milestone 4.1.d). Suggestions for discussion topics include:<br>• Regulatory issues regarding next-generation influenza vaccines.<br>• Comparisons of egg-based and novel technologies, including Sanofi Flublok RIV4.<br><br>Several mRNA-based next-generation seasonal influenza vaccine candidates are in clinical development (additional vaccines in active clinical and preclinical development are profiled in the Landscape):<br>• Phase 3: Moderna mRNA-1010 (NCT05415462, NCT05566639)<br>• Phase 3: Pfizer/BioNTech quadrivalent modified RNA (NCT05540522)<br>• Phase 1: CureVac/GSK CVSQIV (NCT05252338)<br>• Phase 1: Sanofi Pasteur quadrivalent MRT5407 (NCT05553301)<br><br>*Related Work:*<br>The use of mRNA platforms is a frequent topic of discussion at conferences and in the literature. Examples from the published literature include the following:<br>• Alameh 2021 demonstrated that lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines against influenza and SARS-CoV-2 in mice by inducing robust T follicular helper cell and humoral responses.<br>• Chivukula 2021 demonstrated that mRNA vaccine candidates with monovalent or multivalent HA and NA induce functional antibody and cellular immune responses (in NHPs) and protective efficacy against viral challenge (in mice).<br>• Shartouny 2022 reviewed challenges and potential barriers of applying mRNA technology to next-generation influenza vaccines, based on successes with COVID-19 vaccines. |
| **Milestone 3.2.c:** By 2022, document that at least two combined COVID-19 and seasonal influenza vaccines are being evaluated in clinical trials. | Target date met | Combination next-generation vaccine candidates for influenza and SARS-CoV-2 in active clinical development include:<br>• Phase 2: Novavax CIC nanoparticle (NCT05519839)<br>• Phase 1: Moderna mRNA-1073 (NCT05375838)<br>• Phase 1: Pfizer modified mRNA (NCT05596734) |
| *High-Priority Milestone*<br>**Milestone 3.2.e***:* By 2024, conduct a workshop to determine optimum methods for assessing the effectiveness of conventional egg-based | No evidence identified | We found no specific reports on methods for assessing vaccine effectiveness for new vaccine technologies in comparison to conventional technologies.<br><br>*IVR SME Input*: |

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| and cell culture-based vaccines with new vaccine technologies, in coordination with regulatory agencies and using consistent endpoints, to allow data to be combined as appropriate over multiple seasons and to allow better comparability of data across studies. | | • A workshop is needed to address challenges of assessing comparative effectiveness and to establish consensus trial designs to measure vaccine effectiveness.<br><br>*Related work:*<br>• McMenamin 2022 found that approaches to relative vaccine effectiveness (rVE) evaluation are highly varied, requiring improvements in reporting of cases; they concluded that additional methodologic development is needed to inform a more standardized approach.<br>• Trombetta 2022 found that key factors affecting the VE of current seasonal influenza vaccines include age, antigenic matching, and vaccination history. |
| *High-Priority Milestone*<br>**Milestone 3.2.h***:* By 2028, 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. | In progress | *IVR SME Input*:<br>• US CDC is evaluating needle-free vaccine delivery approaches (CDC Afluria/Pharmajet).<br>• US CDC conducted a 2-year randomized controlled trial of LAIV versus IIV among children 2-10 years in India, in collaboration with All-India Institute of Medical Sciences (2015-17) (Krishnan 2021).<br>• US CDC is preparing to conduct an RCT of the immunogenicity and safety of Pharmajet needle-free jet injector for intradermal administration of IIV (Butantan) among adult population in Peru, in collaboration with the US Naval Medical Research Unit (NAMRU-6).<br><br>*Published Reports and Ongoing Projects:*<br>Several studies describe intranasal, oral, or transdermal routes of delivery of influenza vaccines. Examples include:<br>*Intranasal*:<br>• Eiden 2021 demonstrated protection against infection and illness after challenge with a highly drifted, antigenically distinct H3N2 wild-type challenge virus (FluGen/M2SR intranasal vaccine candidate, phase 2).<br>• Kawai 2021 (*see also below under 3.5.d*) found that intranasal administration of rNA, but not rHA, conferred cross-protection against antigenically heterologous challenge (preclinical).<br>• Kunzli 2022 found that IM and IN routes of mRNA vaccination influence humoral and cell-mediated immunity, and that IM prime-boosting establishes respiratory tract resident memory T cells (Trm) that can be further enhanced by additional IN immunization (preclinical). |

