Influenza Vaccines Research & Development (R&D) Roadmap (IVR)

Monitoring, Evaluation and Adjustment (ME&A) Taskforce Meeting

Summary Report

25 September 2022
Belfast, UK

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Background and Meeting Objectives

The Influenza Vaccines Research and Development (R&D) Roadmap (IVR), launched September 2021, is a 10-year effort to accelerate progress toward the improvement of seasonal influenza vaccines and the development of new universal or broadly protective influenza vaccines. By highlighting key research gaps, identifying strategic goals and milestones, and encouraging synergistic R&D activities, the roadmap will serve as a valuable tool to advance the complex field of vaccine research over the next 10 years and stimulate overall investment in influenza vaccine R&D.

The Center for Infectious Disease Research and Policy (CIDRAP), with generous support from Wellcome Trust, has recently embarked on a 3-year project aimed at: (1) tracking progress in meeting the IVR goals and milestones through Monitoring, Evaluation, and Adjustment (ME&A) and (2) assessing funding trends for influenza vaccine R&D. These twin efforts will enhance transparency and accountability, guide the adjustment of IVR milestones, highlight additional funding needs, and identify new opportunities for collaboration.

The IVR expert taskforce plays a critical role in guiding and informing these activities. To enlist their expertise, the first of three anticipated annual meetings was convened in Belfast, UK on September 25, 2022, and took place in a hybrid format combining in-person and virtual participation (for agenda, see Appendix A). Over the course of 8 hours, 29 designated participants and 15 observers (who were also invited to contribute to discussions) examined the methodology and results of CIDRAP's funding tracking efforts and appraised progress toward meeting immediate (i.e., those with a 2022 target date) and high-priority research milestones in each of the IVR's six sections (listed in order of meeting discussion):

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

These discussions accomplished the following meeting objectives:

- Review findings to date from the CIDRAP team's monitoring activities related to current R&D funding.
- Review findings to date on R&D outcomes, focusing on IVR milestones with a 2022 completion and those with a high priority designation.
- To guide meeting discussion, the CIDRAP team compiled and presented findings for research and funding data in tabular form to meeting participants and observers. The six draft discussion tables are also appended to this summary (see Appendices B through G). These tables are in progress and include only preliminary data collected to date, and should not be considered final or comprehensive.
- Share knowledge of additional important funding or research progress relevant to the IVR milestones, including information outside the public domain.
- Consider additional key points relevant to individual milestones:
    - If progress had not been made: (1) review potential reasons for lack of progress, (2) determine whether and how interventions are needed, and (3) identify options for such strategies as necessary.
    - Determine if milestone timelines required adjustment to meet stated goals and make recommendations as necessary.
    - Determine whether milestone language should be modified, or if the milestone should be deleted.

Meeting Participants and Observers

Meeting participants and observers joined both in-person and virtually. Those who participated virtually are noted with an asterisk (*).

IVR Steering Group (SG), Taskforce (TF), and Guest Participants		
William Ampofo (TF)	Rosalind Hollingsworth (SG)	Punnee Pitisuttithum (TF)
Edward Belongia (TF)	Kari Johansen (TF)	Diane Post (SG)
Joseph Bresee (SG)	Eric Karikari-Boateng (TF)	Tiago Rocca (TF)
David Brown (TF)	Stacey Knobler (SG)	Stacey Schultz-Cherry (TF)
Macro Cavaleri (TF)*	Florian Krammer (TF)	Ethan Settembre (TF)
Christopher Chadwick (SG)	John Lim (TF)*	Yue-Long Shu (TF)*
Rebecca Cox (TF)*	John McCauley (TF)	James Southern (TF)*
Bruce Gellin (SG)	Ann Moen (SG)	John Tam (TF)*
Josie Golding (SG)	Michael Osterholm (SG)	Rajeev Venkayya (TF)*
Peter Hart (SG)	John Oxford (Guest Participant)	

Guest Observers		
Pirada Allen	Anna Kinsey*	Julie Schafer
Jessica Flynn	Clarisse Lorin*	Seema Sharma*
Jennifer Gordon*	Emilio Muñoz	Vivek Shinde
Teresa Hauguel*	Raffael Nachbagauer	Brian Ward*
Susan Johnson	Olga Pleguezuelos*	Casey Wright

IVR Core Team (CIDRAP) and Taskforce Meeting Team		
Lauren Bigalke	Anje Mehr*	Angela Ulrich
Eve Lackritz	Kristine Moore	Mary Watson*
Alison Mack	Julie Ostrowsky	

Monitoring and Tracking IVR Progress

Kristine Moore (CIDRAP) described the methods used to monitor progress towards meeting IVR milestones. Specifically:

- **Research outcomes** tracking, which focuses on the following sources to track research activities: published reports (via PubMed), online resources, scientific meetings, CIDRAP's Universal Influenza Vaccines Technology Landscape database, and input from IVR Steering Group and Taskforce members
- **Funding** tracking, which focuses on using publically available online databases and direct outreach to funders to identify funding focused on influenza vaccines R&D (described in more detail below)

In preparation for the meeting, CIDRAP compiled draft tables (Appendices B-G), which summarize the results of research outcomes and funding tracking to date for high-priority milestones and those with a 2022 target date for completion. Because of time limitations, milestones that are not high-priority and with a 2023 or later target date were not included in the tables for meeting discussion.

IVR Funding Tracking Project

Methodology and Progress to Date

Angela Ulrich (CIDRAP) described work in progress on the IVR Funding Tracker project, which launched in July 2022. In the following summary of her presentation, excerpts from the subsequent discussion (*in italics*) are appended to the specific presentation topic addressed by each speaker.

Purpose and Goals of the IVR Funding Tracker

- Tracking funding is essential to coordinate and accelerate influenza vaccine R&D through:
  - Priority setting
  - Identifying gaps or areas of underfunding
  - Informing future funding decisions
  - Improving efficiency in funding allocation
  - Potentially attracting new funders
- The Funding Tracker addresses the IVR Policy, Financing, and Regulation milestone 6.1.c, "Create and implement a mechanism to track influenza vaccine R&D funding trends to better assess where funding is being allocated and identify gaps in funding for priority research."
- Similar R&D funding tracking efforts are underway for tuberculosis by the Treatment Action Group and COVID-19 by UK Collaborative on Development Research (UKCDR) in collaboration with the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). CIDRAP aligned with the COVID-19 tracking efforts to gain lessons learned and feedback; over time, the COVID-19 tracker will likely encompass multiple diseases. Therefore, in the future, the CIDRAP team anticipates sharing their own lessons learned with UKCDR and GloPID-R, as well as potentially incorporating influenza funding tracking information into the future database that will encompass multiple diseases.
- The IVR Funding Tracker is designed to answer these questions:
  - Is investment in global influenza vaccine R&D aligned with the goals and milestones outlined in the IVR?
  - Where do funding gaps exist?
  - Have priorities outlined in the IVR shifted over time?
  - *Participant comment: While it would be useful to discern the impact of COVID-19 on influenza R&D funding, this question is not answerable through the Funding Tracker, nor is this influence being captured by GloPID-R.*

Methods

- Information sources include funders, researchers, the Universal Influenza Vaccine Technology Landscape database, published literature, online sources, clinical trial registries (e.g., ClinicalTrials.gov), industry websites and news sources, conference abstracts, and IVR taskforce members.
  - Initial funding queries were directed through the Global Funders Consortium for Universal Influenza Vaccine Development (GFC) and its industry work group.
  - *CIDRAP comment: The search for funders is ongoing—Taskforce members are encouraged to share funder information with the CIDRAP team.*
  - *Participant comment: GloPID-R and the University of Oxford aim to define adaptable methods to streamline funding tracking methods for disease research. They are also facilitating the establishment of regional funders' groups that can provide information on funding activities yet to be discovered by the IVR Funding Tracker and similar efforts.*
  - *Additional participant comments:*
    - *Industry funding is a major but opaque driver of influenza R&D. What methods could the IVR Funding Tracker use to gain information on what projects industry funds and*

defunds—decisions that are made in boardrooms (question posed to industry representatives)?
    - *Public sources include papers (even on things that don't work) and prospectus data, which reveal if a project is killed by its absence.*
    - *Companies closely track what each other are funding. All post detailed pipeline updates once or twice each year on their websites, or as part of their investor days, or in their quarterly earnings reports.*
  - *When reaching out to funders, request information on open or future calls for proposals—and therefore determine which ideas are being pushed forward.*
  - *Public-private partnership funding is a significant R&D driver in low- and middle-income countries (LMICs). It was key to the COVID-19 response; going forward it is the basis of pandemic preparedness in these countries, particularly with regard to building and maintaining local/regional vaccine manufacturing capacity.*
- Database development through REDCap (Research Electronic Data Capture): a secure web application that enables online and offline data capture for research and which is supported by the University of Minnesota Clinical and Translational Science Institute.
- Work to date prioritized the mapping of IVR topic areas and high-priority milestones; work to come will map strategic goals and all other milestones.
- Data derived from publicly available online sources and from information provided by funders directly contacted by the CIDRAP team, via email, virtual meeting, or survey.
- Identified projects and activities are mapped to IVR topic areas, strategic goals, and milestones.
  - Exclusion criteria: out of scope of IVR (see IVR for scope details); not related to influenza; not related to key IVR topic area
  - Inclusion criteria: within scope of IVR; related to influenza, influenza vaccine R&D, or the six key topic areas outlined in the IVR
  - Coding follows predetermined guidelines
  - Mapping will be validated by the funder, if/when possible
  - All decisions in this process are documented
- *Participant comments: Uptake is not currently within the scope of the IVR. Should it be, given COVID-19 experience?*
  - *R&D investment won't pay off unless there is adequate uptake of the products it delivers. Excluding funding sources aimed at uptake may be excluding a valuable source of information going forward.*
  - *The IVR must be narrow to be effective (CIDRAP).*
  - *The IVR Funding Tracker is already capturing some information on uptake, within data that doesn't map to specific roadmap goals and milestones. It's possible that the IVR could expand beyond R&D, perhaps when it joins the larger GloPID-R effort (CIDRAP).*
  - *This remains a live question—as does that of equity issues in the design of vaccines—and should remain open to discussion.*
  - *Tracking uptake requires information on public health funding sources.*

Outcomes

- Work to date began July 2022. With initial focus on tracking projects/activities funded in 2020 (initiated *or* ongoing funding), more than 900 projects have been entered in the database to date. Mapping to date has focused on high-priority milestones and those with a 2022 target date.
- In addition to answering key questions noted above, the IVR Funding Tracker will provide information on these features, including time trends:
  - Number of funded projects and research groups

  - Funder type (i.e., public, private, philanthropic, multilateral, etc.)
  - Funding amount, in total and dedicated to each topic area
  - Geographic distribution of funders and recipients
- Initial focus has been on discovering whether each high-priority milestone has or has not received funding; determining the total amount of funding assigned to each milestone has proved challenging and these data will have limitations.
- *Participant comments:*
  - *Funding is a leading indicator of emphasis, but the challenge is to know "how much is enough" to meet a milestone, and what constitutes a gap. How is GloPID-R handling this dilemma?*
  - *The GloPID-R COVID-19 roadmap was launched in March 2020 to determine who was investing in those areas and to advocate for investment where gaps were identified. It's not a complete picture, nor can it determine appropriate funding amounts; instead, its findings are used by the World Health Organization (WHO) working groups to inform priority-setting. The roadmap tracks where UK funding for COVID-19 has gone: very little to R&D priorities within LMICs. We need to keep the focus on gaps, and how (all) roadmaps will benefit individual funders and groups.*
- Present limitations of the IVR Funding Tracker include:
  - This is a biased sample (not a random selection or representative sample of all funding projects)
  - Will not be able to identify all funders or projects (hard to capture global funding, looking at English-based resources, inability to obtain proprietary industry information).
    - *Participant comment: India and China are massive vaccine producers. The political situation is difficult but must strive to include them—it's been done before (e.g., US-UK-Russia collaboration despite cold war).*
  - Proportion of funding per project/activity dedicated to strategic goal or milestone is unknown in most instances.
  - Many projects and activities remain to be entered.
  - Not all projects that have been entered to date have been mapped to goals and milestones.

