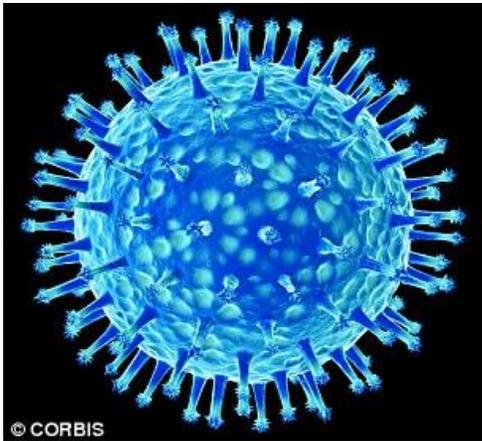

Global Funders Consortium for Universal Influenza Vaccine Development: Shaping a Path Forward

Meeting Report

November 2-3, 2017

The Task Force for Global Health, Atlanta, GA, USA



Background – limitations of current vaccines to address a significant public health threat

Influenza viruses are a substantial public health threat, both because they cause annual epidemics associated with significant mortality and morbidity and because of their ability to cause global pandemics. Seasonal influenza virus infections lead to an estimated 290,000 – 650,000 deaths each year. While influenza vaccination remains the best tool for prevention of annual seasonal disease, the effectiveness of current influenza vaccines remains sub-optimal. Furthermore, because of the continual virus mutation, and resulting antigenic changes to surface proteins on the virus, seasonal influenza vaccines require semi-annual updates and annual vaccination campaigns. The complex processes for vaccine updates and program implementation result in technical and programmatic challenges to achieving high vaccine coverage, particularly in low and middle-income countries.

While seasonal epidemics cause hundreds of thousands of deaths, a severe influenza pandemic may lead to millions or tens of millions of deaths. The 1918 influenza pandemic led to 50 million deaths worldwide. While improvements in healthcare and the availability of antivirals since that time offer promise of lower case-fatality rates during the next pandemic, an increased global population along with the potential for more rapid spread in a more interconnected world, mean that a novel influenza virus, such as the current avian influenza H7N9 virus threat, could lead to a much more severe pandemic than was observed during the recent 2009 H1N1 pandemic. Like for seasonal influenza, vaccines are also a key tool to mitigate the impact of influenza pandemics. However, the requirement for antigenically well-matched vaccine strains to circulating strains using current technologies has meant that the time requirements for developing, manufacturing and distributing influenza vaccines once the pandemic strain is identified results in availability of the vaccine relatively late in the pandemic spread – leading to missed opportunities for prevention.

Better influenza vaccines are needed to address both the ongoing seasonal influenza burden and the persistent pandemic threat. Clearly, vaccines that provide higher levels and more reliable protection from annual epidemic disease could substantially reduce the annual disease and economic impact of influenza. In addition, vaccines that would confer more durable protection against seasonal influenza strains would reduce costs of influenza vaccination programs, potentially increase population coverage, and would be more suitable cost-effective options for use in low-income settings, where disease risks are highest. However, vaccines that could confer both longer-lasting protection and broader protection from antigenically diverse strains, including novel influenza strains would dramatically improve pandemic response efforts, increasing global health security. These “universal” influenza vaccines would be transformational innovations.

While the development of universal influenza vaccines has been a public health goal for decades, progress has been slow. Barriers to progress have included both gaps in scientific knowledge that might facilitate rational vaccine design, the need for substantial investment to bring new candidate technologies with uncertain effectiveness and commercial viability to market in the context of existing approved seasonal vaccines, and uncertain timing of the next pandemic. In addition, and importantly, recent fora have noted the diverse definitions of what a universal vaccine held by key stakeholders and researchers. The lack of a consensus goal or target could reasonably lead to a less efficient research and development enterprise. As a result, a call for a more coordinated, collaborative research and development plan towards a shared goal has been articulated by key stakeholders. This more coordinated approach

would incorporate new scientific disciplines (e.g. system biology, bioinformatics), new tools (e.g. human challenge models) and new partnerships that can address gaps in funding or areas in which combining partners' skills and assets will accelerate progress. In this context, the global research has often been directed at incremental improvements in influenza vaccines. This work has been rewarding, with recent approvals of vaccines with more antigens and higher doses that confer somewhat greater protection. While work towards step-wise improvements in the vaccines continues, calls for increased work towards transformational technologies that would confer protection against a broad variety of influenza viruses, that would better address the pandemic threat have increased.

Two recent events have created increased interest in accelerating the development of universal vaccines. First, the emergence and resulting spread of avian influenza H5N1 in Asia highlighted the threat from novel influenza A viruses, as did the challenges of creating vaccines in a timely manner when a novel influenza A virus developed with pandemic potential. This was reinforced during the H1N1 pandemic, when the monovalent H1N1 vaccine incorporating an A/CA/7/2009-like virus arrived after the first wave of disease had peaked, limiting its impact. The delay in the availability of pandemic H1N1pdm vaccines was particularly noted in low-income countries where rates of severe disease and deaths were highest. The continued occurrence of severe human cases associated with H5-containing viruses and the emergence of avian H7N9 viruses have reinforced the need for expediting the work towards better vaccines to address these threats. Second, annual systems to estimate the vaccine effectiveness (VE) of seasonal influenza vaccines in the United States, Europe, Australia and Canada that were established in the mid-2000s have produced compelling and consistent data that the effectiveness of current influenza vaccines is modest – generally 40-60% - and often lower in especially vulnerable populations, such as elderly persons. These data have served as catalyst for public health officials to promote the need for more effective influenza vaccines.

