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Commentary

Global Funders Consortium for Universal Influenza Vaccine Development

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1. Background

A century after the great influenza pandemic of 1918, influenza remains a major public health threat. Annual epidemics are associated with significant mortality and morbidity globally, leading to an estimated 290,000–650,000 deaths each year [1]. In addition, the ongoing threat of the next pandemic requires significant resources and attention to ensure that communities and governments are prepared to mitigate the health and societal impact that would likely be much larger than the seasonal toll from influenza [2]. Vaccines against influenza have long been used to reduce seasonal disease risk and to reduce illness and spread of pandemic influenza [3–6]. However, the variable and moderate effectiveness, the limited ability to prevent influenza caused by antigenically dissimilar challenge viruses, and the complex and lengthy process for semiannual vaccine production, highlight the limitations of current vaccines to optimally address both seasonal and pandemic threats [7–10]. As a result, growing interest in developing improved influenza vaccines has been voiced by public health authorities and other global stakeholders.

The development of "universal" influenza vaccines would transform influenza control and the efficacy of pandemic and seasonal response. While the definition and desired target product profiles of universal vaccines may vary, the core characteristics include high efficacy, the ability to induce immunity to a broad array of influenza A (and perhaps B) viruses, the ability to prevent severe disease and the ability to confer more durable immunity than current vaccines that are required to be administered annually [11,12]. Such vaccines could be effective for both seasonal and pandemic disease prevention, and could be cost-effective for both low-resource and high-resource settings. To realize the "universal" vaccine goal of reducing 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 also induce cell mediated T-cell responses against internal viral proteins. A recent review identified 38 groups currently working on new vaccine candidates designed to elicit broader, more long-lasting or both protection against disease [13].

To advance universal influenza vaccine development, we must both fill important knowledge gaps related to human immunity to influenza, viral evolution, and immune correlates of protection that could facilitate rational vaccine design, and also make substantial investments in evaluating new candidate technologies with uncertain effectiveness and commercial viability. All of this must be done in the context of continuing to produce existing approved seasonal vaccines and the unknown timing of the next pandemic. In addition, and importantly, diverse definitions of universal vaccines have been developed by key stakeholders and researchers, including World Health Organization (WHO) [11,12]. The lack of a consensus goal or target product profile could result in a less efficient research and development enterprise. Moreover, the breadth of ongoing research makes it difficult for current and potential funders to monitor the landscape and identify the areas in need of greater investment. Progress would likely 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. Funders fora for other disease and vaccines have been convened in the past and were successful in providing similar functions [14,15]. The Global Funders Consortium for Universal Influenza Vaccine Development (Consortium) was initiated in this context in 2017.

2. Global Funders Consortium for Universal Influenza Vaccine Development concept

The Consortium was first convened in November 2017 with a goal to accelerate the development and availability of broadly protective and durable influenza vaccines, reducing the global burden and risk from seasonal and pandemic influenza. It provides a mechanism for open sharing of information about ongoing

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Table 1
Participating organizations in the Global Funders Consortium for Universal Influenza Vaccine Development meeting, November 2017.

Bill and Melinda Gates Foundation
Biomedical Advanced Research and Development Authority
Canadian Institutes of Health Research
Centers for Disease Control and Prevention
China CDC
Defense Advanced Research Projects Agency
European Commission
Food and Drug Administration
Human Vaccines Project
Inserm
National Institute of Allergy and Infectious Diseases
Open Philanthropy Project
Page Family Foundation
PATH
Sabin Institute
Task Force for Global Health (Secretariat)
Wellcome Trust
World Health Organization

investments, strategic plans, institutional perspectives and challenges, and relevant new data among organizations engaged in funding research and development related to universal influenza vaccines. A common landscape should make investments more efficient and informed and lead to avoiding funding overlaps. A common landscape will also identify critical challenges and knowledge gaps that threaten to delay progress in the field. These can then be prioritized for investment. With consensus priorities, the group can determine if targeted funding for a project or research area is desirable, and look for and prioritize opportunities for co-funding projects that align with member organizations' strategic plans. Finally, the voice of the Consortium can be used to raise awareness of the importance of the work and opportunities in the field to encourage additional funders to enter the field.