Next Steps

- Next steps for the IVR funding tracker project include the following:
  - Ongoing outreach to gather additional information
  - Ongoing mapping to topic area, strategic goals, and all milestones
  - Validation of milestone mapping with funders (if possible)
  - Develop online publically available dashboard to communicate results, using the GloPID-R COVID-19 Research Projects Tracker as an example
  - *Participant comment: Assemble a list of high-priority milestones specifying a workshop or other convening for which no responsible party is designated to be presented to/discussed with the GFC in November.*
- The timeline for next steps was presented as follows:
  - Preliminary annual report (Quarter 4 [Q4] 2022) or early Q1 2023
  - Online dashboard (Q2 2023)
  - Publication (Q3 2023)
  - Annual reports (Q4 2023 and Q4 2024)
  - Final report (Q1 2025)
  - Publication (Q1 2025)

Progress on IVR Milestones

Participants discussed progress toward meeting high-priority milestones and/or milestones with a 2022 target date in each of the roadmap's six sections. The starting point for these deliberations were draft discussion tables (Appendices B-G) summarizing the preliminary results of outcome and funding tracking on all high-priority milestones and those with a 2022 completion date.

For each IVR area, a facilitator expert in that field led organized discussion of progress on each milestone to be considered, during which participants:

- Shared additional knowledge of research outcomes not shown in the draft discussion table
- Offered suggestions on language and organizational changes to milestones
- Affirmed or revised milestone status designations
- Affirmed or revised milestone target dates

Based on a taskforce member suggestion, the status designation "Completed" shown in the draft discussion tables has been replaced with "Target Date Met."

Updates to research and funding tracking (as reflected in the "Published Reports, Ongoing Projects, and Related Work" column of the draft discussion tables) will be produced that incorporate sources suggested by meeting participants.

[*Addendum Note*: Two high-priority milestones were inadvertently left off of the discussion tables that were shared at the meeting.

- Milestone 5.2.c (Animal Models and the CHIVIM): By 2023, ensure that a biorepository of diverse, accessible, and well characterized challenge stocks is generated and made available to investigators.
- Milestone 6.4.b (Policy, Financing, and Regulation): By 2023, identify a framework to address post-marketing assessment of safety and effectiveness of new broadly protective or universal influenza vaccines.

CIDRAP will reach out to several IVR steering group or taskforce members to determine if they are aware of progress on these two milestones. Any pertinent information will be incorporated into CIDRAP's first annual report on IVR ME&A.]

Progress on Vaccinology for Seasonal Vaccines Milestones

Joseph Bresee served as facilitator for discussion organized according to the draft table shown in Appendix B. The following table summarizes discussion output.

Strategic Goal 3.2: Identify strategies and policies to optimize seasonal influenza vaccines and improve vaccine effectiveness.			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
Milestone 3.2.a: By 2022, identify lessons learned from COVID-19 vaccine development for improving seasonal influenza vaccines, ensuring reliable delivery of products, and sharing	Target date met*	New technologies (mRNA and others) are being applied to flu; uncertain whether they'll lead to an *improved* vaccine but they are being tested. Relates to Milestone 3.1 (not discussed at this meeting):	Change wording to identifying preliminary lessons (per the National Academies of Sciences, Engineering, and Medicine [NASEM] report); and remove the word "improving" (as we do not know if the lessons learned will result in improvements).

the costs of establishing new technologies or production strategies.		COVID-era vaccine technologies have the potential to speed production of influenza vaccines and eliminate the need for candidate strains (multiple participants); likewise, the US Food and Drug Administration's (FDA's) regulatory model for COVID-19 vaccines could be applied to speed access to influenza vaccines. No lessons yet on cost-sharing.	Add a new milestone regarding the *demonstration* of the applicability of mRNA and other new technologies to influenza vaccines. Possibly remove cost-sharing from among the lessons listed—perhaps by creating separate milestone.
High priority **Milestone 3.2.b:** By 2022, convene a workshop to review the development of novel platforms (e.g., mRNA-based) for COVID-19 vaccines to identify how best to apply them to developing improved seasonal influenza vaccines.	In progress	A workshop on new vaccine technologies is being planned by the Bill & Melinda Gates Foundation (BMGF) for 2023. The topics discussed should include regulatory issues and comparisons of egg-based and novel technologies and data on the Protein Sciences (Sanofi) novel technologies.	Consider changing the target date to 2023.
Milestone 3.2.c: By 2022, ensure that at least two combined COVID-19 and seasonal influenza vaccines are being evaluated in clinical trials.	Target date met	There was general agreement that this milestone has been completed.	Eliminate "ensure" from the milestone language, as this is not within IVR's scope. Clarify description of Moderna mRNA 1073 listed as evidence (as Moderna mRNA-1273 + mRNA-1010).
High priority **Milestone 3.2.e***:* By 2024, determine optimum methods for assessing the effectiveness of conventional egg-based and cell culture-based vaccines with new vaccine technologies, in coordination with regulatory agencies and using consistent end points, to allow data to be combined (WHO 2016a) as appropriate over multiple seasons and to	No evidence identified	Assessing comparative effectiveness is challenging due to requirement for large populations; a possible route is to offer proven immunogenic vaccines on a study basis. The milestone is to assess methods for measuring relative effectiveness, not outcome. A workshop is needed to address challenges of assessing comparative effectiveness and establish a consensus trial	Add language of a workshop to this milestone or create another workshop-specific milestone.

allow better comparability of data across studies.		design to measure vaccine effectiveness. This topic should be addressed during the November 2022 GFC meeting.	
High priority **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 (Calzas 2019, Erbelding 2018).	In progress	US Centers for Disease Control and Prevention (CDC) is evaluating needle-free vaccines; this data will be shared with the CIDRAP team. This is an area where work underway on COVID-19 mucosal vaccines will provide important lessons for influenza vaccines.	Update evidence for milestone with CDC data. The Biomedical Advanced Research and Development Authority (BARDA) conducted a challenge study to compare Fluzone vs. the oral vaccine that should be added to the milestone evidence; include information on this study (Vaxart) and other clinical trials as appropriate (noted in the Landscape).
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**	**Discussion highlights**	**Suggested actions**
Milestone 3.3.a*:* By 2022, develop standardized clinical endpoints for severe influenza disease that can be used in clinical vaccine efficacy studies (WHO 2017).	No evidence identified	A workshop is needed to set consensus definitions of endpoints as part of trial design workshop proposed at a 2021 GFC meeting. Endpoint consensus is currently lacking; same is true when studies compare vaccines employing different antigens. Hospitalization is a potential endpoint given the lack of widespread testing. Transmission should also be considered as an endpoint somewhere in the roadmap.	Milestone should specify need for endpoints relevant to special populations (e.g., infants, elderly, people with chronic conditions); WHO has introduced this language. Add complications from severe influenza to endpoint description. Change target date to 2023 or 2024 to allow for workshop(s) and/or publications to establish endpoint consensus. Add the concept of possibly holding a workshop to address this. Consider adding a transmission endpoint in the roadmap.
Milestone 3.3.b*:* By 2022, develop and validate a	Target date met	See 3.3.a	See 3.3.a

standard scale for assessing influenza disease severity.	for some objectives		
Strategic Goal 3.4: Further assess the role of existing and new adjuvants in creating next-generation seasonal influenza vaccines, informed by recent R&D with adjuvants in new COVID-19 vaccines (Li 2021, Tregoning 2018, Zhu 2021).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
High priority **Milestone 3.4.b***:* By 2026, determine, through clinical studies, if any promising new adjuvant candidates under investigation can substantially improve the immune response to influenza vaccines in the elderly and assess their safety profiles.	In progress	In older adults, differences in adjuvants in current vaccines do not translate into differences in effectiveness. Next-generation vaccines will have to be compared against enhanced vaccines.	In addition to an adjuvant, consider promise of intradermal administration for both effectiveness and for dose-sparing in pandemic. Consider a separate milestone for mode of administration, including milestones that don't specify effectiveness. Consider mixing of both administration routes and adjuvants.
High priority **Milestone 3.4.c***:* By 2026, determine, through clinical studies, if any existing adjuvants substantially improve the immune response to influenza vaccines in the very young, (e.g., as an initial vaccination followed by non-adjuvanted vaccines) and assess their safety profiles.	In progress	There was general agreement with the reported status of this milestone.	No edits suggested.
Strategic Goal 3.5: Determine the role of NA as a vaccine antigen for improving the effectiveness and immunogenicity of seasonal influenza vaccines (Eichelberger 2019, Giurgea 2020, Krammer 2018b, Morens 2019).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
Milestone 3.5.a*:* By 2022, generate standardized, harmonized, and validated assays for measuring NA content in seasonal influenza vaccines.	In progress	Milestone may not be relevant given potential of mRNA and other newer platforms to reveal effects of adding neuraminidase (NA) to vaccines. While standardization may be irrelevant, these assays would	Change milestone wording to reflect the need to know NA content and assays for all influenza vaccines, and not limited to seasonal (egg-based) vaccines.

		be useful for monitoring antigenic drift and should be finalized by a regulator such as FDA or the European Medicines Agency (EMA). Original 2022 target not met due to COVID-19 postponement.	Move target date to 2023 or acknowledge target date not met. We must try to discern why goals were not accomplished.
High priority **Milestone 3.5.d***:* By 2025, determine if the presence of NA improves seasonal influenza vaccines, and, if so, establish the optimal dose of NA that improves immunogenicity and effectiveness.	In progress	Addition of antigens, particularly in the case of intranasal vaccines, raises risk of adverse reactions.	Change language to clarify that this milestone refers to new vaccine technologies rather than current egg-based seasonal vaccines. Revise to add consideration of adverse reactions.

*The draft tables used the terminology "Completed," but the group agreed to change this status to "Target date met" instead. The annual reports will reflect this change.

Progress on Vaccinology for Universal Vaccines Milestones

Rosalind Hollingsworth served as facilitator for discussion organized according to the draft table shown in Appendix C. The following table summarizes discussion output.

Strategic Goal 4.1: Identify the most promising broadly protective or universal influenza vaccine candidates that elicit durable protection against influenza viruses in preclinical studies, with a focus on targeting conserved regions of the virus (Kanekiyo 2019, Krammer 2019b, Yamayoshi 2019).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
Milestone 4.1.a*:* By 2022, 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).	In progress	Full value of influenza vaccines assessment (FVIVA) will not be completed in 2022; however, revising the FVIVA is a key deliverable for 2023. BMGF revised the target product profile (TPP) for universal influenza vaccines (UIV) in early 2022. WHO has not yet revised their PPC.	Revise the milestone target date (to early 2024).
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,	No evidence identified	The Universal Influenza Vaccines Technology Landscape partially addresses this milestone, but there is no analysis linked to the Landscape yet.	Revise status to "in progress" and add CIDRAP's Universal Influenza Vaccines Technology Landscape as evidence.

and create a mechanism to update this summary at least annually.			
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).	No evidence identified	Aiming for transparent, equitable process of down-selection of UIV candidates. Should this be focused instead on an expansion beyond identification of promising candidates, such that it moves to a Warp Speed-type entity that includes a mechanism to move them forward? Pharmaceutical companies will pursue individual goals based clinical trial cost-benefit calculations; this limits consortium membership to academia and government. The WHO technical advisory group is already a key arbiter for COVID-19; consider the same for UIV. The milestone is meant to direct funders toward unmet needs. Regarding terminology: 1) UIV goal is too optimistic; broadly-protective would be more realistic and appropriate; 2) we should continue to aim for UIV; UIV is not the same as broadly-protective. WHO's Product Development for Vaccines Committee (PDVAC) will review the PPC (per 4.1.a., above).	Remove this milestone.
High priority **Milestone 4.1.d***:* By 2022, convene a workshop to review the development of novel platforms (e.g., mRNA-based) for COVID-19	In progress	Workshop discussed during seasonal vaccine session should extend to covering UIV. Consider how to leverage more general discussions on	In keeping with future workshop, revise target date to 2023 or 2024.