Both pandemic fears and recognition of the modest VE led to greater investments in new influenza vaccine development, often to support pandemic readiness. These investments have produced notable gains. New vaccine approaches have resulted in additional vaccine choices, such as cell-based vaccines and recombinant protein vaccines that can be made more quickly in response to an emerging pandemic, high-dose vaccines that are more effective in vulnerable older persons, additional live attenuated vaccines, and intradermally administered products. In addition, international investments in vaccine infrastructure, capacity and technology

investments have effectively reduced the risk from an influenza A pandemic. Two important examples include the development and licensure of adjuvanted pre-pandemic vaccines, that have increased the potential availability of vaccine doses during a pandemic by 12- to 24-fold. In addition, investments in WHO's Global Action Plan for Influenza Vaccines have enabled emerging suppliers to develop new influenza vaccines that have increased global supply of traditional egg-based vaccine products. These advances have produced valuable, incremental improvements in seasonal vaccines and their availability at global level, and in pandemic readiness. The public health impact of these advances to reduce seasonal burden with drifted strains or to mitigate pandemic disease remain limited by the time it takes to produce these vaccines once a new strain emerges.

To realize the goal of having vaccines that are able to reduce both seasonal and pandemic disease risks, a variety of new approaches are being investigated. These may be broadly classified as approaches to induce antibody production that would provide protection against a broader range of virus strains (e.g. antibodies against the more conserved HA stalk region or M protein) and those that induce T-cell responses against internal proteins. A recent review identified 38 groups currently working on new vaccine candidates designed to elicit better or more long-lasting protection against disease. The breadth of currently ongoing work and unknown levels of investment makes it difficult for current and potential funders to monitor the landscape. Progress, therefore, might be accelerated through better coordination of ongoing and planned efforts by establishing and developing a coalition of funders and stakeholders around a common vision, and operating from a common landscape.

Concept of a Funders Forum

The value of a consortium of funders is predicated on the assumptions that: 1) the development and deployment of influenza vaccines with broader and more durable immunity are critically needed to address the current public health burden and vaccine administration challenges; and 2) future investments could be made more wisely if stakeholders had an accurate and common operating picture of the field, and were better coordinated around a common vision.

In 2017, The Bill & Melinda Gates Foundation provided funds to establish the Global Funders' Consortium for Universal Influenza Vaccine Development, and to establish the

Task Force for Global Health as its secretariat. The proposed Consortium's goal is to accelerate the development and availability of broadly protective influenza vaccines, thereby and reducing the global burden and risk from seasonal and pandemic influenza. Objectives for the Consortium include:

1. Provide a mechanism for open sharing of information about ongoing investments, strategic plans, institutional perspectives and challenges, and learnings among organizations engaged in funding research and development related to "universal influenza vaccines."
2. Identify critical challenges and knowledge gaps which are likely to delay progress in the field.
3. Facilitate collaborative approaches to address the challenges and accelerate progress, guided by a common vision.
4. Use the voice of the Consortium to raise awareness of the importance of the work and opportunities in the field to encourage additional funders to enter the field.

The proposed scope of the Consortium's work is intended to complement and build on a variety of ongoing activities and initiatives, but not to interfere with or replace them. The Consortium will rely on the continuing scientific dialogue carried out in forums that already exist. For instance, WHO's biannual meetings to review data on broadly reactive influenza vaccines will serve a critical need to bring together researchers and public health officials to review progress in the field. Meetings such as Options for the Control of Influenza and IDWeek will serve as more technically focused fora. National government programs that fund projects related to next generation vaccine development will likely continue to be a main driver of progress. The US government's intramural and extramural influenza programs at the National Institutes of Health will be critical engines of bench research and vaccine evaluations. The US Biomedical Advanced Research and Development Authority will support development of promising approaches towards regulatory licensure; CDC and FDA will continue to support influenza vaccine development efforts and approvals according to their strategic plans. Similarly, other national governments, and the European Commission will continue to fund significant work in this area. Philanthropic organizations, such as the Bill & Melinda Gates Foundation, Wellcome Trust and the Page Foundation will invest in activities towards reducing pandemic threats. Finally, industry will continue to be a critical and major partner for research and development of new vaccines. The Consortium will not diminish the need for investments by each of these stakeholders, nor serve as the primary forum for sharing of scientific data. Rather, the Consortium is

intended to be a mechanism to bring together the latest data and progress in the field for the benefit of current and future funders and to maximize the opportunities for impactful and efficient investments going forward.

Meeting Goals and Context

The first meeting on the Universal Influenza Vaccine Funders Consortium was held at The Task Force for Global Health (TFGH) in Atlanta, USA on November 2-3, 2017.

The meeting was designed as a shaping meeting in which participants would determine the value for such a consortium and identify objectives and roles for the Consortium going forward. Proposed products of the meeting included:

- Gaining a common understanding of the “universal vaccine” R&D landscape by participants
- Gaining a common understanding of the key challenges and priority activities needed to advance the field
- Agreeing on a consensus statement of need for a universal vaccine
- Discussing a vision/plan for activities of the Consortium along with next steps

The meeting was attended by representatives of governments, international organizations, non-profit organizations and academia (Appendix A). Some participants represented organizations that fund a portfolio of research and development activities related to universal influenza vaccines, while others were representatives of organizations that had a stake in the development of these vaccines. Industry were not represented at this first meeting but will be considered for participation at future convenings of the group.