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| | | • CIHR project to M. Thompson, et al.: Developing thermally stable dry powder vaccine platforms via spray drying tailored for inhalation delivery (CIHR).<br>• CIHR project to E. Wasan, et al.: Intranasal vaccines for pertussis and influenza using novel formulations of a triple adjuvant (CIHR).<br>• CIHR project to H. Vliagoftis et al.: Proteinase-activated receptor-2 agonists as adjuvants for mucosal vaccination (CIHR).<br><br>*Oral*:<br>• Flitter 2022 found that an enterically coated, room temperature-stable oral tablet [Vaxart, VXA-A1.1], based on a non-replicating adenovirus vector (Ad5) vaccine platform containing TLR3 adjuvant, elicited antigen-specific systemic and mucosal responses against influenza (clinical and preclinical studies).<br><br>*Intranasal or oral*:<br>• Matsuda 2021 found that a replication-competent adenovirus vector vaccine platform [Ad4-H5-Vtn], delivered orally or via tonsillar swab or nasal spray, caused prolonged exposure to influenza antigens in the upper respiratory tract, leading to durable systemic and mucosal immunity (phase 1 study).<br><br>*Transdermal/microneedle patches*:<br>• Nguyen 2021 reviewed the development of microneedle-based skin vaccine delivery approaches, designed to deliver key antigens into the cutaneous microenvironment and to provide a noninvasive and self-administered vaccination approach applicable to low-resource settings.<br>• Stinson 2021 developed a microneedle array patch (MIMIX) designed to release antigen over 1-2 weeks, mimicking the time course of an influenza infection, and evaluated it in a preclinical murine model; results suggest the potential for sustained release silk microneedles to improve the effectiveness of seasonal influenza vaccines and enable more effective next-generation vaccines. |
| ***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. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 3.3.a***:* By 2024, develop standardized clinical endpoints for severe influenza disease, including those that are relevant to special populations, that can be | No evidence identified | *IVR SME Input:*<br>• Endpoint consensus is currently lacking; a workshop is needed to establish consensus definitions of endpoints for trial design.<br>• Consider adding transmission and hospitalization endpoints for evaluation. |

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| used in clinical vaccine efficacy studies. This effort should consider including complications from severe influenza as additional endpoints. [*Date changed from 2022 to 2024 and wording changed based on IVR SME recommendation.*] | | *Related work:*<br>• Braunfeld 2022 found that among pediatric influenza vaccine efficacy trials, primary outcome measures and clinical specimen collection criteria were highly variable; policy and implementation decisions based on VE data are limited, given the absence of influenza vaccination programs in most LMICs. |
| **Milestone 3.3.b***:* By 2024, develop and validate a standard scale for assessing influenza disease severity. | Partially met | *Published Reports:*<br>• US CDC developed a scale in adults hospitalized with influenza-associated lower respiratory tract infection demonstrating a broad distribution of physiologic severity (Chow 2021). Efforts are needed to further validate this scale to fully meet the milestone. |
| ***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** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| *High-Priority Milestone*<br>**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 and efficacy profiles. | In progress | *Ongoing Projects:*<br>• EC funded project: Effective and affordable flu vaccines for the world (Additional Information).<br>• EC funded project: Evaluation of rationally designed influenza vaccines (Additional Information).<br>• CIHR project to E. Wasan, et al: Intranasal vaccines for pertussis and influenza using novel formulations of a triple adjuvant (Additional Information).<br>• CIHR project to H. Vliagoftis et al.: Proteinase-activated receptor-2 agonists as adjuvants for mucosal vaccination (Additional Information).<br><br>*Published Reports:*<br>• Shinde 2022 reported that the Novavax Matrix-M-adjuvanted quadrivalent nanoparticle influenza vaccine (qNIV) was well tolerated and produced qualitatively and quantitatively enhanced humoral and cellular immune response in older adults compared with IIV4 [phase 3 randomized clinical trial].<br>• Crofts 2022 found that R848 increased IgG antibody responses in elderly NHP following responses observed in newborn NHP [preclinical study].<br>• Gorse 2022 found that MAS-1-adjuvanted IIV(an investigational water-in-oil emulsion-based adjuvant/delivery system comprised of stable nanoglobular aqueous droplets) induced higher HAI antibody responses with prolonged durability including |

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| | | against historical strains, potentially providing greater VE in the elderly throughout an influenza season (phase 1 study). |
| *High-Priority Milestone*<br>**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 and efficacy profiles. | In progress | *Ongoing activities:*<br>• US CDC is conducting studies in Peru to assess if enhanced vaccines can overcome low antibody responses, randomizing adjuvanted vs standard egg based influenza vaccine.<br>• US CDC is continuing laboratory testing for the 4-year study randomizing high dose, Flublok, adjuvanted and standard egg-based vaccine in older adults.<br>• Seqirus is sponsoring a Phase 2 trial to evaluate responses to vaccination with different MF59 adjuvanted pandemic influenza vaccine formulations of an H5N1 vaccine in pediatric subjects (NCT04669691).<br><br>*Published Reports:*<br>• Barman 2022 found that individually encapsulated and admixed cGAMP-PS and CL075-PS shape the quantity and quality of neonatal immune responses and Th1 polarized neonatal rHA-specific humoral and cell-mediated immune responses [preclinical study in mice].<br>• Clemens 2022 found that inclusion of TLR7/8 adjuvant R848 in an inactivated IAV vaccine can promote a lasting IgG response to the HA stem. |
| ***Strategic Goal 3.5:*** Determine the role of NA as a vaccine antigen for improving the effectiveness and immunogenicity of seasonal influenza vaccines. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 3.5.a***:* By 2023, generate standardized, harmonized, and validated assays for measuring NA content in seasonal influenza vaccines. [*Date changed from 2022 to 2023 based on IVR SME recommendation.*] | In progress | *Published Reports*:<br>• Bernard 2022 validated an ELLA-NA Inhibition (NI) SOP for N1 influenza antigen and provided a detailed, harmonized SOP for ELLA-NI. |