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).		mRNA vaccines; keep a narrow focus on influenza, possibly include COVID-19 and RSV in discussions on broadly protective vaccines.	
High priority **Milestone 4.1.e***:* By 2024, identify the most promising influenza vaccine candidates that elicit robust and broadly protective immunity.	In progress	There is a lot of work ongoing related to this milestone; how comprehensive does the evidence need to be? In advance of this meeting, CIDRAP put in as much evidence as the team had time, but there are additional data that are not yet included (e.g., the National Institute of Allergy and Infectious Diseases [NIAID] CIVICs program). This milestone suggests that the IVR can shape markets—it can't—so milestone doesn't merit much effort; keep milestone as it gives IVR leverage to review PPC.	Add NIAID's CIVICs program, the Universal Influenza Vaccine Technology Landscape, and European Union-India work on broadly protective influenza vaccines as evidence for progress towards this milestone. Consider combining the 4.1.b and 4.1.e milestones. Rewrite the milestone to include criteria for selection of candidates as "promising," e.g., PPC and at which stage of development; remove "most"; make this an annual stock-taking review based on PPC.
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**	**Discussion highlights**	**Suggested actions**
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	DCVMN has members (India, China) capable of developing use cases, but work is in early stages. As noted above, FVIVA will not be completed in 2022. Development of use cases are close to being done and validated—possibly by end 2022.	The two items listed as evidence for this milestone are the same (i.e., should not be listed as separate bullet points).
High priority **Milestone 4.2.e:** By 2023, develop consensus on streamlining clinical	No evidence identified	The workshop discussed for seasonal vaccines could accomplish this for UIV as well.	No edits suggested.

research for evaluating broadly protective influenza vaccines, drawing on COVID-19 vaccine experience.		Discuss establishment of consensus for regulatory and clinical streamlining on issues such as animal rule, challenge models needed to define broadly-protective or UIV status for a pandemic vaccine. A milestone that might be more appropriate in animal model or policy sections; agreed, but a new vaccine's clinical efficacy must be demonstrated. Regulators do not like the term "universal," and it won't be used on product information or labels; however, we need to understand a new vaccine's breadth of protection. Also need to establish how to demonstrate durability of protection; demonstrating effectiveness across seasons is included in BMGF TPP for UIV.	
High priority **Milestone 4.2.f***:* By 2024, identify several vaccine candidates that demonstrate broad-based immunity—humoral, cell-mediated, or both—in preclinical research and assess them for safety and immunogenicity in phase 1 clinical trials in healthy adults.	In progress	Important to characterize strain diversity/coverage for seasonal as for "beyond seasonal" vaccine candidates. Important also to characterize negative results, e.g., BiondVax's UIV candidate that failed phase 3 trials. BMGF aims for revolutionary change, not incremental improvement—but no information that warrants extending milestone beyond phase 1.	This process will be ongoing—there should be no target date; could identify an initial set of candidates by target date. The definition of 'broadly protective' remains uncertain; next-generation may be preferable term to describe ongoing improvement.
High priority **Milestone 4.2.g***:* By 2024, determine correlates of protection for assessing broadly protective or universal influenza vaccines	No evidence identified	ISIRV is planning a correlates of protection meeting for March 1-3, 2023, in New Orleans, LA. (*Note*: This location was later changed to Seattle, WA.) The	Change status to "in progress" since upcoming 2022 Wellcome Trust meeting will address this issue.

that are appropriate for different stages of vaccine development.		development of standardized assays (e.g., through FLUCOP) should be discussed at this meeting. Wellcome Trust is convening a correlates of protection meeting this week, with a deep dive on influenza and COVID-19; a publication will result from the meeting. Is focus of milestone solely on regulatory-defined correlates of protection? Research has identified multiple correlates, but the FDA doesn't consider the identification meaningful without correlating phase 3 clinical trial data; should we advocate for regulatory agencies to evaluate them for potential adoption? Is correlation only important for regulators or for making research decisions as well? Correlates of protection is a precise term to be used carefully—we should consider using a different term (e.g., "surrogate markers") if expanding milestone goal. Language around "correlates" and "surrogate markers" is a potential workshop topic.	Change milestone language to "universal candidate vaccine." Consider adding consideration of vaccine "platforms" as well as "stages of development." No agreement was reached regarding whether to change language of "correlates of protection" to "surrogate markers" (or other), but this may be revised in the future following additional workshops/discussions.
High priority **Milestone 4.2.h***:* By 2025, identify the most promising vaccine candidates from phase 1 trials and advance them into phase 2 or directly to phase 3 clinical trials in at-risk populations.	In progress	Need an indicator of progress, not just "advance."	Modify the milestone to advocate that clinical trials include high-risk populations. In multiple settings, IVR is tracking and potentially influencing several aspects of UIV R&D. Milestones referring

			to this influence should be consolidated.
High priority **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	This milestone both measures progress and identifies funding gaps. Do we want to contrast results among different populations with different levels of risk? Yes, and emphasize the necessity for scientific recommendations specific to special populations.	Per 4.2.h discussion, consolidate this tracking effort with others into a single milestone and publish findings.

Progress on Immunology and Immune Correlates of Protection Milestones

Kristine Moore served as facilitator for discussion organized according to the draft table shown in Appendix D. The following table summarizes discussion output.

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**	**Discussion highlights**	**Suggested actions**
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 vaccines; and (3) develop guidance to support the management, storage, and distribution of the clinical samples.	No evidence identified	The National Institutes of Health (NIH) is developing a comprehensive list of influenza cohort studies they fund that could be publicly available within a year. NIH is planning multiple workshops, including one (in early stages of planning) on cohort studies that will discuss establishment of a sample repository; it will involve mostly academic researchers. Commercial clinical trial samples are unobtainable without a non-disclosure agreement (NDA); access to commercial samples from clinical trials needs to become more open. This issue could be included in workshop.	Change status to "in progress" based on NIH activities. Guidance for sample collection (serology, respiratory) is lacking; need to add the term "collection" to point (3).

		Industry perspective on sharing samples: possible in some cases and has occurred, but legally difficult and hampered by informed consent and limitations of sample volumes; discussions ongoing and involve establishment of industry consortium to set policy. Denmark and Sweden have COVID-related sample repositories; these may provide a model.	
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**	**Discussion highlights**	**Suggested actions**
High priority **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	Additional work not noted as evidence for milestone progress include CIVICs centers (Duke and University of Georgia) working on biomarkers and Centers for Excellence for Influenza Research and Response (CEIRR) sites working on long-term infant immunity. There is also elderly immunity that is missing from the table and ongoing CDC work that is not currently reflected. Kristine Moore noted that NIAID-related evidence for progress not yet included in the table is due to the CIDRAP team still working through NIAID data.	Update evidence for progress with NIAID and CDC work.
Strategic Goal 2.4: Determine the impact of prior influenza virus infection or vaccination on future immune responses to influenza viruses or vaccines (Cobey 2017, Guthmiller 2018, Henry 2018, Worobey 2020, Zhang 2019).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
Milestone 2.4.a*:* By 2022, establish longitudinal clinical studies to follow cohorts of different age-groups in various geographic locations to enable characterization of immune responses to	Target date met	Geographic and risk group diversity are lacking in studies conducted to date. Target considered to be met because longitudinal studies have been established.	Update evidence for milestone with CDC immunity studies. Change status to “in progress” and change date to later.

naturally occurring influenza infection and vaccination over time.		CDC has ongoing immunity studies in all 10 US Department of Health and Human Services (HHS) regions covering ages 0-70 years.	
High priority **Milestone 2.4.b***:* By 2026, determine through prospective birth-year cohort studies how repeated influenza vaccinations affect the immune response to subsequent influenza vaccinations (Ranjeva 2019).	In progress	No comments.	No edits suggested.
High priority **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 (Arevalo 2020, Zhang 2019), including immunologic responses to subsequent influenza virus infection or vaccination.	In progress	Florian Krammer will be presenting work at OPTIONS XI that is related to this milestone.	Update the evidence for milestone progress with data from Florian Krammer.
High priority **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 (Zhang 2019).	In progress	CDC has data related to this milestone that has been provided to CIDRAP but has not yet been incorporated into the evidence for this milestone. Given imprinting work being conducted, should the roadmap include consideration of tailoring a vaccine to the pediatric population to control their first exposure to influenza?	Consider crafting a new milestone on how to use imprinting data (or incorporating the issue into existing milestones) related to clinical trial design. (CIDRAP noted that this topic may be an issue for a future IVR Steering Group discussion.)
Strategic Goal 2.6: Improve understanding of the role of mucosal immunity in protecting against influenza.			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
High priority **Milestone 2.6.a***:* By 2023, further determine the	In progress	Lots of preclinical work being done in this area but no clinical	Update the evidence for milestone progress with additional preclinical work

role of mucosal antibodies in protecting against influenza virus infection, disease, and transmission.		studies; COVID-directed research will be informative.	(CIDRAP to connect with Florian Krammer if needed).
High priority **Milestone 2.6.d***:* By 2026, determine the role of mucosal T cells in protecting against influenza virus infection, disease, and transmission.	In progress	Lots of COVID-directed work will be relevant to this research, which may inform the milestone progress in the future.	Update the evidence for milestone progress with work being conducted by David Masopust.
Strategic Goal 2.7: Develop novel correlates of protection for assessing seasonal influenza vaccines and broadly protective or universal influenza vaccines, as part of clinical studies that demonstrate efficacy against a disease end point (Erbelding 2018, Krammer 2020, Lim 2019, Plotkin 2018).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
High priority **Milestone 2.7.a***:* By 2025, develop functional assays to accurately capture the breadth and range of protective responses other than virus neutralization, such as influenza virus–specific ADCC, antibody-dependent cellular phagocytosis, and complement dependent cytotoxicity (Coughlan 2018, Gianchecchi 2019, Krammer 2019).	In progress	Assays have been developed by multiple academic labs, but whether they will be used to advance vaccine development remains to be determined. Establishing criteria for qualification, validation is difficult—requires considerable thought and effort going forward.	Consider adding a milestone pertaining to making assays "fit for clinical trial purpose."
High priority **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 (Reber 2013).	In progress	Lots of progress to date and more to come in this area pertaining to COVID-19; flu should build on that.	Update evidence for milestone progress to incorporate SARS-CoV-2 progress (as related work).

Progress on Policy, Financing, and Regulation Milestones

Christopher Chadwick served as facilitator for discussion organized according to the draft table shown in Appendix E. The following table summarizes discussion output.