The meeting was conducted over two days (Appendix B), roughly divided into sharing information about current activities by the participants (Day 1) and discussing potential roles and values of the Consortium (Day 2).

Meeting Key Points

Key points from the meeting included the following:

1. ***Goal of the effort needs to be defined, and reflected in the nomenclature used to describe the desired vaccine.*** Some participants thought that the use of “universal vaccine” might create confusion given the various ways that this term can be interpreted, and therefore preferred “next-generation” influenza vaccines is a more acceptable phrasing, both in terms of the discussion and potentially in future communications and nomenclature of the Consortium. Others supported continued use of “universal” to connote the goal of creating a transformational product. This nomenclature discussion pointed to fundamental differences in perspectives about the goals of research and development related to improving influenza vaccines. These perspectives included:
 - While the need for better vaccines was a consensus opinion, some participants preferred a greater focus on incremental improvements in vaccines towards a “universal” vaccine, while others desired a primary focus on game-changing vaccines. While these ideas are not mutually exclusive, balancing the two perspectives in the context of the Consortium’s goals will be important, and any “roadmap” of universal vaccine development will have to acknowledge these two perspectives and perhaps include separate work plans towards each type of goal. One can imagine that investments in current candidates (e.g. clinical trials) might produce important incremental improvements in vaccination program performance, while investments in basic science (e.g. understanding influenza immunology towards rational design of future approaches) might result in larger gains. In a budget-constrained environment, decisions might be made to focus on one area versus another. However, the group discussed the value of work that would support both incremental and more aggressive goals, and the need to increase the funds available for the work so as not to slow progress towards either. Additionally, a natural approach would be to identify short-, mid-, and longer-term goals that would provide a structure for achieving incremental improvements early towards large gains over time.
 - Several participants expressed the priority of ensuring that low-cost solutions were developed with product characteristics relevant to low-income populations. The recently completed WHO Preferred Product Characteristics was presented as a model for developers. This PPC was developed to promote development of vaccines suitable for use in low and middle-income countries

and prioritizes the reduction of severe disease. The WHO PPC articulates two goals – one 5-year goals and one 10-year goal – that describe incremental improvements desired by each time point. In addition, the main target population for the goals are young children. The BMGF Intervention Target Profile was discussed as another example of this perspective, as was the European Commission’s approach.

- Participants discussed whether R&D should be directed at producing better vaccines primarily for pandemic disease mitigation or for seasonal disease burden reduction. Divergent organizational perspectives were discussed, but all acknowledged the overlap between these goals, even while organizational strategic goals might be directed primarily at pandemic mitigation or seasonal vaccine improvements.
 - Some discussion included the outcomes desired of next generation vaccines. While all agreed that vaccines should be developed that reduce severe outcomes of influenza infection as a primary goal, some highlighted the potential value of a vaccine that reduced virus transmission in the setting of pandemic spread.
2. Each stakeholder necessarily has and articulated their unique perspective on these issues based on their institutional missions and resources. Even so, the group developed a ***draft consensus Consortium target for next generation vaccines***: “to develop vaccines and vaccination strategies that will reduce severe influenza disease and deaths, whether caused by seasonal and pandemic influenza viruses, and be available before they are needed.” This will be further discussed and refined at future meetings.
 3. ***A portfolio of ongoing and planned research and investments related to next-generation influenza vaccines was reviewed.*** Participants were presented with a landscape of ongoing and planned research from the various presentations given during the first day of the meeting, briefly summarized below:
 - **US National Institute of Allergy and Infectious Diseases** presented their portfolio of current and planned research in this area. They have a next-generation influenza vaccine development strategy that includes: clinical evaluation, assay development, improving vaccine efficacy and production, provision of reagents to support development, and development of outreach and partnerships.

- The extramural program supports a broad portfolio of work related to basic science, natural history of infection, universal vaccine strategies, preclinical services and clinical trials. They have substantial funding in bench work to understand the components of the immune responses to influenza and to vaccines. They support longitudinal cohort studies, including a Nicaraguan pediatric cohort that generates data on host and viral factors related to disease severity, immunity and disease transmission, as well as information on the role of pre-existing immunity on protection. They fund a large number of projects related to a spectrum of universal vaccine approaches, including research to understand and develop the relevant antigens for new vaccines, to develop and evaluate delivery systems, to evaluate options for immune activation (e.g. adjuvants), and to develop relevant assays to advance the work of the research community. They support pre-clinical development and early phase clinical trials for more than 20 vaccine candidates. Finally, they provide support services, such as vaccine manufacturing and testing for candidates in pre-clinical stages of development.
- The intramural program is supporting the pre-clinical development of a cocktail of inactivated avian influenza viruses expressing at least 4 different HA subtypes, that will soon be in Phase 1 testing. They also conduct human volunteer challenge studies and hope to expand this work. The Vaccine Research Center has a universal vaccine strategy and currently conducts research on reagent and assay development, antigen design, antibody design and phenotyping, clinical evaluation of novel products and developing improved animal models. They are currently testing a variety of universal vaccine approaches.
- The **Biomedical Advanced Research and Development Authority (BARDA)** provided an assessment of vaccine candidates in pre-clinical and clinical development and summarized the status of ongoing, BARDA-supported clinical development of new vaccine approaches and heterologous prime-boost strategies using licensed pre-pandemic vaccines. They support innovative antigen delivery platforms, including an orally administered, temperature-stable, virus vector vaccine and an HA-stem recombinant vaccine. BARDA promotes industry partnerships and interagency efforts for Phase 2a studies using human challenge platforms and leverages HHS' technology pipeline. They