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| *High-Priority Milestone*<br>**Milestone 3.5.d***:* By 2025, determine if the presence of NA improves new or next-generation seasonal influenza vaccines, and, if so, establish the optimal dose of NA that improves immunogenicity and effectiveness, and maintains an acceptable safety profile. [*Wording changed based on IVR SME recommendation*.] | In progress | *Ongoing Projects:*<br>• EC funded project: Evaluation of rationally designed influenza vaccines (Additional Information).<br><br>*Published Reports*:<br>Several preclinical studies have examined the potential for NA antigens to enhance immunogenicity of different influenza vaccine constructs.<br>• Gao 2021 found that optimizing the design of rNA (via tetramerization motifs and NA domains included in the rNA construct design) affects the immunogenicity and protective efficacy of the influenza vaccine in mice.<br>• Kawai 2021 found that NA antigen in an intranasal vaccine confers broad cross-protection in the upper respiratory tract by inducing NA-specific IgA that recognizes a wide range of epitopes in mice.<br>• Rosu 2022 demonstrated the potential of NA immunity to protect against disease, virus replication in the lower respiratory tract, and virus shedding in the ferret model.<br>• Strohmeier 2022 (NIAID/CIVICs rNA vaccine development) characterized the immunogenicity of CpG 1018-adjuvanted rNA vaccines (N1-MPP, N2-MPP, and B-NA-MPP) in a naïve mouse model. |

## VACCINOLOGY FOR 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. | | |
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| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 4.1.a***:* By 2024, 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). [*Date changed from 2022 to 2024 based on IVR SME recommendation*.] | In progress | *IVR SME Input*:<br>• In early 2022, BMGF revised its Target Product Profile for universal influenza vaccines (unpublished).<br>• WHO (PDVAC) has started updating the 2017 WHO guidance on PPCs and will establish an expert group to guide the review/update throughout 2023.<br><br>*Ongoing projects:*<br>• WHO and LSHTM, with funding from US CDC as part of a 5-year cooperative agreement ending in 2024, are engaged in a full value of influenza vaccine |

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| | | assessment (FVIVA) project aimed at identifying critical success factors that would enable the development, approval, and introduction of next-generation influenza vaccines. Part of this effort involves revising the WHO's 2017 PPC guidance (WHO FVVA). [*See Milestone 6.1.a*]. |
| **Milestone 4.1.b***:* By 2022, 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. | In progress | *Ongoing projects*:<br>• The Universal Influenza Vaccine Technology Landscape, a CIDRAP project funded by the Global Funders Consortium for Universal Influenza Vaccine Development, profiles vaccine candidates designed to provide broader and more durable protection against circulating and pandemic influenza viruses (Ostrowsky 2021).<br>• To date, no comprehensive analyses have been done, but reviews of next-generation or universal influenza vaccine approaches have been reported, e.g., Hendy 2022, McMillan 2021, Wang 2022. |
| ~~**Milestone 4.1.c** By 2022, develop a transparent process, such as an international consortium, for identifying the most promising influenza vaccine candidates that warrant further investigation (Epstein 2018).~~ | | *IVR SME Input:*<br>• Recommendation to remove milestone. |
| *High-Priority Milestone*<br>**Milestone 4.1.d***:* By 2024, 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 Vaccinology for Seasonal Influenza Vaccines.) [*Date changed from 2022 to 2024 based on IVR SME recommendation.*] | In progress | *IVR SME Input*:<br>• BMGF is planning a workshop for 2023 that will include a review of novel platforms for both seasonal and broadly protective or universal influenza vaccines (see Milestone 3.2.b).<br><br>*Related work:*<br>• Deviatkin 2022 reviewed new platforms and approaches for improved influenza vaccines, particularly RNA-based strategies for broadly protective influenza vaccines.<br>• Hendy 2022 reviewed nano/microparticle platforms for improved seasonal and universal influenza vaccine development. |
| *High-Priority Milestone*<br>**Milestone 4.1.e***:* By 2024, identify promising influenza vaccine candidates that elicit robust and broadly protective immunity, based on a set of defined selection criteria. [*Wording changed based on IVR SME recommendation.*] | In progress | *Ongoing Projects:*<br>• NIAID CIVICs program<br>• Universal Influenza Vaccine Technology Landscape<br>• EU-India project on broadly protective influenza vaccines<br>• NIH-funded project to A. Garcia-Sastre: Toward a universal influenza virus vaccine based on live attenuated NS1-deleted influenza viruses (Additional Information) |

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| | | • NIH-funded project to K. Bagley: Universal influenza A/B vaccine (Additional Information)<br>• NIH-funded project to SM Kang: Influenza vaccines inducing broadly cross protective immunity (Additional Information) |
| ***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** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 4.2.a:** By 2022, develop use cases for broadly protective vaccines, defining how, where, and under what circumstances such vaccines would be used. | In progress | *Ongoing projects:*<br>• WHO and LSHTM, with funding from US CDC as part of a 5-year cooperative agreement ending in 2024, are engaged in a full value of influenza vaccine assessment (FVIVA) project aimed at identifying critical success factors that would enable the development, approval, and introduction of next-generation influenza vaccines (WHO FVVA).<br>• US CDC is developing a generic use case analytical framework and validating use cases and country archetypes for current seasonal influenza vaccines (MMGH Consulting).<br>• The Developing Countries Vaccine Manufacturing Network (DCVMN) held a consultation in May 2022 to further develop the use cases for seasonal influenza vaccines (DCVMN). |
| *High-Priority Milestone*<br>**Milestone 4.2.e:** By 2023, develop consensus on streamlining clinical research for evaluating broadly protective influenza vaccines, drawing on COVID-19 vaccine experience. | No evidence identified | We are not aware of any progress relating to this milestone.<br><br>*IVR SME input:*<br>• IVR SMEs noted that this effort could be included within other activities related to clinical trial design. This will be reassessed in future annual reports. |
| *High-Priority Milestone*<br>**Milestone 4.2.f***:* By 2024 and ongoing, identify an initial set of vaccine candidates that demonstrate broad-based immunity—humoral, cell-mediated, or both—in preclinical research and assess them for safety and | In progress | *Ongoing Projects:*<br>• Several phase 1 clinical trials are in development in the NIAID/CIVICs network.<br>• NIH-funded project to A. Garcia-Sastre (PI): Toward a universal influenza virus vaccine based on live attenuated NS1-deleted influenza viruses (Additional Information).<br><br>*Published reports from recently completed phase 1 studies include:* |