Strategic Goal 6.1: Catalyze broad support and sustained funding for developing improved seasonal influenza vaccines and broadly protective or universal influenza vaccines.			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
High priority **Milestone 6.1.a***:* By 2022, develop and disseminate a full value of vaccine assessment (FVVA) for improved seasonal and broadly protective, universal influenza vaccines that addresses different vaccine use cases and includes an assessment for LMICs (NASEM 2019).	In progress	FVIVA is now proceeding formally; three work streams: R&D/supply, demand (use case), and impact (two country-level studies and one global modeling study on economic impact and disease burden). Diverse results will be available within 18 months, including PPCs.	Change the target date to 2023 or early 2024.
High priority **Milestone 6.1.b***:* By 2022, develop targeted and creative communications and advocacy strategies and necessary communication tools that build on the FVVA and provide information on economic costs, the risk of future influenza pandemics, and the need for investment in influenza vaccine R&D (Navarro-Torné 2019, Sabin 2019).	In progress	See 6.1.a	See 6.1.a
Strategic Goal 6.2: Promote innovation for developing improved seasonal influenza vaccines and broadly protective or universal influenza vaccines.			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
High priority **Milestone 6.2.a***:* By 2022, distill lessons learned for influenza vaccines from experience with COVID-19 vaccine R&D, including clinical	Target date met	Milestone involves distilling lessons, not applying them.	No edits suggested.

research and study designs, manufacturing, distribution, advocacy, financing, and global collaboration (Sabin 2021).			
High priority **Milestone 6.2.b***:* By 2023, identify a set of strategies for accelerating the development of universal influenza vaccines through innovative approaches (Sabin 2019).	In progress	Definitions lacking: (1) Do "strategies" refer to funding, identifying promising candidates? (2) What constitutes an "innovative approach"? The IVR annual report should discuss the negative effects of the COVID-19 pandemic on progress towards IVR milestones, in addition to lessons learned and opportunity for testing new technologies afforded by pandemic and limitations of novel platforms used for COVID-19 vaccines. In the Sabin-Aspen report cited in the milestone, strategies refer to investment in untested new technologies; COVID-19 allowed much of that to happen. These strategies lie outside the remit of roadmap, which is a tool to drive such strategic investments. Institutional strategies to address these issues exist.	Milestone seems too vague to be helpful; consider removing or consider it to have been met.
Strategic Goal 6.3: Promote information sharing aimed at moving influenza vaccine development forward.			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
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	Target date met for some objectives	Target date could be considered met through the Universal Influenza Vaccine Technology Landscape, which will be updated throughout the life of the roadmap.	Work needed on special population assessment, so this milestone status should be considered "in progress."

update and analyze the landscape, including identifying key factors underlying successful R&D efforts as well as persistent challenges and obstacles (Global Funders Consortium 2018).			
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).	No evidence identified	NIH data-sharing mandate takes effect in 2023 and is already applied in influenza research in Collaborative Influenza Vaccine Innovation Centers (CIVICs). Processes are still being developed and worth continuing; this is a potential topic for the NIAID workshop on cohorts. If a workshop on cohorts is coordinated, participants should include industry. Note Flu Lab/Center for Open Science project incentivizing sharing of negative results, poster at OPTIONS XI.	Consider combining this milestone with 6.3.d; note institutional efforts toward this goal.
High priority **Milestone 6.3.c***:* By 2022, assess the impact of the Nagoya protocol, and possibly related national ABS legislation, on sharing of influenza isolates and gene sequences in relation to influenza vaccine R&D and determine strategies to address potential unintended consequences.	In progress	The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and WHO have been working on this. The WHO Pandemic Influenza Preparedness (PIP) advisory group will issue a preliminary report by the end of 2022 on different mitigation strategies to ensure seasonal influenza virus sharing is not impacted. The collaborating centers and IFPMA have a list of all impacts (i.e. which countries are at what stage in the Nagoya protocol). The IVR annual report could acknowledge the ongoing discussions following	Change the date of this milestone, given ongoing discussions. Consider splitting the milestone into two: (1) assessment, date to reflect WHO and other study results and (2) development of strategies for data-sharing, with relatively distant date. (If milestone date is changed, the date of (1) could be 2023 given WHO report due in late 2022.)

		consequences of the SARS-CoV-2 Omicron variant discovery in South Africa (i.e. updated vaccines not being provided to the country that identified the variant). There is a need for incentives for local researchers to share data and not suffer consequences. The IVR should focus on this issue specifically as an impediment to influenza R&D, including repercussions for public health (e.g., strain selection). Relate progress to assessment under PIP Framework.	
Milestone 6.3.d*:* By 2022, implement a plan that improves existing data management and sharing among influenza R&D researchers (Erbelding 2018).	No evidence identified	See 6.3.b. Wellcome Trust has a clinical data platform focused on acute respiratory infection; Wellcome will share with CIDRAP to determine whether the work should be included as evidence for progress.	Merge with 6.3b.
Milestone 6.3.e*:* By 2022, conduct mapping of intellectual property for improved influenza vaccines to identify synergies in approaches that may be used to develop new partnerships.	In progress	The FVIVA work described above will include IP mapping.	Change the target date to 2023.
Strategic Goal 6.4: Further explore regulatory challenges associated with development and manufacturing of improved seasonal and broadly protective or universal influenza vaccines (Navarro-Torné 2019).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
High priority **Milestone 6.4.a***:* By 2022, conduct a workshop that includes regulators and vaccine manufacturers to: (1) clarify regulatory	In progress	See previous discussions of necessary workshop(s); expect PPCs to emerge from these discussions. Workshop discussions should aim to establish consensus	Create a timeline to connect this field of topics across IVR sections; anticipate progress through a series of workshops through early 2024.

processes related to the development and evaluation of broadly protective or universal influenza vaccines, (2) develop a regulatory science agenda that anticipates the challenges of evaluating and licensing these new vaccines, (3) review the regulatory experience with COVID-19 vaccines and identify ways to streamline the process for new influenza vaccines, and (4) generate additional recommendations regarding how best to provide guidance on vaccine development, manufacture, approval, and delivery.		definitions of breadth, duration of protection, and consider special populations. Regulators and appropriate companies should be included in the workshops; outcome of workshops will provide regulatory, policy guidance if timing is optimal. There will be opportunities to introduce these topics at upcoming International Coalition of Medicines Regulatory Authorities (ICMRA) meetings. Milestone goals may be achieved over the course of a series of workshops, perhaps capped with a guidance document or final meeting.	Change milestone date to account for various workshops/discussions.
High priority **Milestone 6.4.b***:* By 2023, identify a framework to address post-marketing assessment of safety and effectiveness of new broadly protective or universal influenza vaccines.	No evidence identified	This milestone was not discussed during the meeting (See Addendum Note on page 7.)	--

Progress on Animal Models and the Controlled Human Influenza Virus Infection Model (CHIVIM) Milestones

Diane Post served as facilitator for discussion organized according to the draft table shown in Appendix F. The following table summarizes discussion output.

Strategic Goal 5.1: Optimize animal models for influenza vaccine research.			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**

Milestone 5.1.a*:* By 2022, develop a strategic plan for standardizing and harmonizing current animal models for influenza vaccine research, which is particularly important for head-to-head comparisons of vaccines and other products (D'Alessio 2018).	No evidence identified	NIAID hosted a workshop in 2019 on optimization of animal models to better predict influenza vaccine efficacy. Meetings on reagents have occurred, but few comparative studies of animal models. Harmonizing *protocols* will be very difficult. The Coalition for Epidemic Preparedness Innovations (CEPI) set up comparative laboratory networks for animal models during COVID-19 vaccine development—perhaps a model that could be applied to influenza. Regulatory guidelines for animal studies are unclear, which is a major problem for novel vaccine and platform development and post-marketing studies. It is important to understand what evidence animal models will contribute to clinical study processes. A workshop on this topic should be part of a future workshop focused on regulatory issues. The IVR could include animal models other than ferrets, so as not to be limited to ferrets only. Evaluating new models could reduce pressure on ferrets. Consider moving from harmonizing to sharing controls, which would help academic labs. Funders have to support data packages that they want pushed forward; instead of standardizing/harmonizing,	Rework the milestone to shift from "strategic plan" to actual standardization/harmonization of animal models. Rather than "standardizing" or "harmonizing," the milestone should endorse the broad sharing of controls among investigators not limited to academics and their networks, and use a date of 2023 or 2024. The IVR should address the tight ferret supply, and the likelihood that ferrets are not disease-naïve.

		consider focus on sharing best protocols widely to ensure wider community has access to that information. (Also note that 5.1.c addresses this point.) Could the milestone be changed to "develop and make available controls that are shared"? Within CIVICs, controls are already shared, and beyond that a repository would be required. Sharing beyond existing community is critical for activation; there are many non-academic investigators for whom these data are important.	
High priority **Milestone 5.1.b***:* By 2022, ensure that validated reagents, updated viral stocks, and harmonized assays are available to improve understanding of the innate and adaptive immune responses in ferrets and to facilitate comparison of studies across laboratories.	In progress	There is lots of work related to this milestone underway, including at NIAID; see the Influenza Data Processing and Communication Center (iDPCC) website. NIAID is in the process of building a new website to the community has easy access to reagents. Validated reagents, as well as high-throughput assays, for both ferrets and hamsters are increasingly available worldwide through both academic labs and companies. NIAID is also actively making hamster reagents.	Move target date to 2023, as COVID-19 slowed progress. Add hamsters to the milestone. Consider including controls (see 5.1.a) to this milestone as well.
Milestone 5.1.c*:* By 2022, develop best practices for conducting influenza virus transmission studies in ferrets, to include naive and infected or vaccinated animals (Belser 2018, Neumann 2019). (Also see Virology Applicable to Vaccine Development.)	In progress	There are few transmission studies in ferrets; there are best practices for studies in both ferrets and guinea pigs. Vaxart did hamster transmission studies for COVID-19. Multiple industry observers noted that they are not conducting transmission studies. Hundreds of transmission studies in ferret model	Add guinea pigs to the milestone. Change milestone target date to 2023.

		beginning in the 1930s should be mined. Progress in studying transmission depends on regulatory prioritizing/ incentivizing reduction of community transmission, as opposed to individual benefit.	
High priority **Milestone 5.1.d***:* By 2023, convene a workshop on the development of pre-exposure animal models to address the fact that humans generally have pre-existing immunity to influenza (D'Alessio 2018).	No evidence identified	NIAID has discussed a workshop on animal models for COVID-19 and on including influenza in that workshop; no firm plans, but could happen in 2023. Models are developed but not harmonized. A workshop on this subject is needed; likely would not be scheduled until late 2023 or 2024.	Move target date to 2024.
High priority **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	There is a broad spectrum of variation within species and between models, particularly with regard to adjuvants. There is also variation in dynamics of immune responses among animal models compared to humans. It is important to summarize these differences to illustrate what can be expected from a given animal, improve model, selection, etc.	No edits suggested.
High priority **Milestone 5.1.g**: By 2026, develop and validate novel animal models, as needed, for evaluating immune responses—including durability—to broadly protective influenza vaccines (D'Alessio 2018).	In progress	Lots of projects are ongoing here, including those listed as evidence and many that are likely not yet incorporated. Given the "as needed" language in the milestone, who will decide what is needed? How is "as needed" defined? The clause is unnecessary here.	Remove "as needed" from the milestone.
Strategic Goal 5.2: Address steps needed to further develop and refine the CHIVIM (Innis 2019a, Innis 2019b).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**

High priority **Milestone 5.2.a***:* By 2022, determine the use cases for the CHIVIM and generate guidance, including ethical and safety considerations, for using the model.	No evidence identified	At a 2018 BMGF meeting on this topic, the agreement was that WHO should take on this issue; BMGF is considering hosting a workshop for 2023 to monitor progress on this topic. July 2022 Wellcome Trust meeting (not specific to influenza) clarified some of the questions regarding how models are used for other pathogens. This topic is potentially a component of the FVIVA; there maybe also be non-influenza WHO guidance on human infection models that applies. Significant information exists on model for COVID-19, but it is not yet public; status is key guide for influenza studies. Unless regulators agree to use results of human challenge studies in licensing decisions, they won't contribute to advancement of novel vaccines. Lots of progress on both in terms of model and regulatory acceptance has occurred over past few years for respiratory syncytial virus (RSV). Potential model for progress in influenza. "Use cases" is a good goal, as it is not too prescriptive.	Change target date to 2024, given planned workshops.
High priority **Milestone 5.2.b***:* By 2023, ensure that reagents for the CHIVIM are broadly available.	No evidence identified	What reagents is this referring to? NIAID is in process of producing and making available challenge strains for H3N2 and H1N1. hVIVO may have modified H5N1, but that needs confirmation.	Change milestone status to "in progress." Change "reagents" to "strains" in the milestone. Consider summarizing the availability and accessibility of challenge strains as part of the

		The expense and time required to manufacture strains are significant. Matthew Memoli was working on an H10 strain; uncertain if work has continued. Research availability of additional challenge strains in preparation for future workshops (to determine what is still needed). Ensuring equitable access to right strains is important and challenging.	Universal Influenza Vaccine Technology Landscape.
High priority **Milestone 5.2.c***:* By 2023, ensure that a bio-repository of diverse, accessible, and well-characterized challenge stocks is generated and made available to investigators.	No evidence identified	This milestone was not discussed during the meeting. (See Addendum Note on page 7.)	--
High priority **Milestone 5.2.d***:* By 2024, further develop the CHIVIM to ensure that it can be widely used by different investigators.	In progress	Wellcome Trust is supporting the development of human challenge study sites in LMICs; can provide an update on sites under development and how they're progressing. Tracking should include sites working to conduct CHIVIM. Consider also studies of pre-infected people: obviates need for costly challenge viruses; upcoming workshop should consider alternatives to challenge strains.	No edits suggested. Consider summarizing the sites capable of conducting human challenge studies as part of the Universal Influenza Vaccine Technology Landscape.