published a new Broad Agency Announcement to support new work in this area.¹

- The **European Commission** presented its recent and current portfolio of activities that includes work on basic immunology of influenza and on vaccine candidate development. They invested €25.5M in 5 consortia designed to develop candidate vaccines, to work together to address existing knowledge gaps in the understanding of influenza immunology, and to develop assays for next generation vaccine research. The results of these multi-year consortia, including EDUFLUVAC, FLUNIVAC, FLUTCORE, UNISEC and UNIVAX were presented at a meeting in Brussels in June 2017. They have also provided €30M to fund ADITEC to develop new adjuvants, vectors, formulations, delivery devices, routes, schedules, that may be relevant to new influenza vaccine approaches. Along with the Innovative Medicines Initiative², they invested €14M in FLUCOP, a multi-partner effort to improve, standardize and develop immunological assays for influenza correlates of protection, and in similar collaborations to develop innovative tools to speed-up and improve the testing and monitoring of vaccine safety. Finally, they are currently supporting Biondavax' universal vaccine candidate through the Infectious Diseases Financing Facility³. EC has expressed interest in continuing support of research in this area.
- **The Bill & Melinda Gates Foundation** has updated its influenza strategic approach to focus on reducing pandemic mortality through accelerating R&D for truly transformative Universal flu vaccines offering breadth and longevity of response. This has resulted in recent investments in universal influenza vaccine development for use in the interpandemic period. They have developed an intervention target product profile reflecting the need for transformative approach keeping in mind breadth and longevity of protection alleviating a need for annual vaccination. They currently have funded the development of a chimeric HA stalk-based candidate (with Mt. Sinai School of Medicine, GSK, and PATH), multivalent universal flu vaccines (NIAID) and studies of prime-boost strategies (with NIAID and JHU). They have also provided funds to support the Global Funders Consortium for Universal Influenza Vaccine Development.
- **Canadian Institutes of Health Research's (CIHR) Institute of Infection and Immunity (III)** supports research in this area based on a strategic goal of

¹https://www.fbo.gov/index?s=opportunity&mode=form&id=5e39c8f4430e3eda55a16a66df229c2f&tab=core&_cview=1

² <http://www.imi.europa.eu/>

³ <http://www.eib.org/products/blending/innovfin/products/infectious-diseases.htm>

preparing for and responding to emerging threats, that include funding research on existing and emerging microbial threats and vaccine development. Between 2009 and 2017, IIR has supported several projects on pre-clinical universal vaccine development and development of broadly protective mAbs. They also support vaccine evaluation sites that could be relevant for assessing next generation vaccines. CIHR works in close collaboration with the public Health Agency of Canada and the National Research Council of Canada.

- **Wellcome Trust** has funded research and program support activities related to influenza and pandemic preparedness for many years, and invested £14m in the last 10 years. While the Trust does not currently have funds dedicated specifically to next generation vaccines, they do fund several research projects related to gaps identified during the meeting. These include work on influenza virus evolution and host factors, genomic surveillance, viral transmission, and human immune responses to vaccination and natural infection. They have also supported pandemic risk assessment through their Global Policy team. They currently support a variety of activities⁴ that are meant to improve epidemic readiness, notably CEPI's work, which includes supporting vaccine platform technologies. They have articulated four priority objectives for future funding that are relevant to the Consortium's efforts, including: a world prepared for epidemics; innovation in vaccine development; evidence for decision making; and increased vaccine expertise. They noted that, while they do not have a specific universal vaccine strategy, they accept funding proposals that are investigator generated.
- **The Human Vaccines Project** has initiated a universal vaccine project that aims to address gaps in understanding of the human immunology to influenza that is impeding the development of universal influenza vaccines. Their proposed work will focus on understanding the mechanisms of immunologic imprinting through natural history studies, vaccine trials, and machine learning simulation models and to understand correlates and mechanisms of broad and durable protective immunity, through experimental medicine trials, human infection models, and using systems immunology approaches.

4. **Scientific knowledge gaps remain that are impeding progress** towards the development of influenza vaccines with greater effectiveness, breadth of immunity, and longer duration of protection. These gaps were summarized at the recent NIH-

⁴ <https://wellcome.ac.uk/what-we-do/our-work/vaccines>

sponsored meeting, “Pathway to a Universal Influenza Vaccine” in June 2017, and reviewed and discussed at this meeting. They included:

- Understanding factors that affect the course of human influenza infections such as viral and host factors, innate and mucosal immunity, inflammatory response, and prior exposure to natural infection and vaccines, and to identify immune markers of severity.
- Developing a greater understanding of human immunity to influenza, including understanding the role of immunologic imprinting, innate and adaptive immunity, responses to natural infection and vaccination, and immune mechanisms and correlates of protection.
- Improved understanding of viral evolution by developing predictive models of viral evolution and techniques to detect changes in animal influenza viruses more efficiently that are predictive of threat to humans.
- Developing new tools to study immune responses to vaccine and natural infection, such as antibody responses to HA stem and cell-mediated immune response. Standardized assays will be needed for the study and regulation of new approaches to influenza vaccines.