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| immunogenicity in phase 1 clinical trials in healthy adults. [*Date changed from 2024 to 2024 and ongoing and wording changed based on IVR SME recommendation*.] | | • Park 2022 BPL-1357; 4 whole, BPL-inactivated avian influenza virus-based vaccine (NIAID)<br>• Folschweiller 2022; Nachbagauer 2021 Chimeric HA-based vaccines (NIAID/CIVICs)<br>• Emergent BioSolutions 2021 EBS-UFV-001; self-assembling HA stabilized stem nanoparticle<br>• Houser 2022 FluMos-v1; novel ferritin (H2HA-Ferritin) nanoparticle (NIAID)<br>• Darricarrère 2021 Headless HA stabilized stem antigens on ferritin nanoparticles (NIAID)<br>• Eiden 2022 M2SR; M2-deficient single replication live influenza virus vaccine (FluGen) |
| *High-Priority Milestone*<br>**Milestone 4.2.g***:* By 2024, determine correlates of protection for assessing broadly protective or universal influenza vaccines that are appropriate for different stages of vaccine development and different vaccine platforms. [*Wording changed based on IVR SME recommendation*.] | In progress | *Ongoing projects:*<br>• Conference held Mar 1-3, 2023: Correlates of protection for next generation influenza vaccines: lessons learned from the COVID pandemic (ISIRV).<br>• US CDC is developing serological assays to measure correlates of protection for the next-generation influenza vaccines. |
| *High-Priority Milestone*<br>**Milestone 4.2.h***:* By 2025, identify the most promising vaccine candidates from phase 1 trials and advance them into phase 2 or directly to phase 3 clinical trials in high-risk populations. [*Wording changed based on IVR SME recommendation*.] | In progress | *Ongoing Projects:*<br>• Universal influenza vaccine candidates in recently launched phase 2 studies include:<br>  ○ Flitter 2022 VXA-A1.1 (Vaxart) Oral, adenovirus-5-vectored, monovalent HA vaccine candidate<br>  ○ Leroux-Roels 2022 IVX836 (Osivax) Recombinant NP nanoparticle vaccine candidate |
| *High-Priority Milestone*<br>**Milestone 4.2.i***:* By 2027, identify the most promising vaccine candidates from phase 2 trials for general and pediatric populations that demonstrate broad protection and provide durable immunity (more than 1 year) and assess them for efficacy in phase 3 clinical trials. | In progress | *Ongoing Projects:*<br>• Vaccine candidates in phase 3 trials, designed to be broadly protective or universal influenza vaccines include:<br>  ○ Shinde 2022 Nano-Flu qNIV (Novavax) Matrix-M-adjuvanted quadrivalent nanoparticle influenza vaccine candidate |

## ANIMAL MODELS AND THE CONTROLLED HUMAN INFLUENZA VIRUS INFECTION MODEL (CHIVIM)

| ***Strategic Goal 5.1:*** Optimize animal models for influenza vaccine research. | | |
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| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| **Milestone 5.1.a***:* By 2023, develop a mechanism for the broad sharing of animal model resources (e.g., standardized and validated viruses, protocols, reagents, and/or tissue samples) that can be used among a wide range of investigators as standards for influenza vaccine research, which is particularly important given constraints in the availability of experimental animals. [*Date changed from 2022 to 2023; wording changed based on IVR SME recommendation.*] | No evidence identified | We are not aware of any evidence on progress towards this milestone. |
| *High-Priority Milestone*<br>**Milestone 5.1.b***:* By 2023, 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 other animals such as hamsters and to facilitate comparison of studies across laboratories. [*Date changed from 2022 to 2023 and wording changed based on IVR SME recommendation.*] | In progress | *Ongoing Projects:*<br>• NIH RFI: Highest priority needs for ferret and hamster immunoreagents; issued Aug 2021 (Additional Information).<br><br>*Completed Projects*:<br>• T. Race project: Development of ferret reagents for use in the characterization of immune responses to respiratory infections in the ferret model (Additional Information).<br>• S. Tzipori project: Development of ferret and hamster reagents for immunological studies (Additional Information). |
| **Milestone 5.1.c***:* By 2023, develop best practices for conducting influenza virus transmission studies in ferrets and other animals such as hamsters and guinea pigs, to include naive and infected or vaccinated animals. [*Date changed from 2022 to 2023 and wording changed based on IVR SME recommendation.*] | In progress | *Published Reports:*<br>• Belser 2022 conducted a cross-laboratory exercise for influenza risk assessment studies in ferrets. Among environmental parameters that varied across laboratories, donor-to-contact airflow directionality was associated with increased transmissibility.<br>• Nguyen 2021 summarized findings from 2020-21 in influenza virus transmission research with ferret models, such as the "importance of pre-existing heterosubtypic immunity to airborne transmission of influenza viruses." |
| *High-Priority Milestone* | No evidence identified | We are not aware of any evidence on progress towards this milestone. |