Progress on Virology Milestones

Ann Moen served as facilitator for discussion organized according to the draft table shown in Appendix G. The following table summarizes discussion output.

Strategic Goal 1.1: Improve understanding of human and animal influenza virus evolution (Wille 2020).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
Milestone 1.1.a*:* Beginning in 2022, and then every 2 years thereafter, assess and evaluate sampling strategies for obtaining isolates of circulating influenza viruses in geographically diverse areas, with the aim of developing an adequately resourced, enduring, globally comprehensive, and geographically diverse system, as well as to increase, refine, and standardize the types of metadata collected. As part of this effort, public health officials should consider initiating a demonstration project to obtain data over several years at sites in both hemispheres and the tropics to assess differences among regions over time.	No evidence identified	Significant data relevant to this milestone will be available from WHO through multiple channels. WHO's Global Influenza Surveillance and Response System (GISRS) would be the go-to for data on this topic. Important to obtain sequences as well as isolates; need to identify ways to translate this data into public health policy and action. Assessment of sampling strategies is ongoing. Strategies are imperfect but rest on a sound foundation that is always improving. Consider assessing global circulation patterns of respiratory viruses as a group, given implications for immunity recognized as a result of COVID-era respiratory viral disease patterns and H5N1 distribution patterns, e.g., respiratory viral interference. There are some regions that connect surveillance for multiple respiratory pathogens (e.g., the Pan American Health Organization [PAHO] region combining surveillance for RSV, influenza, etc.). As we look at our research, how do we prioritize understanding the natural history of viral respiratory pathogens that may have implications for understanding human immunity? The seasonality of influenza in the northern and southern hemispheres allows for a surveillance system that wouldn't	Change status to ongoing: plenty of existing evidence; don't impose a secondary structure but identify gaps and propose solutions. Consider adding obtaining of sequences (in addition to isolates) in the milestone. The Global Influenza Hospital Surveillance Network (GIHSN) should be included with data under milestone progress. Look into the Institute for Pathogen Genomics (IPG) and determine if any work they are doing should be included as evidence for milestone progress.

		be as well-suited to incorporating COVID-19 surveillance data (since COVID-19 isn't seasonal like influenza). Instead, we should consider a focus on severe disease outcomes.	
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**	**Discussion highlights**	**Suggested actions**
Milestone 1.2.a*:* By 2022, review available data on antigenic mismatches between vaccine strains and circulating strains over past years to identify causes and determine steps that could have minimized or avoided them. Information obtained may be useful in developing contingency response plans in advance for when antigenic mismatches occur in the future.	In progress	There are unavoidable mismatches; the predominant strain can't currently be predicted. We have significantly de-risked mismatch by having two components for the B lineage, although that may no longer be needed after disappearance of B/Yamagata. Potential to learn from history of past mismatches. CDC funds and collaborates with modeling and forecast groups to optimize influenza vaccine strain selection. More sequencing means earlier detection of novel strains and holds potential for developing predictive modeling; however, modeling is unlikely to predict virus behavior or severity of disease.	Change milestone wording to "monitor when mismatch occurs" and investigate how the use of genetic sequences, modeling, forecasting, etc., improves match in future.
High priority **Milestone 1.2.e:** 2025, develop, standardize, and implement methods to improve antigenic characterization of H1N1 and H3N2 viruses (Allen 2018, Harding 2018, Zost 2017).	In progress	Information on CDC projects on mapping human epitopes to identify escape variants will be shared with the CIDRAP team. Both H1N1 and H3N2 are needed in this milestone as currently written.	This milestone status is ongoing; this will be continual. Update evidence for milestone progress with CDC projects on mapping human epitopes to identify escape variants. Update milestone language to specify the use of predictive artificial intelligence (AI) and

			other new technologies now included in this effort.
Strategic Goal 1.3: Improve the ability to detect and understand the emergence of novel influenza viruses with pandemic potential (Neumann 2019).			
Milestone	**Status**	**Discussion highlights**	**Suggested actions**
Milestone 1.3.a*:* By 2022, develop a plan to continue surveillance of influenza viruses at the human-animal interface and expand global influenza surveillance in poultry and swine, particularly in Africa, Asia, and South America. The plan should highlight the need for coordination among international groups, stress the importance of understanding the emergence of novel and potentially pandemic viruses in animal reservoirs, and promote data sharing and integration across different surveillance systems.	No evidence identified	Build on existing OFFLU network for animal influenza surveillance; expand funding for LMICs pursue interface surveillance, identify and fill other geographic gaps. The UK project Flu Map monitors highly pathogenic avian influenza (HPAI) in wildlife and domestic animals in the UK and Europe; potential for engagement. Challenges include geographic gaps and disincentives for countries with large agricultural sector (e.g., Brazil). OFFLU should be the starting point in an analysis of surveillance gaps. Need to use surveillance findings to alert public health authorities about potential for human cases.	Change status to "in progress" as this work will be ongoing. Change the target date to 2023 and update language to identify geographic surveillance gaps.

ME&A Process and Methods Going Forward

Kristine Moore facilitated a discussion of next steps for IVR funding and research tracking activities. Key points:

- Revisions and updates to IVR milestones resulting from this meeting will be compiled and circulated to the IVR taskforce in the coming months.
- A report on progress to date on IVR ME&A activities will be issued at year-end 2022 or in early 2023.
- The IVR Funding Tracker continues to be developed. The November 2022 GFC meeting provides a key opportunity for input and guidance. Construction of the funding tracking database will be completed in 2023.
- The CIDRAP team continues actively to seek ideas on how to track information on both funding and on research outcomes.
- A post-meeting survey, conducted through REDCap, would allow the team to capture additional information for both streams.
- *Participant comments: The survey could potentially be extended/modified to tap:*
    - *OPTIONS XI participants, via engaging the International Society for Influenza and other Respiratory Virus Diseases (ISIRV) OPTIONS XI planning committee*

- *Public health officials (e.g., WHO regional contacts, CDC Africa, ministries of health to involve governments)*
- *The International Association of National Public Health Institutes (IANPHI)*
- *Veterinarians/wildlife biologists*

Closing Remarks

Before thanking participants and the meeting team, Michael Osterholm made the case for humility in addressing influenza. Much remains to be understood about the virus and the disease because "we don't know what we don't know," as exemplified by the unpredictable behavior of H5N1. Influenza's mysteries are "both a gift and a scourge," he said.

Josie Golding offered the following take-away points from the meeting:

- Several milestones pose the question as to where responsibility lies for accomplishing them.
- Other influential actors and funders, beyond GFC, should be brought to the table and solicited for support to meet IVR milestones.
- Consider the funding audience when assigning/defining milestone status (e.g., "complete," "in progress").
- The COVID-19 pandemic demonstrated the importance of both equity and uptake to vaccine impact: issues not within the current scope of the IVR. They need to be brought out and given appropriate consideration.
- Keep in mind how tracking and landscaping efforts will be used to advocate for increased investment in improving influenza vaccines.
- Consider how to leverage the lessons of the COVID-19 pandemic.

Follow-up Comments

After the meeting, CIDRAP requested any feedback or follow-up comments. The following points were made via email:

- Creating a clearer development path is needed for industry to have a better sense of how to move forward with developing broadly protective influenza vaccines.
- Identifying what would satisfy regulators to demonstrate broad-spectrum protection, such as demonstration of efficacy against circulating strains in a phase 3 trial followed by functional in vitro assays against other strains, or animal studies or human challenge studies.
- Determining how many strains and what strains are needed to consider that a vaccine offers broad protection; a list of specific strains would be useful and knowing which model (e.g., in vitro, animal, human) can be used to demonstrate protection for each strain.
- Creating and disseminating a list of centres that can perform human challenge studies to include the infection rate and maximum number of volunteers per study and the strains available for human challenge studies.

APPENDIX A: IVR ME&A Taskforce Meeting Agenda

IVR ME&A Taskforce Meeting Agenda
September 25, 2022, Belfast, UK

BACKGROUND

The Influenza Vaccines Research and Development (R&D) Roadmap (IVR), which was launched in September 2021, is aimed at accelerating progress toward the improvement of seasonal influenza vaccines and the development of new universal or broadly protective influenza vaccines. By highlighting key research gaps, identifying strategic goals and milestones, and encouraging synergistic R&D activities, the roadmap will serve as a valuable tool to advance the complex field of vaccine research over the next 10 years and stimulate overall investment in influenza vaccine R&D.

The Center for Infectious Disease Research and Policy (CIDRAP), with generous support from Wellcome Trust, has recently embarked on a 3-year project aimed at: (1) tracking progress in meeting the IVR goals and milestones (Monitoring, Evaluation, and Adjustment [ME&A]) and (2) assessing funding trends for influenza vaccine R&D. The IVR expert taskforce plays a critical role in guiding and informing this effort. This is the first of three anticipated annual meetings that will be convened for this project.

The Influenza Vaccines R&D Roadmap is organized into the following sections; progress in each of these areas will be discussed during the meeting:

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

MEETING OBJECTIVES

1. Meeting participants will review findings on monitoring activities to date that are related to research outcomes and current R&D funding. The focus for this meeting will be milestones that either have a 2022 date for completion or are considered high priority.
2. Meeting participants will be asked to share any additional important progress or funding relevant to the IVR milestones beyond what the CIDRAP team has identified in the public domain.
3. Key additional points to be discussed for each milestone, as time allows, include the following:
    - If progress has not been made: (1) discuss potential reasons for lack of progress, (2) determine whether and how interventions are needed, and (3) identify options for such strategies as necessary.
    - Determine if milestone timelines need to be adjusted and make recommendations as necessary.
    - Determine whether certain milestones should be changed or deleted.

FORMAT

The meeting is by invitation only and will be geared toward interactive participation. All presentations will be in English. The meeting will be hybrid, with some participants attending in person and others joining virtually via Zoom. The meeting will include:

- An overview of the meeting
- An opening presentation on the methodology for tracking funding for influenza vaccine R&D
- Sessions on progress for research outcomes and funding for each of the six IVR topic areas, with discussion of specific milestones under each area.
- A closing discussion on the methodology for tracking outcomes and recommendations for going forward.