5. Continued and accelerated work on new vaccine approaches/candidates is critical, focused on the most promising technologies.

- Several candidate vaccines are in development that employ a variety of approaches. Trials of these vaccines will generate valuable data on human immune responses.
- The group agreed that continuing to support clinical trials with promising candidates, together with a rationale to advance or down-select candidates is needed. Several participants presented ongoing or planned pre-clinical and clinical trials related to a variety of vaccine candidates. The group agreed that continuing to support this work and to intensify funding towards promising approaches is the most expeditious pathway towards needed incremental improvements in vaccines, while more basic science efforts are underway that might produce “game-changing” vaccines.
- The group discussed the potential for studying combinations of diverse vaccine approaches (e.g. regimens of sequential vaccination with candidates that elicit different components of the human immune response) and delivery systems. Development of such regimens would face funding and IP challenges, and one would expect challenges in creating an opportunity for industry collaborations

that involve more than one company's candidates. Further discussion of how to address this sort of need will be needed.

- More work is needed to identify new antigens that elicit a wider breadth of protection and on the use of novel adjuvants and alternative delivery systems that enhance breadth and durability of immunity.
- It was acknowledged that clinical trials designed to demonstrate superiority of a vaccine candidate, with respect to breadth of protection, efficacy, or duration will be technically complex and require large sample sizes and multiple years. As a result, this work will be complex and expensive. In this context, again, the concept of human challenge models was raised as one tool that might be employed to down-select candidates, allowing for fewer most promising candidates to be tested in large clinical trials.
- Consideration should be given to developing vaccine presentation and formulations that facilitate their use in low and middle income countries, such as novel delivery systems that don't require needles and attention to temperature stability.

6. *Developing new research tools and platforms that can be used by multiple groups to accelerate progress in the field will be a high priority.* Four priority types of needs were discussed:

- **Human challenge platforms** – human challenge models represent a tool that would allow for a better understanding of influenza disease pathogenesis and human immunologic responses to natural infection and vaccines. They would also allow for rapid testing of promising vaccine candidates towards a potentially more efficient way to advance the most promising candidates. The current capacity in this area is severely limited in terms of the size of the study site's capacity to enroll and follow subjects, and by the number of available challenge virus strains. The expense of these platforms will be an obstacle to providing sufficient testing capacity. Even so, all participants expressed the value of more work in this area. In general, the group felt that better tools for vaccine evaluation were needed, and while the human challenge models were mentioned most frequently, improved animal models were also mentioned.
- **Animal models that better reproduce human immunity** - to understand the effects of pre-existing immunity in the context of vaccine exposure.
- **Establishing longitudinal cohorts to better understand human immune response and the effects of prior immunity.** Having a large cohort of humans available for study over time, and in which detailed data on exposure and outcomes could

be collected, and from which appropriate samples could be collected and shared, would be invaluable. Conducted properly, this cohort could offer information on the effects of multiple sequential vaccinations on vaccine effectiveness. NIH has announced a request for information⁵ for such work, and the Human Vaccines Project is also planning work in this area with their consortium of researchers. One key to the design of the work will be to ensure sufficient size and duration of the cohort to ensure answers to key gaps that can't be approximated with other observational or trial data.

- **Developing systems biology approaches** that include analysis of diverse genome-wide multiscale datasets, identifying vaccine targets from molecular signatures, and developing computational models that predict influenza responses based on molecular signatures.
- **Employ new tools and approaches** such as artificial intelligence and machine learning for modelling the transmission of influenza; Bioinformatics for the large data sets that will be generated from the genetic and immune monitoring assays that are now being used; reagents for the standardized assays i.e. virus panels for evaluating breadth; challenge viruses for controlled human infection models; tissue sampling tools.

7. ***Regulation of new vaccine approaches will follow existing regulatory pathways, but will be complex in many ways.*** The key tenets of vaccine approval will be relevant for these vaccines – that vaccines must be demonstrated to be safe and effective, and must provide evidence that they can be manufactured in a consistent manner.
- Design of clinical trials of candidates that are intended to provide more broadly reactive protection or longer durations will have to ensure that they can produce data for these outcomes. The particular complexity to show evidence of likely protection against pandemic strains was discussed. All current influenza vaccines are indicated for “the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine”. For next generation vaccines that seek to be approved for drifted strains or certainly pandemic strains, the phrase “contained in the vaccine” would have no meaning.
 - Human challenge studies could have a role in the clinical development and approval of new vaccines.

⁵ <https://www.niaid.nih.gov/grants-contracts/influenza-related-rfi-send-information>

- Universal/broadly protective vaccines may have unique safety concerns, which may be product-specific.
- Because vaccines will elicit a variety of immune responses depending on the approach, the measurement of immunogenicity in trials of new vaccines will likely be class and product-specific. New clinical assays are likely to be needed to measure the immune responses and the assays will need to be transferable between laboratories and validated prior to pivotal studies. Assays may need standards and if applicable to multiple types of vaccines, may need collaborative studies to establish variability and reproducibility. While not required for licensure, identifying a correlate of protection would greatly facilitate vaccine development. An indication for protection of strains not contained in the vaccine may depend on developing assays to measure cross-protection and establishing the significance of the laboratory data as evidence of cross-protection.
- Extensive characterization will be required to ensure critical product attributes and consistency of manufacture. Each vaccine will require a relevant assay to determine potency and stability.