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| **Milestone 5.1.d***:* By 2024, convene a workshop on the development of pre-exposure animal models to address the fact that humans generally have pre-existing immunity to influenza. [*Date changed from 2023 to 2024 based on IVR SME recommendation*] | | *Related work:*<br>• Allen 2022 used a pre-immune mouse model to study bivalent COBRA rHA vaccines. |
| *High-Priority Milestone*<br>**Milestone 5.1.f***:* By 2025, complete and publish a comprehensive analysis of the predictive value of different animal models, including natural hosts such as pigs and horses, for influenza vaccine studies (both seasonal and broadly protective vaccines). | No evidence identified | We are not aware of any evidence on progress towards this milestone.<br><br>*Related work:*<br>• Roubidoux 2021 summarized animal models used in the development of "seasonal and novel influenza virus vaccines," including advantages and disadvantages.<br>• Nguyen 2021 reviewed animal models for influenza virus vaccine R&D, including advantages and disadvantages of each model.<br>• Fiege 2022 compared laboratory and pet-store mice (aka "dirty mice") and concluded that "dirty mice better recapitulate transcriptional signatures observed after human vaccinations." |
| *High-Priority Milestone*<br>**Milestone 5.1.g**: By 2026, develop and validate novel animal models for evaluating immune responses—including durability—to broadly protective influenza vaccines. [*Wording changed based on IVR SME recommendation*.] | In progress | *IVR SME input:*<br>• Research projects to improve the predictive value of animal models in recapitulating human immunity to influenza infection and vaccination presented at the Oct 2022 Global Funders Consortium for Universal Influenza Vaccine Development meeting:<br>  ○ AI151231; B. Koller: Genetically humanized mice for modeling human Fc-receptor interaction during influenza infection; mouse model<br>  ○ AI151229; J. Richt: A miniature pig model for the study of host-immune responses against influenza A virus; pig model<br>  ○ AI150678; Y. Kawaoka: Syrian hamsters as an animal model for influenza virus research; hamster model<br>  ○ AI150740; F. Lund: Identification and characterization of effector memory B cell populations that dominate memory responses to subsequent influenza infection and vaccination; mouse model<br>  ○ AI158477-01A1; J. Driver: Genetically modified pigs to model NKT cell immunity to influenza virus infection; pig model<br>  ○ AI58484-01A1; S. Lakdawala: Role of preexisting immunity on airborne transmission of influenza viruses; ferret model |

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| | | *Ongoing Projects:*<br>• NIAID PAR-19-247 and PAR-19-248: Research projects to improve the predictive value of animal models in recapitulating human immunity to influenza infection and vaccination.<br>  ○ J. Harty project: Evaluation of CC mice as an improved model for influenza immunity (Additional Information).<br>  ○ D. Masopust project: New mouse model to better predict human immunity to influenza vaccination and infection (Additional Information).<br>  ○ R. Webby project: The project goal is to "provide superior preclinical models via three aims: 1) optimal modeling of human serologic responses to repeat influenza antigen exposure via animal models; 2) improving the quantitative nature of the ferret influenza challenge model; and (3) defining serologic correlates of influenza virus induced clinical symptoms (Additional Information).<br>• A. Garcia-Sastre project: Evaluation of the immune responses to influenza virus vaccines and efficacy of immunotherapeutics in the ferret model (Additional Information).<br>• K. Waldorf project: Influenza pathogenesis in pregnancy using the NHP model (Additional Information).<br>• M. Wane project: RSV and LAIV infection in zebrafish gills as a model for human respiratory disease (funded by Wellcome Trust).<br><br>*Completed Projects:*<br>• K. Walters projects: Ferret models for the evaluation of universal influenza vaccines and vaccine strategies (Additional Information) and ferret models for the evaluation of influenza vaccines and vaccine strategies (Additional Information).<br>• J. Yount project: Establishing a relevant mouse model with susceptibility to non-adapted influenza viruses for vaccine challenge studies (Additional Information). |
| ***Strategic Goal 5.2:*** Address steps needed to further develop and refine the CHIVIM. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| *High-Priority Milestone*<br>**Milestone 5.2.a***:* By 2024, determine the use cases for the CHIVIM and generate guidance, including ethical and safety considerations, for using the model. [*Date changed from 2022 to 2024 based on IVR SME recommendation.*] | In progress | *IVR SME Input:*<br>• In Jan 2022, WHO published global guidance on the ethical conduct of controlled human infection studies, which includes language on influenza (WHO 2022). |

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| *High-Priority Milestone*<br>**Milestone 5.2.b***:* By 2024, ensure that virus strains for the CHIVIM are broadly available. [*Date changed from 2023 t0 2024 and wording changed based on IVR SME recommendation*.] | In progress | *IVR SME Input:*<br>• NIAID is in the process of making challenge strains available for H3N2 and H1N1. |
| *High-Priority Milestone*<br>**Milestone 5.2.c***:* By 2024, ensure that a bio-repository of diverse, accessible, and well-characterized challenge stocks is generated and made available to investigators. [*Date changed from 2023 to 2024 based on IVR SME recommendation*.] | No evidence identified | We are not aware of any evidence on progress towards this milestone. |
| *High-Priority Milestone*<br>**Milestone 5.2.d***:* By 2024, further develop the CHIVIM to ensure that it can be widely used by different investigators. | In progress | *IVR SME Input:*<br>• Multiple longitudinal cohort studies on influenza immunity in infants and older adults were discussed during the Oct 2022 Global Funders Consortium for Universal Influenza Vaccine Development meeting:<br>◦ AI144673-01; M. Staat: Impact of the initial influenza exposure on the quality, magnitude, breadth, potency and durability of influenza immunity (Additional Information)<br>◦ (U01)AI165826-01; S. Xiao Leng: Leveraging an ongoing longitudinal study of influenza vaccination to define immune signatures of response and risk of infection in older adults >75 (Additional Information)<br>◦ (U01)AI165442-01; W. Marasco: Identification of metabolic and immune deficits in the aged population and their restoration to achieve youthful anti-influenza vaccine responsiveness (Additional Information)<br>◦ (U01)AI165452-01; D. Ucar: A deep longitudinal analysis of next generation influenza vaccines in older adults (Additional Information)<br>◦ AI144616-01; P. Thomas: DIVINCI (Additional Information)<br>◦ RFA-AI-20-008: AI162130-01; D. Milton: Evaluation models of influenza transmission using innovative technologies and designs in controlled environments (Additional Information)<br><br>*Ongoing Projects:*<br>• Per NIAID's Dec 2021 update to the Global Funders Consortium for Universal Influenza Vaccine Development: NIAID is supporting human clinical challenge studies |