The Consortium's members include national government agencies with influenza research and development programs, philanthropic organizations whose mission included reducing epidemic and pandemic threats, and key stakeholder organizations that provide information and valuable perspectives to other members (Table 1). Member organizations have unique missions and mandates, some working towards transformational approaches that would result in truly universal influenza vaccines, and others focusing on incremental improvements in breadth and durability of immunity, recognizing the value of improved vaccine effectiveness on annual influenza burden. Even so, the Consortium agrees on a common target: to develop vaccines and vaccination strategies that will reduce severe influenza disease and deaths, whether caused by seasonal or pandemic influenza viruses, and be available before the next pandemic begins. This target implies the need for vaccines that confer broad protection so that a person can be protected from a drifted seasonal strain and novel or pandemic influenza if exposed, and more durable protection so that pandemic protection does not rely on a vaccine developed once a pandemic strain is detected. The target aligns with the recent preferred product characteristics articulated by Consortium members, including WHO [11,12,16]. It is also critical that the development of next-generation influenza vaccines must consider developing vaccine presentation and formulations that facilitate their use in low and middle-income countries.

3. Key gaps identified

A review of the landscape of ongoing and planned research related to universal vaccines identified substantial work underway related to development of candidate vaccines using a variety of approaches, and identified key scientific and resource gaps that may slow progress.

New rational design of universal vaccine approaches would benefit from improved understanding of 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. This includes a better understanding of the role of immunologic imprinting, innate and adaptive immunity, responses to natural infection and vaccination, and immune mechanisms and correlates of protection. This work will require developing new and standardized tools to study immune responses to vaccine and natural infection, especially for cell-mediated immune response. One approach to address this knowledge gap are large longitudinal cohorts which can be followed to assess immune responses over time while collecting data on infections and vaccine exposures and ensure appropriate samples are collected and shared.

Another priority identified was the creation of greater capacity and improved methods for conducting controlled human influenza virus challenge studies. Human challenge models represent a tool 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 and potentially provide a more efficient way to advance the most promising candidates, or down-select less promising approaches. Such studies are currently limited by study site capacity to enroll and follow subjects and by the number of available challenge virus strains. Greater use of human challenge study sites in the developmental pathway of candidates may be cost and time-saving, compared with large clinical trials, but will require clarity concerning their use by regulators in vaccine approvals.

Other tools identified that would support progress include 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. The greater use of artificial intelligence and machine learning will allow for improved modelling of influenza transmission, and better bioinformatics tools and capacity will be needed as more data are generated from the genetic and immune monitoring assays in future studies. Finally, reagents for the standardized assays, such as virus panels for evaluating breadth, challenge viruses for controlled human infection models, and tissue sampling tools will be needed both for clinical trials and for regulatory agencies.

Advances in the field will require substantial industry involvement. Market considerations may result in industry prioritizing incremental changes in vaccines that involve less technical risk. Industry may also 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 can help spread risk. Early stage investment (e.g. by programs at the National Institute for Allergy and Infectious Diseases (NIAID) and the European Commission) and late stage investment (e.g. the US' Biomedical Advanced Research and Development Authority) 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.

4. Ongoing work identified by consortium and progress:

The Consortium members and secretariat have undertaken work to focus on its initial priorities which include:

- Create a common landscape among funders and stakeholders,
- Develop a consensus "Roadmap" to guide and coordinate research and development, and be a tool for advocacy. Plans for such a roadmap are in development and is expected in 2019.

- Towards facilitating solutions to address critical knowledge gaps and challenges, NIAID has included in its work plan, support for establishing a prospective longitudinal cohort that will increase knowledge of human immunity to influenza [17].
- Increase human challenge study capacity and quality. A meeting was convened in London in 2018 and the participants are producing a plan to improve and standardize the methods for human challenge studies, create additional challenge strains and to increase global capacity for conducting these studies.
- Create and maintain a dashboard of vaccine candidates in clinical development that are underway. The dashboard is expected to be available by the end of 2018.
- Increase funding available for research and development. NIAID has released its plan for advancing universal vaccine development and their commitment to additional funding [17]. The European Commission has recently published a call for proposals in this area, together the India's Department of Biotechnology [18]. BMGF and the Page Family Foundation have announced funding for Grand Challenge grants that will grow funding for new innovative approaches to developing improved vaccines [16].
- The Consortium has developed a website (www.unifluvac.org) and regular newsletters that will provide updates on developments in the field and serve as a source of information on new funding available from members. The secretariat at the Task Force for Global Health will convene annual meetings of members and triennial calls for maintaining an accurate shared landscape and discuss opportunities for co-funding.

In summary, it is expected that the new Consortium of funders and stakeholders will have a significant positive impact and advance the field. 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, through increased advocacy form the members and from the secretariat, we expect that the Consortium can be a mechanism to increase funding into the field and articulate a consensus message with a recognized voice.

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