8. ***Advances in the field will require substantial industry involvement.*** Market considerations may result in industry prioritizing incremental changes in vaccines that may involve less risk. Industry may be hesitant to support transformative technologies that would disrupt the current market. Companies have focused more on late-stage development, and less on proof of concept studies. Therefore, co-investment from governments and other partners is critical to spread risk. Early stage investment (e.g. NIAID, EC) and late stage investment (e.g. BARDA) are critical, but new, flexible mechanisms to support product development from end to end may be needed to ensure that the transformative approaches are advanced.
9. ***A “consortium” of funders and stakeholders will be a valuable entity.*** By providing a landscape of activities, candidates and gaps in the field, stakeholders can make more informed and efficient investments, and the risk of duplicative funding is reduced. Opportunities for co-funding or complementary funding of large, complex projects are increased. Finally, such a consortium might increase funding into the field if it could articulate a consensus message and become a recognized voice. Examples of other versions of funders consortia, including those focused on malaria vaccine development and TB control, were discussed, and might provide examples for organizing an influenza vaccine group. Therefore, it will be critical to be clear

about the activities/roles of the Consortium and key milestones to measure its value to the community (see below).

Conclusions and Next Steps

A consensus was expressed that the Consortium has sufficient potential value to continue. The main roles for the Consortium include:

1. Creating and maintaining a mechanism to share a current and accurate landscape of the field with funders and stakeholders. This includes knowledge of the major funders and researchers in the field, promising candidates and approaches, critical gaps and funding opportunities.
2. Facilitating solutions to address critical knowledge and funding gaps and challenges that might delay progress in the field.
3. Providing a forum for advocacy to increase funding and interest in the field, guided by a common vision.

The Consortium would aim to capitalize on other relevant initiatives' work and to create possible synergies with them, whether focused in influenza vaccines or other diseases.

Given these roles, a variety of activities were identified for 2018:

1. *Creating and maintaining a common landscape* –
 - a. Develop a “Roadmap” that can guide research and development efforts towards creating next generation influenza vaccines. This document would be a concise statement of the need for better influenza vaccines, significant gaps and enabling factors, high priority near-term activities, and perhaps the roles of various partners in ensuring progress. This roadmap should take into consideration and build on work already conducted, such as WHO’s PPC.
 - o The Roadmap would be a collaborative undertaking with participation of key stakeholders, including the Consortium members, and include industry perspectives.
 - o It would be a tool for advocacy and common messaging among Consortium members.
 - o It would not replace institutional strategic plans or priorities; but these perspectives would be incorporated into the Roadmap.
 - o The “home” of the Roadmap was not determined, but similar efforts have been coordinated by WHO and by the TFGH; either or both organizations can consider leading this effort.

Next steps:

- Consortium secretariat to meet with key partners to outline and plan for draft
- Complete draft of Roadmap – by Q3 2018.

b. Map the allocation of resources being spent in the various parts of the universal influenza vaccine development space – e.g., basic immunologic research, assay development, antigen design, candidate development, etc. This mapping exercise would enable current and prospective funders to appreciate where future investments may be most impactful.

Next steps:

- Create a structure for the mapping (e.g. categories of investments) and determine a plan for data collection and presentation – Q1 2018.

c. Consider establishing a compendium of funding opportunities that can provide a clearinghouse for researchers seeking information. This could be based on the paradigm of the TB Funders Forum.

Next step:

- Discuss the value of a compendium at the next Consortium teleconference – Q1 2018

d. Convene the regular Consortium meetings - by teleconference every 4 months and in person each year. The call would be structured to provide updates to participants on key developments in the field and to determine how best to use Consortium resources to advance the field.

Next steps:

- Hold Teleconference in Q1 2018 – date to be determined
- Convene a 2nd annual meeting of the members in 2018.

2. *Facilitating solutions to address critical knowledge gaps and challenges*

a. Create partnerships to address highest priority needs.

- Improving our understanding human immunity to influenza, including understanding the role of immunologic imprinting, innate and adaptive immunity, responses to natural infection and vaccination, and immune mechanisms and correlates of protection. Mechanisms to address these

knowledge gaps included: 1) establish large, collaborative prospective cohort studies that collected quality data and specimens over many years. NIH has issued an RFP for such work, and HVP has initiated work in this area as well; 2) continue to take advantage of observational studies and samples collected within them. US CDC, European VE consortia, and Canadian work is underway and expected to continue; 3) consider human challenge models (see below); 4) use data collected from clinical trials of novel vaccine approaches.

Next steps:

- NIAID to provide update on applications for the RFP for longitudinal cohorts at next consortium teleconference – Q1 2018
- Consortium to explore developing mechanisms to monitor relevant results from observational vaccine studies and key research relevant to this area.
- Consortium can serve to share member institutions' work plans/priorities/needs in this area with potential funders if increased funding in this space is needed. (e.g. NIAID universal vaccine work plan; HVP proposals).

o Increasing human challenge study capacity

Next steps:

- Consortium to support and help plan a meeting of experts to identify and develop new, influenza virus strains appropriate for human challenge studies.
- Consortium to support the development of a work plan towards expansion and enhancement of human challenge models.
- Consortium can advocate for increase funds to expand global capacity of human challenge platforms, so that they have adequate bed space to accommodate testing of promising vaccine candidates, or to study immunologic responses in humans to influenza infections.

o Supporting clinical trials of promising candidates, including potential for trials that include a regimen of more than one vaccine candidate/approach. BARDA has a BAA published recently for this work.