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| | | to help advance the development of universal influenza vaccine candidates by providing an efficient and comprehensive method of examining the durability and efficacy of the vaccines. An influenza H1N1 human challenge study to assess the effect of preexisting immunity on clinical and immunological responses to infection completed enrollment in Dec 2019. Primary and secondary endpoints results were posted in Apr 2021 and exploratory laboratory analyses are currently ongoing (Additional Information).<br>• N. Rouphael project: Human challenge study on "how the immune system responds to [H3N2] during and after infection and how the flu virus is transmitted in the environment" (Additional Information).<br>• M. Memoli project: A "dose-finding and pathogenicity study following human challenge with a low pathogenicity avian influenza A H10N7" clinical study (Additional Information).<br>• Multiple respiratory viral human challenge programs were highlighted during the Jul 2022 CIVICs meeting, including:<br>  ○ DARPA: Predicting health and disease (n=~120) used HRV, RSV, and influenza (H3N2, H1N1) to study pre-symptomatic disease<br>  ○ DARPA: Prometheus (n=39) used influenza pH1N1 to study contagiousness<br>  ○ DARPA: SIGMA Plus (n=20) used influenza H3N2 to study pre-symptomatic disease and wearables<br>• Project: Support the development and validation of influenza strains that could eventually be utilized to evaluate candidate universal influenza vaccines in human challenge studies (funded by BMGF)<br>• Project: Innovations to accelerate vaccine development and manufacture (Additional Information; funded by EC) |

## 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. | | |
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| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| *High-Priority Milestone*<br>**Milestone 6.1.a***:* By 2024, develop and disseminate a full value of vaccine assessment | In progress | *IVR SME Input:*<br>• US CDC is supporting WHO efforts to develop material for the FVIVA. |

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| (FVVA; also referred to as the full value of influenza vaccine assessment [FVIVA]) for improved seasonal and broadly protective, universal influenza vaccines that addresses different vaccine use cases and includes an assessment for LMICs. [*Date changed from 2022 to 2024 based on IVR SME recommendation*.] | | • The WHO Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC) met in Sep 2022 and reviewed FVIVA methodology (WHO 2022).<br><br>*Published Reports:*<br>• Hutubessy 2021 outlined "a framework on the [FVIVA] to guide the assessment and communication of the value of vaccines, to facilitate alignment among key stakeholders, and to improve decision-making around investment in vaccine development, policy, procurement, and introduction, for vaccines indented for use in LMICs."<br>• The WHO Product Development for Vaccines Advisory Committee (PDVAC) has initiated a Vaccine Value Profile (VVP) to inform the FVIVA for influenza vaccines.<br><br>*Ongoing projects:*<br>• WHO and LSHTM, with funding from US CDC as part of a five-year cooperative agreement ending in 2024, are engaged in a full value of influenza vaccine assessment (FVIVA) project aimed at identifying critical success factors that would enable the development, approval, and introduction of next-generation influenza vaccines (Additional Information). |
| *High-Priority Milestone*<br>**Milestone 6.1.b***:* By 2024, develop targeted and creative communications and advocacy strategies and necessary communication tools that build on the FVIVA and provide information on economic costs, the risk of future influenza pandemics, and the need for investment in influenza vaccine R&D. [*Date changed from 2022 to 2024 based on IVR SME recommendation*.] | In progress | *IVR SME Input:*<br>• US CDC is supporting WHO efforts to develop material for the FVIVA.<br><br>*Ongoing Projects:*<br>• WHO and LSHTM are engaged in the FVIVA project that will include addressing communication tools and advocacy strategies (Additional Information).<br><br>*Related Work*:<br>• M. Hudgens project: Causal inference in infectious disease prevention studies (Additional Information).<br>• M. Paulden project: Optimizing adult vaccination outcomes under public health budgetary constraints (Additional Information).<br>• A. Krishnan project Strengthening evidence-based advocacy for influenza prevention and control in India (Additional Information). |
| ***Strategic Goal 6.2:*** Promote innovation for developing improved seasonal influenza vaccines and broadly protective or universal influenza vaccines. | | |