AGENDA

Times below are in British Summer Time (BST); Attendance may be in-person or virtual

7:30 am	Coffee/tea
8:00 am	Welcome and introductions (*Michael Osterholm and Josie Golding*)
8:20 am	Meeting overview and objectives (*Kristine Moore*)
8:35 am	Influenza vaccine R&D funding tracking project: Methodology and progress to date (*Angela Ulrich*)
9:15 am	Progress on milestones for Vaccinology for Seasonal Vaccines and discussion • See table on progress for this topic area • Discussion of milestones (*Joseph Bresee*)
10:20 am	**BREAK**
10:40 am	Progress on milestones for Vaccinology for Universal Vaccines and discussion • See table on progress for this topic area • Discussion of milestones (*Rosalind Hollingsworth*)
11:45 am	**LUNCH**
12:45 pm	Progress on milestones for Immunology and Immune Correlates of Protection and discussion • See table on progress for this topic area • Discussion of milestones (*Kristine Moore*)
1:50 pm	Progress on milestones for Policy, Financing, & Regulation and discussion • See table on progress for this topic area • Discussion of milestones (*Christopher Chadwick*)

2:45 pm **BREAK**

3:00 pm Progress on milestones for Animal Models and the Controlled Human Influenza Virus Infection Model (CHIVIM) and discussion

- See table on progress for this topic area
- Discussion of milestones (*Diane Post*)

3:50 pm Progress on milestones for Virology and discussion

- See table on progress for this topic area
- Discussion of milestones (*Ann Moen*)

4:35 pm Discussion of ME&A processes and methods going forward (*Kristine Moore*)

4:55 pm Wrap up and closing remarks (*Michael Osterholm and Josie Golding*)

5:00 pm **ADJOURN**

APPENDIX B: Vaccinology for Seasonal Influenza Vaccines

DRAFT FOR DISCUSSION ONLY

Color coding: Green=Completed or Partially Completed; Yellow=In Progress; Red=No Evidence of Progress Identified

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.		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
None of the milestones for this goal were either 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**	**Published Reports, Ongoing Projects, and Related Work**
Milestone 3.2.a: By 2022, identify lessons learned from COVID-19 vaccine development for improving seasonal influenza vaccines, ensuring reliable delivery of products, and sharing the costs of establishing new technologies or production strategies.	Completed	• 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. • 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. • WHO and LSHTM, with funding from 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). This project will also include additional lessons learned from the COVID-19 experience.
High-Priority Milestone **Milestone 3.2.b***:* By 2022, convene a workshop to review the development of novel platforms (e.g., mRNA-based) for COVID-19 vaccines to identify how best to apply them to developing improved seasonal influenza vaccines.	In progress	We found no evidence regarding planning a workshop; however, progress is being made on this issue through other mechanisms. *Related Work:* 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: • 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.

		• 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). • Shartouny 2022 reviewed challenges and potential barriers of applying mRNA technology to next-generation influenza vaccines, based on successes with COVID-19 vaccines. Several mRNA-based vaccine candidates for (next-generation) seasonal influenza are in clinical development, with additional candidates preparing for clinical evaluation: 1. Phase 3: Moderna mRNA-1010 (Additional Information). 2. Phase 2: Pfizer monovalent/bivalent/quadrivalent modified RNA (Additional Information). 3. Phase 1: GSK/CureVac quadrivalent mRNA (Additional Information). 4. Phase 1: Sanofi Pasteur monovalent NA mRNA (Additional Information). Other novel platforms used for approved COVID-19 vaccines for (next-generation) seasonal influenza vaccine in clinical development include: 1. Phase 3: Novavax NanoFlu (quadrivalent HA nanoparticle with Matrix M adjuvant (Additional Information) 2. Phase 3: Medicago QVLP (quadrivalent HA virus-like particle) (Additional Information, Additional Information, Additional Information) Several vaccine candidates are in the manufacturing phase for clinical studies (NIAID/CIVICs), e.g., H1ssF-3928 (stabilized stem ferritin), H1 HA mRNA-LNP, and 20 HA mRNA.
Milestone 3.2.c: By 2022, ensure that at least two combined COVID-19 and seasonal influenza vaccines are being evaluated in clinical trials.	Completed	Combination mRNA vaccine candidates for influenza and SARS-CoV-2 in clinical development include: 1. Phase 2: Moderna mRNA-1073 COVID-19 + Sanofi Fluzone quadrivalent high-dose influenza vaccine (Additional Information) 2. Phase 1/2: Novavax ICC NanoFlu/NVX-CoV2373 quadrivalent HA influenza nanoparticle + SARS-CoV-2 recombinant spike nanoparticle with Matrix-M1 adjuvant (Additional Information)
High-Priority Milestone **Milestone 3.2.e***:* By 2024, determine optimum methods for assessing the effectiveness of conventional egg-based and cell culture-based vaccines with new vaccine technologies, in coordination	No evidence identified	We found no specific reports on methods for assessing vaccine effectiveness for new vaccine technologies in comparison to conventional technologies. *Related work:* • 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.

with regulatory agencies and using consistent end points, to allow data to be combined (WHO 2016a) as appropriate over multiple seasons and to allow better comparability of data across studies.		• Trombetta 2022 found that key factors affecting the VE of current seasonal influenza vaccines include age, antigenic matching, and vaccination history.
High-Priority Milestone **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 (Calzas 2019, Erbelding 2018).	In progress	*Published Reports and Ongoing Projects:* Several studies describe intranasal, oral, or transdermal routes of delivery of influenza vaccines. Examples include: Intranasal: • 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). • 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). • 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). • Canadian Institutes of Health Research project to Michael Thompson, Zhenyu Wang, and Zhou Xing: Developing Thermally Stable Dry Powder Vaccine Platforms Via Spray Drying Tailored for Inhalation Delivery. • Canadian Institutes of Health Research project to Ellen Wasan, Volker Gerdts, and Yan Zhou: Intranasal Vaccines for Pertussis and Influenza Using Novel Formulations of a Triple Adjuvant (Additional Information). • Canadian Institutes of Health Research project to Harissios Vliagoftis and Kevin Kane (PIs): Proteinase-Activated Receptor-2 Agonists as Adjuvants for Mucosal Vaccination (Additional Information). Oral: • 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). Intranasal or oral:

		• 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). Transdermal/microneedle patches: • 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.
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**	**Published Reports, Ongoing Projects, and Related Work**
Milestone 3.3.a*:* By 2022, develop standardized clinical endpoints for severe influenza disease that can be used in clinical vaccine efficacy studies (WHO 2017).	No evidence identified	*Related work:* • 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 2022, develop and validate a standard scale for assessing influenza disease severity.	Partially completed	*Published Reports:* • Chow 2021 developed a scale in adults hospitalized with influenza-associated lower respiratory tract infection demonstrating a broad distribution of physiologic severity.
Strategic Goal 3.4: Further assess the role of existing and new adjuvants in creating next-generation seasonal influenza vaccines, informed by recent R&D with adjuvants in new COVID-19 vaccines (Li 2021, Tregoning 2018, Zhu 2021).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **Milestone 3.4.b***:* By 2026, determine, through clinical studies, if any promising new adjuvant candidates under investigation can substantially improve the immune response to influenza vaccines in the elderly and assess their safety profiles.	In progress	*Ongoing Projects:* • European Commission funded project: Effective and Affordable Flu Vaccines for the World (Additional Information). • European Commission funded project: Evaluation of rationally Designed Influenza vaccines (Additional Information). • Canadian Institutes of Health Research project to Ellen Wasan, Volker Gerdts, and Yan Zhou (PIs): Intranasal Vaccines for Pertussis and Influenza Using Novel Formulations of a Triple Adjuvant (Additional Information). • Canadian Institutes of Health Research project to Harissios Vliagoftis and Kevin Kane (PIs): Proteinase-Activated Receptor-2 Agonists as Adjuvants for Mucosal Vaccination (Additional Information).

		Published Reports: • Crofts 2022 found that R848 increased IgG antibody responses in elderly NHP following responses observed in newborn NHP [preclinical study]. • 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 against historical strains, potentially providing greater VE in the elderly throughout an influenza season [phase 1 study].
High-Priority Milestone **Milestone 3.4.c***:* By 2026, determine, through clinical studies, if any existing adjuvants substantially improve the immune response to influenza vaccines in the very young, (e.g., as an initial vaccination followed by non-adjuvanted vaccines) and assess their safety profiles.	In progress	*Published Reports:* • Phase 2 clinical trial to evaluate responses to vaccination with different MF59 adjuvanted pandemic influenza vaccine formulations of an H5N1 vaccine in pediatric subjects (Additional Information). • 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]. • 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 (Eichelberger 2019, Giurgea 2020, Krammer 2018b, Morens 2019).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
Milestone 3.5.a*:* By 2022, generate standardized, harmonized, and validated assays for measuring NA content in seasonal influenza vaccines.	In progress	*Published Reports*: • Bernard 2022 validated an ELLA- Neuraminidase Inhibition (NI) SOP for N1 influenza antigen and provided a detailed, harmonized SOP for ELLA-NI.

High-Priority Milestone **Milestone 3.5.d***:* By 2025, determine if the presence of NA improves seasonal influenza vaccines, and, if so, establish the optimal dose of NA that improves immunogenicity and effectiveness.	In progress	*Ongoing Projects:* • European Commission funded project: Evaluation of Rationally Designed Influenza vaccines (Additional Information). *Published Reports*: Several preclinical studies have examined the potential for NA antigens to enhance immunogenicity of different influenza vaccine constructs. • 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 [preclinical study in mice assessing different formulations of rNAs in influenza vaccines.] • 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 [preclinical study in mice comparing NA and HA as antigens for nasal vaccines]. • Rosu 2022 demonstrated the potential of NA immunity to protect against disease, virus replication in the lower respiratory tract, and virus shedding [preclinical study in the ferret model, matching and mismatching the HA and NA components of monovalent split inactivated vaccines]. • 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.

APPENDIX C: Vaccinology for Universal Influenza Vaccines

DRAFT FOR DISCUSSION ONLY

Color coding: Green=Completed or Partially Completed; Yellow=In Progress; Red=No Evidence of Progress Identified

Strategic Goal 4.1: Identify the most promising broadly protective or universal influenza vaccine candidates that elicit durable protection against influenza viruses in preclinical studies, with a focus on targeting conserved regions of the virus (Kanekiyo 2019, Krammer 2019b, Yamayoshi 2019).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
Milestone 4.1.a*:* By 2022, 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).	In progress	*Ongoing projects:* • WHO and LSHTM, with funding from 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. Part of this effort is to revise the PPC guidance from 2017. (Additional Information). [*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.	No evidence identified	To date, no critical landscape analyses of outcomes and promising candidates has been done, but several reviews of the next-generation or universal influenza vaccine approaches have been reported, e.g., Becker 2021, Khalil 2022, Nuwarda 2022, and 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).	No evidence identified	We are not aware of any effort to develop a transparent process for identifying the most promising vaccine candidates.
High-Priority Milestone **Milestone 4.1.d***:* By 2022, convene a workshop to review the development of novel platforms (e.g., mRNA-based) for COVID-19 vaccines to identify how best to	In progress	We are not aware of any effort to plan a workshop; however, progress is being made on this issue through other mechanisms. *Related work:*

apply them to developing broadly protective or universal influenza vaccines. (See similar milestone under Vaccinology for Seasonal Influenza Vaccines).		• Deviatkin 2022 reviewed new platforms and approaches for improved influenza vaccines, particularly RNA-based strategies for broadly protective influenza vaccines. • Hendy 2022 reviewed nano/microparticle platforms for improved seasonal and universal influenza vaccine development.
High-Priority Milestone **Milestone 4.1.e***:* By 2024, identify the most promising influenza vaccine candidates that elicit robust and broadly protective immunity.	In progress	*Ongoing Projects:* • NIH-funded project to Adolfo Garcia-Sastre (PI): Toward a universal influenza virus vaccine based on live attenuated NS1-deleted influenza viruses (Additional Information). • NIH-funded project to Kenneth Bagley (PI): Universal Influenza A/B Vaccine (Additional Information). • NIH-funded project to Sang-Moo Kang (PI): 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**	**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:* • WHO and LSHTM, with funding from 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. That effort will identify use cases. (Additional Information). *Related work*: • US CDC is developing a generic use case analytical framework and validating use cases and country archetypes for current seasonal influenza vaccines (MMGH Consulting); 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 **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.