Next steps:

- Consortium could support the development of mechanisms to fund studies involving more than one product (from more than one company).
- Advocate for consensus immunological and clinical measures in clinical trials to help assure comparability of results as much as possible

- b. Consider ways to engage industry stakeholders in the Consortium discussions. It was agreed that industry perspectives are important for the discussions, but that issues that may impede full sharing of information had the potential to interfere with the goals of the Consortium. Thus, a mechanism to engage with relevant biotechnology companies and influenza vaccine manufacturers would be needed going forward.

Next step:

- Consortium secretariat to present options for industry involvement at next teleconference – Q1 2018.

3. *Providing a forum for advocacy*

- a. Develop an inclusive goal statement. The draft developed during the meeting was: “To develop vaccines and vaccination strategies that will reduce severe influenza disease and deaths caused by seasonal and pandemic influenza viruses, that can be administered less often than current vaccines.”

Next steps:

- Solicit edits to this statement
- Finalize by the first teleconference – Q1 2018

- b. Discuss methods to raise awareness of the need for next generation influenza vaccines, and to leverage the centennial of the 1918 pandemic in doing so

Next steps:

- Consider engaging leaders of highly influential organizations to create a collective call for action
 - Consider promoting this work as a Grand Challenge (BMGF)
-

- Identify meetings/conferences in 2018 in which a presentation on 1918 pandemic and the need for better vaccines might be placed – reach out to members for participation in the meetings
- Consider Consortium website
- Develop core slide sets that can be available for presentations by Consortium members

Appendix 1 – List of Participants

Jon Abramson, MD

Chair, Department of Pediatrics
Wake Forest University School of Medicine
jabrams@wakehealth.edu

Joe Bresee, MD

Associate Director for Global Health Affairs
Influenza Division
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention Director
jsb6@cdc.gov

Nancy Cox, PhD

Consultant
ncox@cdc.gov

Armen Donabedian, PhD

Influenza and Emerging Diseases Deputy Director (Acting)
Biomedical Advanced Research and Development Authority
armen.donabedian@hhs.gov

Emily Erbeling, MD, MPH

Director, Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases, National Institute of Health
emily.erbelding@nih.gov

Luzhao Feng, MD, PhD

Chief, Branch of Respiratory Infectious Disease
Division of Infectious Diseases
Chinese Center for Disease Control and Prevention
fenglz@chinacdc.cn

Bruce Gellin, MD, MPH

President, Global Immunization
Sabin Vaccine Institute
Bruce.Gellin@Sabin.org

Josie Golding, PhD

Programme Officer, Epidemic Preparedness
Wellcome Trust

J.Golding@wellcome.ac.uk

COL Matthew Hepburn, MD

Program Manager, Biological Technologies Office
Defense Advanced Research Projects Agency

matthew.hepburn@darpa.mil

Joachim Hombach, PhD, MPH

Senior Adviser in the Department of Immunisation, Vaccines and Biologicals
World Health Organization

hombachj@who.int

Amy Jenkins, PhD

Infectious Disease Subject – Matter Expert (SME)
Defense Advanced Research Projects Agency

amy.jenkins.ctr@darpa.mil

Lalit Kant, MBBS, MD, MSc, FIPHA, Dip LSHTM

Senior Adviser, Infectious Diseases
Public Health Foundation of India

drlalitkant@gmail.com

Jackie Katz, PhD

Deputy Director, Influenza Division
Centers for Disease Control and Prevention

jmk9@cdc.gov

Barbara Kerstiens, MD, MPH

Deputy Head, Unit and Research and Innovation
European Commission

Barbara.KERSTIENS@ec.europa.eu

Samantha Kluglein

Deputy Director
Center for Vaccine Equity
Task Force for Global Health

skluglein@taskforce.org

Keith Klugman, MD, PhD

Director for Pneumonia

Bill & Melinda Gates Foundation

keith.klugman@gatesfoundation.org

Wayne Koff, PhD

President & Chief Executive Officer

Human Vaccines Project

wkoff@humanvaccinesproject.org

Isabelle Létourneau, PhD

Associate, Institute Strategic Initiatives

Canadian Institutes of Health Research

Isabelle.Letourneau@crchudequebec.ulaval.ca

Mark McKinlay, PhD

Director

Center for Vaccine Equity

Task Force for Global Health

mmckinlay@taskforce.org

Diane Post, PhD

Influenza Program Officer

Contracting Officer Representative (COR), CEIRS

Respiratory Diseases Branch

National Institute of Allergy and Infectious Diseases, National Institute of Health

postd@niaid.nih.gov

Niteen Wairagkar, MD

Senior Program Officer

Global Initiative Lead for Influenza and RSV

Pneumonia Strategy Team

Global Health Program

Bill & Melinda Gates Foundation

niteen.wairagkar@gatesfoundation.org

Jerry Weir, PhD

Director, Division of Viral Products

US Food and Drug Administration

Jerry.Weir@fda.hhs.gov

Casey Wright, ScM

Director, Shoo the Flu Program

Page Family Foundation

cwright@pagefamilyfoundation.org

Darin Zehrung, PhD

Program Advisor, Portfolio Leader

Vaccine and Pharmaceutical Technologies

PATH

dzehrung@path.org

Appendix 2 – Agenda

**Global Funders Consortium for Universal Influenza Vaccine
Development:
Preliminary Shaping Meeting
November 2-3, 2017**