| Milestone | Status | IVR SME Input, Published Reports, Ongoing Projects, and Related Work |
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| *High-Priority Milestone*<br>**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. | Target date met | *IVR SME Input:*<br>• US CDC is a collaborator to this work, including via collaborative work through the Partnership for Influenza Vaccine Introduction (PIVI).<br><br>*Published Reports:*<br>• The National Academy of Medicine convened a workshop in May 2021 focused on lessons learned from COVID-19 to "inform and advance pandemic and seasonal influenza vaccine preparedness efforts and subsequent response."<br>• Arinaminpathy 2022 summarized lessons learned for influenza vaccine R&D from the COVID-19 pandemic in the topic areas of epidemiological implications, economic implications, global production capacity, and roles for donors and policy-makers.<br>• Pecetta 2022 summarized economic and regulatory lessons learned from the COVID-19 pandemic.<br>• Bollyky 2021 highlighted lessons learned from the COVID-19 pandemic to "(1) identify the greatest opportunities and workable ideas for shortening the time to vaccine availability and (2) eliminate disparities in access in future pandemics by proposing ways to rework the architecture that supports the end-to-end vaccine R&D and response ecosystem."<br>• A 2022 report from IFPMA summarizes lessons learned for vaccine manufacturing during a pandemic (e.g., regarding pathogen surveillance and data sharing, equitable distribution, and pharmaceutical partnerships to accelerate R&D and manufacturing).<br><br>*Ongoing Projects:*<br>• WHO and LSHTM are engaged in the FVIVA project aimed at identifying critical success factors that would enable the development, approval, and introduction of next-generation influenza vaccines (Additional Information). This effort will contribute to identifying lessons learned from COVID-19. |
| ~~*High-Priority Milestone*~~<br>~~**Milestone 6.2.b***: Identify a set of strategies for accelerating the development of universal influenza vaccines through innovative approaches (Sabin 2019).~~ | | *IVR SME Input:*<br>• Recommendation to remove milestone. |
| ***Strategic Goal 6.3:*** Promote information sharing aimed at moving influenza vaccine development forward. | | |

| Milestone | Status | IVR SME Input, Published Reports, Ongoing Projects, and Related Work |
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| **Milestone 6.3.a***:* By 2021, 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. | Partially met | *Ongoing Projects:*<br>• CIDRAP at the University of Minnesota, with funding from the Global Funders Consortium for Universal Influenza Vaccine Development, developed and maintains the Universal Influenza Vaccine Technology Landscape. The landscape is updated regularly. Efforts are still needed to develop a mechanism to analyze the landscape; this has not yet been done. |
| ~~**Milestone 6.3.b***: By 2022, 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).~~ | | *IVR SME Input:*<br>• Recommendation to remove milestone. |
| *High-Priority Milestone*<br>**Milestone 6.3.c***:* By 2023, 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. [*Date changed from 2022 to 2023 based on IVR SME recommendation.*] | In progress | While no formal assessment has been done, this issue is being recognized and is under discussion.<br><br>*IVR SME Input:*<br>• US CDC is supporting this work through WHO working groups and input to the WHO World Health Assembly.<br>• WHO has published several reports on the public health implications of the Nagoya protocol:<br>  ○ Implementation of Decision WHA72(12), which included requests related to influenza virus sharing:<br>  ○ Report on influenza virus sharing<br>  ○ Summary report on national legislation and regulatory measures related to influenza<br>  ○ Public health implications of the Nagoya Protocol<br><br>*Related Work:*<br>• IFPMA noted agreement "across UN agencies and member states, along with science, public health, and legal experts, civil society, foundations, and industry… that access to pathogen samples and their genetic information is fundamental to improved preparedness and response." One of the "approaches under consideration to improve pandemic preparedness and response related to pathogen sharing" |

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| | | includes "changes to the Convention on Biological Diversity's Nagoya Protocol expressly to exclude outbreak pathogens…" (Additional Information). |
| **Milestone 6.3.d***:* By 2023, implement a plan that improves existing data management and sharing among influenza R&D researchers that includes developing and approach for reusing influenza vaccine study data (e.g., secondary mining of datasets). [*Date changed from 2022 to 2023 and wording changed based on IVR SME recommendation*.] | No evidence identified | We are not aware of any evidence on progress towards this milestone. |
| **Milestone 6.3.e***:* By 2023, conduct mapping of intellectual property for improved influenza vaccines to identify synergies in approaches that may be used to develop new partnerships. [*Date changed from 2022 to 2023 based on IVR SME recommendation*] | In progress | *Ongoing projects:*<br>• WHO and LSHTM are engaged in the FVIVA project that will contribute to mapping intellectual property for improved influenza vaccines (Additional Information). |
| *High-Priority Milestone*<br>**Milestone 6.3.h**: By 2025, develop strategies for international data sharing that take into account the impact of the Nagoya protocol and other limitations on data sharing. [*New milestone as of Sep 2022 based on IVR SME recommendation.]* | In progress | *IVR SME Input:*<br>• New milestone as of Sep 2022.<br>• US CDC is supporting this work through WHO working groups and input to the WHO World Health Assembly.<br>• WHO has published several reports on the public health implications of the Nagoya protocol:<br>  ○ Implementation of Decision WHA72(12), which included requests related to influenza virus sharing:<br>  ○ Report on influenza virus sharing<br>  ○ Summary report on national legislation and regulatory measures related to influenza<br>  ○ Public health implications of the Nagoya Protocol |
| ***Strategic Goal 6.4:*** Further explore regulatory challenges associated with development and manufacturing of improved seasonal and broadly protective or universal influenza vaccines. | | |
| **Milestone** | **Status** | **IVR SME Input, Published Reports, Ongoing Projects, and Related Work** |
| *High-Priority Milestone*<br>**Milestone 6.4.a***:* By 2024, conduct one or more workshop(s) that includes regulators and | In progress | *IVR SME Input:*<br>• Issues around regulatory approval will likely need to be addressed in multiple different workshops or other fora (e.g., EMA and FDA regulators participated in |