High-Priority Milestone **Milestone 4.2.f***:* By 2024, identify several vaccine candidates that demonstrate broad-based immunity—humoral, cell-mediated, or both—in preclinical research and assess them for safety and immunogenicity in phase 1 clinical trials in healthy adults.	In progress	*Ongoing Projects:* • Several phase 1 clinical trials are in development in the NIAID/CIVICs network. • NIH-funded project to Adolfo Garcia-Sastre (PI): Toward a universal influenza virus vaccine based on live attenuated NS1-deleted influenza viruses (Additional Information). *Published reports from recently completed phase 1 studies include:* 1. Park 2022 BPL-1357; 4 whole, BPL-inactivated avian influenza virus-based vaccine (NIAID) 2. Folschweiller 2022; Nachbagauer 2021; Bernstein 2020 Chimeric HA-based vaccines (NIAID/CIVICs) 3. Emergent BioSolutions 2021 EBS-UFV-001; self-assembling HA stabilized stem nanoparticle 4. Houser 2022 FluMos-v1; novel ferritin (H2HA-Ferritin) nanoparticle (NIAID) 5. Darricarrère 2021 Headless HA stabilized stem antigens on ferritin nanoparticles (NIAID) 6. Eiden 2021 M2SR; M2-deficient single replication, live intranasal influenza virus based vaccine (FluGen)
High-Priority Milestone **Milestone 4.2.g***:* By 2024, determine correlates of protection for assessing broadly protective or universal influenza vaccines that are appropriate for different stages of vaccine development.	No evidence identified	We are not aware of any progress relating to this milestone.
High-Priority Milestone **Milestone 4.2.h***:* By 2025, identify the most promising vaccine candidates from phase 1 trials and advance them into phase 2 or directly to phase 3 clinical trials in at-risk populations.	In progress	*Ongoing Projects:* • Universal influenza vaccine candidates in recently launched phase 2 studies include: 1. Flitter 2022 VXA-A1.1 (Vaxart) Oral, adenovirus-5-vectored, monovalent HA vaccine candidate 2. Leroux-Roels 2022 IVX836 (Osivax) Recombinant NP nanoparticle vaccine candidate
High-Priority Milestone **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:* • Vaccine candidates in phase 3 trials, designed to be broadly protective or universal influenza vaccines include: 1. Ward 2020 QVLP (Medicago) HA-bearing quadrivalent virus-like particle vaccine candidate 2. Shinde 2022 Nano-Flu (Novavax) Matrix-M-adjuvanted quadrivalent nanoparticle influenza vaccine candidate

APPENDIX D: Immunology and Immune Correlates of Protection

DRAFT FOR DISCUSSION ONLY

Color coding: Green=Completed or Partially Completed; Yellow=In Progress; Red=No Evidence of Progress Identified

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**	**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 vaccines; and (3) develop guidance to support the management, storage, and distribution of the clinical samples.	No evidence identified	We are unaware of any progress toward achieving this milestone.
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**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **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	In progress	*Ongoing Progress:* • NIH-funded project to Frances Lund (PI): Identification and characterization of effector memory B cell populations that dominate memory responses to subsequent influenza infection and vaccination (Additional Information). *Related work*:

of early biomarkers associated with durable immune responses, to inform the development of durable vaccine-induced protection.		• 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, PIs, NIAID-SEM-CIVIC network). *Published report:* • Swain 2021 examined mechanisms underlying CD4 T and B cell effector responses and memory after influenza virus infection, and found that CD4 T cells require strong initial and extended signals from antigen and pathogen recognition to drive memory and specialized CD4 effectors (such as T follicular helper cell generation).
Strategic Goal 2.3: Improve understanding of aspects of the B cell immune response to influenza infection that are important for developing better vaccines and optimal strategies for vaccination, particularly in the context of partial preexisting immunity from continual exposure to influenza viruses (Linderman 2020).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
None of the milestones for this goal were either 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 (Cobey 2017, Guthmiller 2018, Henry 2018, Worobey 2020, Zhang 2019).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**

Milestone 2.4.a*:* By 2022, 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.	Completed	*Ongoing Projects*:
		• Open Philanthropy funded project to Mary Staat (PI): Cincinnati Children's Hospital Medical Center - Infant Immunome and Influenza Studies (Additional Information).
		• Canadian Institutes of Health Research project to Matthew Miller (PI): Defining the mechanisms of original antigenic sin to improve influenza virus vaccine effectiveness (Additional Information).
		• 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:
		  ○ Assess how Ab responses to seasonal influenza vaccination differ in individuals across multiple age groups.
		  ○ 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.
		  ○ Compare nAb titers between groups of individuals with different birth years.
		
		Related Work:

		• Wellcome Trust funded project to Steven Riley (PI): The life course of human immune responses to influenza infection and vaccination. • European Commission project to Helmholtz-Zentrum **für** Infektionsforschung GmbH: (Additional Information).

High-Priority Milestone
Milestone 2.4.b*:* By 2026, determine through prospective birth-year cohort studies how repeated influenza vaccinations affect the immune response to subsequent influenza vaccinations (Ranjeva 2019).
	In progress	*Ongoing Projects*:
		• 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:
		  ○ Measure humoral and selected cellular immune responses to repeated influenza vaccination with Flublok, and their associations with age, birth year, and prior vaccination history.
		  ○ 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.
		  ○ Predict how influenza vaccinations and infections shape immunity.
		• Canadian Institutes of Health Research project to Mark Loeb (PI): Towards a better understanding of Influenza Vaccination: Lessons from the Hutterite Community (Additional Information).
		
		Related Work:
		• Wellcome Trust funded project to Steven Riley (PI): The life course of human immune responses to influenza infection and vaccination.

High-Priority Milestone
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 (Arevalo 2020, Zhang 2019), including immunologic responses to subsequent influenza virus infection or vaccination.
	In progress	*Ongoing Projects:*
		• 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:
		  ○ 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.
		  ○ Define immune responses to the infants' initial influenza exposure (vaccine or infection) and how those responses affect the immune response to subsequent influenza exposures.
		• Canadian Institutes of Health Research project to Matthew Miller (PI): Defining the mechanisms of original antigenic sin to improve influenza virus vaccine effectiveness (Additional Information).
		• NIH-funded project to Philip Arevalo (PI): Identifying determinants of human immunity against influenza: a multiscale approach (Additional Information).
		
		Related work:

		• 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. • 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. • Bill & Melinda Gates Foundation 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. • European Commission 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
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 (Zhang 2019).
	In progress	*Published Reports:*
		• 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:
		  ○ Repeated vaccination results in significant boosting of a durable bNAb response.
		  ○ IIV and LAIV formulations elicit comparable boosting of serological bNAb titers (anti-stalk IgG and IgA).

Strategic Goal 2.5: Clarify the role of T cells in generating or supporting protective immunity to influenza virus infection and vaccination.		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
None of the milestones for this goal were either 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**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **Milestone 2.6.a***:* By 2023, further determine the role of mucosal antibodies in protecting against	In progress	*Ongoing Projects:* • European Commission funded project to Institut National de la Santé et de la Recherche Médicale (INSERM): Induction of B cell immunity in the lung mucosa (Additional Information).

influenza virus infection, disease, and transmission.		*Published Reports:* • 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). *Related work:* • 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. • Canadian Institutes of Health Research funded project to Ellen Wasan, Volker Gerdts, Yan Zhou (PIs): Intranasal Vaccines for Pertussis and Influenza Using Novel Formulations of a Triple Adjuvant (Additional Information).
High-Priority Milestone **Milestone 2.6.d***:* By 2026, determine the role of mucosal T cells in protecting against influenza virus infection, disease, and transmission.	In progress	*Ongoing Projects*: • NIH-funded project to Andrea Sant (PI): Potentiating broadly protective local immunity to influenza virus (Additional Information). *Related Work*: • Wellcome Trust funded project to Ali Amini (PI): 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 end point (Erbelding 2018, Krammer 2020, Lim 2019, Plotkin 2018).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **Milestone 2.7.a***:* By 2025, develop functional assays to accurately capture the breadth and range of protective responses other than virus neutralization, such as influenza virus–specific ADCC, antibody-dependent cellular phagocytosis, and complement dependent cytotoxicity (Coughlan	In progress	*Ongoing Projects:* • European Commission funded project to Patricia Londono-Hayes (PI): Standardization and Development of Assays for Assessment of Influenza Vaccines Correlates of Protection (Additional Information). *Published Reports:* • 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. • Cheung 2022 developed two ELISA-based potency assays for group 1 influenza A viruses using cross-reactive nanobodies.

2018, Gianchecchi 2019, Krammer 2019).		• Waerlop 2022 described the harmonization and qualification of the influenza-specific interferon-gamma ELISpot assay to detect and qualify vaccine-induced cellular immune responses. *Related work:* • Janssens 2022 reviewed current assays for evaluating cell-mediated immune responses to influenza.
High-Priority Milestone **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 (Reber 2013).	In progress	*Published Reports:* • 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). *Related Work*: • European Commission funded project to the University of Oxford: Tracing the influenza vaccine imprint on immune system to identify cellular signature of protection (Additional Information).

APPENDIX E: Policy, Financing, and Regulation

DRAFT FOR DISCUSSION ONLY

Color coding: Green=Completed or Partially Completed; Yellow=In Progress; Red=No Evidence of Progress Identified

Strategic Goal 6.1: Catalyze broad support and sustained funding for developing improved seasonal influenza vaccines and broadly protective or universal influenza vaccines.		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **Milestone 6.1.a***:* By 2022, develop and disseminate a full value of vaccine assessment (FVVA) for improved seasonal and broadly protective, universal influenza vaccines that addresses different vaccine use cases and includes an assessment for LMICs (NASEM 2019).	In progress	*Published Reports:* • Hutubessy 2021 outlined "a framework on the Full Value of Vaccines Assessments (FVVA) 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." • The WHO Product Development for Vaccines Advisory Committee (PDVAC) has initiated a Vaccine Value Profile (VVP) to inform the FVVA for influenza vaccines. *Ongoing projects:* • WHO and LSHTM, with funding from 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 **Milestone 6.1.b***:* By 2022, develop targeted and creative communications and advocacy strategies and necessary communication tools that build on the FVVA and provide information on economic costs, the risk of future influenza pandemics, and the need for investment in influenza vaccine R&D (Navarro-Torné 2019, Sabin 2019).	In progress	*Ongoing Projects:* • WHO and LSHTM are engaged in a FVIVA project that will include addressing communication tools and advocacy strategies (Additional Information). *Related Work*: • NIH-funded project to Michael Hudgens (PI): Causal Inference in Infectious Disease Prevention Studies (Additional Information). • Canadian Institutes of Health Research funded project to Mike Paulden, Shannon MacDonald, and Stephanie Montesanti (PIs): Optimizing adult vaccination outcomes under public health budgetary constraints (Additional Information). • CDC-funded project to Anand Krishnan (PI): 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**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **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 (Sabin 2021).	Completed	*Published Reports:* • 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." The workshop report details the discussions on critical themes, gaps, and topics related to the topic. • 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. • Pecetta 2022 summarized economic and regulatory lessons learned from the COVID-19 pandemic and detailed the "quantum shift in vaccine investment [that] is needed to prepare against future pandemic and non-pandemic global health threats." • 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." This is mostly focused on pandemic planning, but provides useful information. • 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). *Ongoing Projects:* • WHO and LSHTM are engaged in a 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 **Milestone 6.2.b***:* Identify a set of strategies for accelerating the development of universal influenza vaccines through innovative approaches (Sabin 2019).	In progress	*Ongoing Projects:* • European Commission funded project to European Vaccine Initiative: European Vaccine Research and Development Infrastructure (Additional Information). *Related Work*:

		• BARDA's Strategic Plan for 2022-2026 details how the office will prepare for a public health emergency (such as an influenza pandemic) impacting the US, including "enhancing preparedness by investing in development of a robust pipeline of innovative MCMs." • Giersing 2021 noted that "examination] of historical case studies and consultation with diverse stakeholders in the immunization community has underscored the importance of close collaboration of all stakeholders across the entire product lifecycle continuum from the outset, to derive and implement holistic strategies founded on immunization needs of countries and to de-risk investments by improving clarity in innovation priorities, demonstrating potential socio-economic value, and increasing certainty on the demand and potential return on investment." • Bollyky 2021 recommended various funding/financing approaches as lessons learned from the COVID-19 pandemic, some of which may be relevant to universal influenza vaccines R&D. • The National Academy of Medicine workshop on lessons learned from COVID-19 to inform seasonal and pandemic influenza preparedness and response included discussions on how to improve influenza vaccines financing.
Strategic Goal 6.3: Promote information sharing aimed at moving influenza vaccine development forward.		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
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 (Global Funders Consortium 2018).	Partially completed	*Ongoing Projects:* • 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).	No evidence identified	We are not aware of any evidence on implementing an approach to reuse vaccine study data.
High-Priority Milestone **Milestone 6.3.c***:* By 2022, assess the impact of the Nagoya protocol, and	In progress	While no formal assessment has been done, this issue is being recognized and is under discussion. *Related Work:*

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.		• IFPMA, in detailing lessons learned from COVID-19, 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" includes "changes to the Convention on Biological Diversity's Nagoya Protocol expressly to exclude outbreak pathogens… "Inconsistent implementation of the Nagoya Protocol and its associated access and benefit-sharing provisions has proved complex and counterproductive for timely access to pathogens in many countries. It has delayed sharing of both genetic information and physical samples for pathogens including influenza, Zika, and Ebola, in some cases by months" (Additional Information).
Milestone 6.3.d*:* By 2022, implement a plan that improves existing data management and sharing among influenza R&D researchers (Erbelding 2018).	No evidence identified	We are not aware of any progress related to a plan to improve data management among influenza vaccine researchers.
Milestone 6.3.e*:* By 2022, conduct mapping of intellectual property for improved influenza vaccines to identify synergies in approaches that may be used to develop new partnerships.	In progress	*Ongoing projects:* • WHO and LSHTM are engaged in the FVIVA project that will contribute to mapping intellectual property for improved influenza vaccines (Additional Information).
Strategic Goal 6.4: Further explore regulatory challenges associated with development and manufacturing of improved seasonal and broadly protective or universal influenza vaccines (Navarro-Torné 2019).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **Milestone 6.4.a***:* By 2022, conduct a workshop that includes regulators and vaccine manufacturers to: (1) clarify regulatory processes related to the development and evaluation of broadly protective or universal influenza vaccines, (2) develop a regulatory science agenda that anticipates the challenges of evaluating and licensing these new	In progress	*Ongoing projects:* • 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).

vaccines, (3) review the regulatory experience with COVID-19 vaccines and identify ways to streamline the process for new influenza vaccines, and (4) generate additional recommendations regarding how best to provide guidance on vaccine development, manufacture, approval, and delivery.		

APPENDIX F: Animal Models and the Controlled Human Influenza Virus Infection Model (CHIVIM)

DRAFT FOR DISCUSSION ONLY

Color coding: Green=Completed or Partially Completed; Yellow=In Progress; Red=No Evidence of Progress Identified

Strategic Goal 5.1: Optimize animal models for influenza vaccine research.		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
Milestone 5.1.a*:* By 2022, develop a strategic plan for standardizing and harmonizing current animal models for influenza vaccine research, which is particularly important for head-to-head comparisons of vaccines and other products (D'Alessio 2018).	No evidence identified	We are not aware of any effort specifically related to developing a strategic plan.
High-Priority Milestone **Milestone 5.1.b***:* By 2022, ensure that validated reagents, updated viral stocks, and harmonized assays are available to improve understanding of the innate and adaptive immune responses in ferrets and to facilitate comparison of studies across laboratories.	In progress	*Ongoing Projects:* • NIH Request for Information (RFI): Highest Priority Needs for Ferret and Hamster Immunoreagents; issued Aug 18, 2021, response requested by Jan 4, 2022. Current status unknown (Additional Information). *Completed Projects*: • NIH-funded project to Tori Race (PI): Development of ferret reagents for use in the characterization of immune responses to respiratory infections in the ferret model. The project aim is "to generate antibodies for analyzing immune cells and cytokine responses during respiratory infections in ferrets." Project end date: 2022 (Additional Information). • NIH-funded project to Saul Tzipori (PI): Development of ferret and hamster reagents for immunological studies. Project end date: 2022 (Additional Information).
Milestone 5.1.c*:* By 2022, develop best practices for conducting influenza virus transmission studies in ferrets, to include naive and infected or vaccinated animals (Belser 2018, Neumann 2019). (Also see Virology Applicable to Vaccine Development.)	In progress	*Published Reports:* • 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. Standardization of the donor contact ratio appeared to be particularly important. • 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 **Milestone 5.1.d***:* By 2023, convene a workshop on the development of pre-exposure animal models to address the fact that humans generally have pre-existing immunity to influenza (D'Alessio 2018).	No evidence identified	We are not aware of any effort to convene a workshop. *Related work:* • Allen 2022 used a pre-immune mouse model to study bivalent COBRA rHA vaccines.
High-Priority Milestone **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	A comprehensive analysis has not been developed. *Related work:* • Roubidoux 2021 summarized animal models used in the development of "seasonal and novel influenza virus vaccines," including advantages and disadvantages of each model. • Nguyen 2021 reviewed animal models for influenza virus vaccine R&D, including advantages and disadvantages of each model. • 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
Milestone 5.1.g: By 2026, develop and validate novel animal models, as needed, for evaluating immune responses—including durability—to broadly protective influenza vaccines (D'Alessio 2018).
	In progress	*Ongoing Projects:*
		• See 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.
		  ○ For PAR-19-247, see NIH-funded project to John Harty: Evaluation of CC mice as an improved model for influenza immunity. Project end date: 2023 (Additional Information).
		  ○ For PAR-19-248, see NIH-funded project to David Masopust: New mouse model to better predict human immunity to influenza vaccination and infection. The project aims to "evaluate immunity to influenza virus infection and vaccination in a new mouse model that more accurately captures cellular and molecular immune signatures seen in humans." Project end date: 2025 (Additional Information).
		  ○ For PAR-19-248, see NIH-funded project to Richard Webby: 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. Project end date: 2024 (Additional Information).
		• NIH-funded project to Adolfo Garcia-Sastre (PI): Evaluation of the immune responses to influenza virus vaccines and efficacy of immunotherapeutics in the ferret model. One of the project aims is "to investigate prime/boost vaccination strategies to generate broad durable protection against influenza

		A virus challenge in the ferret, and the immune mechanisms (antibodies, T cells) correlating with protection" . . . Project end date: 2023 (Additional Information). • NIH-funded project to Kristina Waldorf (PI): Influenza pathogenesis in pregnancy. Using the NHP model, the study aims to "comprehensively analyze innate/adaptive immune responses during an acute IAV infection to elucidate the pathogenesis of severe lung disease in pregnant women." Project end date: 2026 (Additional Information). • Wellcome Trust funded project to Madina Wane (PI): Respiratory syncytial virus (RSV) and live-attenuated influenza virus (LAIV) infection in zebrafish gills as a model for human respiratory disease. Project end date: 2022. *Completed Projects:* • NIH-funded project to Kevin Walters: Ferret models for the evaluation of universal influenza vaccines and vaccine strategies. Project end date: 2022 (Additional Information). • NIH-funded project to Kevin Walters: Ferret models for the evaluation of influenza vaccines and vaccine strategies. Project end date: 2022 (Additional Information). • NIH-funded project to Jacob Yount (PI): Establishing a relevant mouse model with susceptibility to non-adapted influenza viruses for vaccine challenge studies. Project end date: 2022 (Additional Information).
Strategic Goal 5.2: Address steps needed to further develop and refine the CHIVIM (Innis 2019a, Innis 2019b).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
High-Priority Milestone **Milestone 5.2.a***:* By 2022, determine the use cases for the CHIVIM and generate guidance, including ethical and safety considerations, for using the model.	No evidence identified	We are not aware of any effort related to the completion of this milestone.
High-Priority Milestone **Milestone 5.2.b***:* By 2023, ensure that reagents for the CHIVIM are broadly available.	No evidence identified	We are not aware of any effort related to the completion of this milestone.
High-Priority Milestone **Milestone 5.2.d***:* By 2024, further develop the CHIVIM to ensure that it can be widely used by different investigators.	In progress	*Ongoing Projects:* • Per NIAID's Dec 2021 update to the Global Funders Consortium for Universal Influenza Vaccine Development: NIAID is supporting human clinical challenge studies 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).
		• Emory University project to Nadine Rouphael (PI): human challenge study on "how the immune system responds to the flu virus (H3N2) during and after infection and how the flu virus is transmitted in the environment"; completion by Feb 2023 (Additional Information).
		• NIAID-funded project to Matthew Memoli: A "dose-finding and pathogenicity study following human challenge with a low pathogenicity avian influenza A H10N7" clinical study; estimated study completion date is May 2024 (Additional Information).
		• Multiple respiratory viral human challenge programs were highlighted during the Jul 2022 CIVICs meeting, including:
		  ○ DARPA: Predicting health and disease (n=~120) used HRV, RSV, and Influenza (H3N2, H1N1) to study pre-symptomatic disease
		  ○ DARPA: Prometheus (n=39) used Influenza pH1N1 to study contagiousness
		  ○ DARPA: SIGMA Plus (n=20) used Influenza H3N2 to study pre-symptomatic disease and wearables
		• Bill & Melinda Gates Foundation funded project: Support the development and validation of influenza strains that could eventually be utilized to evaluate candidate universal influenza vaccines in human challenge studies. Project end date: 2023.
		• European Commission funded project: Innovations to accelerate vaccine development and manufacture. Project end date: 2027 (Additional Information).

APPENDIX G: Virology Applicable to Vaccine Development

DRAFT FOR DISCUSSION ONLY

Color coding: Green=Completed or Partially Completed; Yellow=In Progress; Red=No Evidence of Progress Identified

Strategic Goal 1.1: Improve understanding of human and animal influenza virus evolution (Wille 2020).		
Milestone	**Status**	**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 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.	No evidence identified	We found no publically available evidence of progress on completing this milestone. As an extension of current sampling strategies, this effort would likely involve the WHO Global Influenza Programme, GISRS, and the WHO Collaborating Centers.
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**	**Published Reports, Ongoing Projects, and Related Work**
Milestone 1.2.a*:* By 2022, review available data on antigenic mismatches between vaccine strains and circulating strains over past years to identify causes and determine steps that could have minimized or avoided them. Information obtained may be useful in developing contingency response plans in advance for when antigenic mismatches occur in the future.	In progress	An overarching review evaluating global data has not been conducted. *Published Reports:* • 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	*Published Reports:*

Milestone 1.2.e: 2025, develop, standardize, and implement methods to improve antigenic characterization of H1N1 and H3N2 viruses (Allen 2018, Harding 2018, Zost 2017).		• 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. • 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. • 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**	**Published Reports, Ongoing Projects, and Related Work**
Milestone 1.3.a*:* By 2022, develop a plan to continue surveillance of influenza viruses at the human-animal interface and expand global influenza surveillance in poultry and swine, particularly in Africa, Asia, and South America. The plan should highlight the need for coordination among international groups, stress the importance of understanding the emergence of novel and potentially pandemic viruses in animal reservoirs, and promote data sharing and integration across different surveillance systems.	No evidence identified	We are not aware of any effort to develop this plan. This effort would likely involve FAO, WHO, and/or NIAID-CEIRR.
Strategic Goal 1.4: Enhance understanding of factors associated with viral transmissibility (Crank 2019).		
Milestone	**Status**	**Published Reports, Ongoing Projects, and Related Work**
There are no high-priority milestones for this goal or milestones with a 2022 target date.		