Task Force for Global Health
325 Swanton Way
Decatur, GA, USA

Agenda

November 2		
13:00	Welcome and Introductions	Joseph Bresee, Keith Klugman
13:10	Background and goals of the meeting	Joseph Bresee
Session 1: Gaining a common landscape		Moderator: Jon Abramson
13:30	Approaches and key challenges to realizing universal influenza vaccines	Emily Erbeling
13:55	Current vaccine candidates and industry perspective	Armen Donabedian
14:20	Issues related to the regulatory environment for universal vaccines <i>Objectives: This session is designed to create a common understanding of the state of the science and technology, and of the key challenges. Participants will have a shared view of the landscape in advance of and for the discussions to follow.</i>	Jerry Weir
14:45	Break	
Session 2: Funders' and stakeholders' perspectives		Mod: Jon Abramson

<p>15:00</p>	<p>Part 1: Review of current funders portfolios and strategies (10-12 min per presentation)</p> <p><i>This first part will be a series of short, structured overviews of current funders’ portfolios and goals/strategies</i></p> <p><i>Each organization is asked to review:</i></p> <ul style="list-style-type: none"> -The organization’s vision/goals for a universal vaccine -Organization’s strategies in this area. What is the current or planned focus of funding (e.g. candidate vaccine development, basic immunology, clinical trials, etc.)? -Currently funded activities. Provide a summary of currently funded projects, including title, organizations receiving the funding, key partners, objectives, status of the project(s), key results (if any), timeline, and other relevant information. (will be further discussed in Session 3) -Key gaps/priorities. What does your organization see as critical knowledge gaps towards which work to address should be prioritized? (will be further discussed in Session 3) <p><i>Objective: Participants have a common understanding of the landscape of currently funded work in this area</i></p>	<p>Niteen Wairagkar (BMGF) Armen Donabedian (BARDA) Teresa Hauguel (NIAID) Barbara Kerstiens (EC) Josie Golding (Wellcome Trust) Isabelle Létourneau (CIHR)</p>
--------------	--	--

16:30	<p>Part 2: Stakeholder perspectives (3-4 min per statement)</p> <p><i>In the session, other organizations attending will be asked for brief comments on their organizations' strategic visions and their areas of interest and current/planned activities related to influenza.</i></p> <p><i>Objective: Participants have a common understanding of the perspectives, areas of interest, and current work of key stakeholders in this area.</i></p>	<p>Joachim Hombach (WHO) Jackie Katz (US CDC) Casey Wright (Page Family Foundation) Amy Jenkins (DARPA) Feng Luzhao (China CDC) Jerome Weir (FDA) Bruce Gellin (Sabin) Wayne Koff (HVP) Darin Zehrung (PATH)</p>
17:30	Wrap up of the day	Jon Abramson, Joseph Bresee
18:45	<p>Dinner at Joe Bresee's house</p> <p>Participants will be given time (if they wish) to return to the hotel before dinner. Transport from the hotel to Joe's house (10 min away) will be provided and depart at 18:45 and return around 21:00. People can choose to take their own transport as well if more convenient.</p>	2234 Fair Oaks Ct, Decatur, GA 30033
November 3		
Session 3: Gaining a common vision		
08:30	<p>Goals of universal vaccines</p> <p>WHO's Preferred Product Characteristics (10 min)</p> <p>Group Discussion (50 min)</p> <p><i>This session will allow for discussion of the various participant perspectives of the need for or goals of a universal vaccine. We will start with a review of the goals/strategies articulated by participants on the first day.</i></p>	<p>Moderators: Lalit Kant, Joachim Hombach</p> <p>Joachim Hombach</p> <p>All</p>

	<p><i>Recognizing that each institution will have its own mission and therefore, its own strategies for universal vaccine development, can we identify the common features that could form the starting place for developing a consensus goal/use case for the Consortium?</i></p> <p><i>Objective: draft a consensus statement of the goals of universal influenza vaccines.</i></p>	
09:30	<p>Priority areas for investment and priority gaps</p> <p><i>The session would begin with a review of the gaps/needs identified on day 1. The discussion is designed to identify consensus areas of need that the group thinks are particularly important to address in order to advance the field. Topics of discussion might include:</i></p> <ul style="list-style-type: none"> <i>-Areas/gaps identified by multiple participants</i> <i>-Gaps that are bottlenecks or common to multiple approaches.</i> <i>-Gaps that are not yet identified in participants' strategies or work plans</i> <i>-Gaps that will require resources in excess of those currently identified as available (i.e., possible opportunities for co-funding).</i> <p><i>Objective: Identify and gain consensus on priority questions/needs for research in the next 5 years.</i></p>	<p>Moderator: Nancy Cox</p> <p>All</p>
11:00	Break	
Session 4: Shaping the Consortium		Moderator: Jon Abramson, Niteen Wairagkar
11:15	<p>This session will be designed to discuss and come to consensus on how this Consortium could help accelerate advances towards “universal” influenza vaccines, taking into account the previous sessions’ results.</p>	

	<ul style="list-style-type: none">-What can this group do to support addressing the priorities identified?-Should industry partners be participants in future meetings?-What metrics are needed for measuring success of the Consortium?-What can we learn from other initiatives (e.g. TB, malaria)-What is the role of the secretariat?	
12:30	Summary and next steps	Joseph Bresee,
12:45	Adjourn	Jon Abramson