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| 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, (4) generate additional recommendations regarding how best to provide guidance on vaccine development, manufacture, approval, and delivery, and (5) create a timeline of critical dependencies needed to produce new regulator guidance for approval of improved seasonal and broadly protective or universal influenza vaccines. [*Date changed from 2022 to 2024 and wording changed based on IVR SME recommendation.*] | | discussions at the ISIRV Correlates of Protection for Next Generation Influenza Vaccines conference in Seattle, March 1-3, 2023). IVR SMEs agreed that it is unlikely for one workshop to be able to address all of these issues.<br><br>*Ongoing projects:*<br>• WHO and LSHTM are engaged in the FVIVA project, which includes conducting an introductory workshop on regulatory considerations for next-generation influenza vaccines (Additional Information). |
| *High-Priority Milestone*<br>**Milestone 6.4.b**: By 2024, identify a framework to address post-marketing assessment of safety and effectiveness of new broadly protective or universal influenza vaccines. [*Date changed from 2023 to 2024 based on IVR SME recommendation.*] | No evidence identified | We are not aware of any evidence on progress towards this milestone. |

**Abbreviations:**
Ab: antibody; ABS: Access and benefit sharing; Ad5: Adenovirus-5; ADCC: Antibody-dependent cellular cytotoxicity; BMGF: Bill & Melinda Gates Foundation; bNAb: broadly neutralizing antibody; BPL: β-propiolactone; CC: Collaborative cross (mice); CDC: Centers for Disease Control and Prevention; CEIRR: Centers of Excellence for Influenza Research and Response; cGAMP: Cyclic guanosine monophosphate–adenosine monophosphate; cHA: chimeric hemagglutinin; CHIVIM: Controlled human influenza virus infection model; CIC: Combined influenza-COVID vaccine; CIDRAP: Center for Infectious Disease Research and Policy (University of Minnesota); CIHR: Canadian Institutes of Health Research; CIVICs: Collaborative Influenza Vaccine Innovation Centers;

COBRA: Computationally optimized broadly reactive antigen; COVID-19: Coronavirus disease 2019; DARPA: Defense Advanced Research Projects Agency; DCVMN: Developing Countries Vaccine Manufacturing Network; DIVINCI: Dissection of Influenza Vaccination and Infection for Childhood Immunity (consortium); DRIVE: Dynamics of the immune responses to repeat influenza vaccination exposures study; EC: European Commission; ELISA: Enzyme-linked immunoassay; ELLA: Enzyme-linked lectin assay; EMA: European Medicines Agency; EU: European Union; FAO: Food & Agriculture Organization of the United Nations; $F_c$: Fragment crystallizable; FDA: US Food and Drug Administration; FVIVA: Full value of influenza vaccine assessment; FVVA: Full value of vaccine assessment; GIHSN: Global Influenza Hospital Surveillance Network; GISRS: Global Influenza Surveillance and Response System; HA: Hemagglutinin; HAI: Hemagglutinin inhibition assay; HHS: US Health and Human Services Department; HRV: Human rhinovirus; IFPMA: International Federation of Pharmaceutical Manufacturers and Associations; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IIV: Inactivated influenza virus vaccine; IM: Intramuscular; IN: Intranasal; INSERM: National Institute of Health and Medical Research (France); IPG: Institute for Pathogen Genomics; ISIRV: International Society for Influenza and other Respiratory Virus Diseases; IVIR-AC: Immunization and Vaccine-related Implementation Advisory Committee; IVR: Influenza Vaccines Research & Development Roadmap; LAIV: Live-attenuated influenza vaccine; LMICs: Low- and middle-income countries; LSHTM: London School of Hygiene & Tropical Medicine; MAIT: Mucosal-associated invariant T cells; MAS-1: Macrophage activation syndrome-1; MPP: Measles virus phosphoprotein; MRC: Medical Research Council; mRNA: Messenger ribonucleic acid; NA: Neuraminidase; N1: Neuraminidase-1
nAb: Neutralizing antibody; NAMRU-6: Naval Medical Research Unit Six; NASEM: National Academies of Sciences, Engineering, and Medicine; NHP: Nonhuman primate; NIAID: US National Institute of Allergy and Infectious Diseases; NIAID-SEM-CIVIC: NIAID Sinai-Emory Multi-Institutional CIVIC center; NIH: National Institutes of Health; NKT: Natural Killer T (cells); NP: Nucleoprotein; NS-1: Nonstructural gene 1; OFFLU: Global Network of Expertise on Animal Influenza; PAHO: Pan American Health Organization; PDVAC: Product Development for Vaccines Advisory Committee (WHO); PPCs: Preferred product characteristics; QIV: Quadrivalent inactivated influenza vaccine; R&D: Research and development; RCT: Randomized clinical trial; RFI: Request for information; rHA: Recombinant hemagglutinin; rNA: Recombinant neuraminidase; rVE: Relative vaccine effectiveness; RIV4: Recombinant influenza virus vaccine, quadrivalent; RNA: Ribonucleic acid; RSV: Respiratory syncytial virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SME: Subject matter expert; SOP: Standard operating procedure; TIV: Trivalent inactivated influenza vaccine; TLR-3: Toll-like receptor-3; $T_{RM}$: Resident memory T cells; UGA: University of Georgia; UN: United Nations; US: United States; VE: Vaccine efficacy/effectiveness; VVP: Vaccine value profile; WHO: World Health Organization