The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Preparing for the Next Influenza Pandemic: The Development of a Universal Influenza Vaccine

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Keywords. Influenza; Vaccine; Pandemic.

At the centenary of the 1918 influenza pandemic that took upward of 100 million lives within 1 year [1], the world remains unprepared to prevent a similar catastrophic event from occurring. In addition, seasonal epidemic influenza continues to cause worldwide disease and death on a yearly basis, and current vaccines offer suboptimal protective immunity. In this collection of articles [2–15], we review the scientific opportunities for developing influenza vaccines with broad coverage, commonly referred to as "universal" influenza vaccines, that would better protect us against the global burden of seasonal epidemics and offer the potential to protect us from a 1918-like pandemic event.

New vaccines are often derived by exploiting new technologies [16]. Seventy years ago, the ability to grow high titers of influenza virus in chicken eggs made the current inactivated influenza vaccine approach feasible. Although we have made major advances in understanding the virology, immunology, epidemiology, genetics and clinical consequences of influenza virus disease, current vaccines, updated annually to protect against anticipated seasonal virus strains, are at best 60% effective and often less so [17]. Antigenic drift resulting from mutations in critical proteins of the influenza virus allows the virus to evade the strain-specific immunity elicited by current vaccines. Moreover, over the past hundred years, antigenic shifts or major changes in influenza strains have resulted in pandemics, occurring in 1918, 1957, 1968, and 2009. Thus, influenza has proved itself time and again to be not only a pandemic threat, but a pandemic inevitability. Concurrently, modern forms and volume of travel have made it easier for viruses to spread rapidly around the globe [18]. Clearly, a better approach to influenza vaccination is needed.

During the last 10 years, newer technologies have emerged, stimulating scientists to answer old questions in new, more precise ways and to ask novel questions that could not previously be addressed [19]. Scientific advances that directly benefit vaccinology include monoclonal antibody isolation and identification, structural biology, protein engineering, and antigen delivery amenable to platform manufacturing approaches. Molecular- and atomic-level information about the immune-viral interface combined with new capacities for surveillance and rapid response to pandemics are shaping a new conceptual framework for vaccine development. As a result of these advances, high-level, broad, and durable immunity against the large universe of influenza viruses may now be within reach [20].

This issue of *The Journal of Infectious Diseases* was motivated by the confluence of the 1918 influenza pandemic centenary and the new opportunities afforded by technological advances and breakthroughs along with the improved understanding of influenza biology. We have gathered information, opinions, and ideas from thought leaders in immunology, virology, epidemiology, and vaccinology to address the challenge of developing a universal influenza vaccine and articulate some of the knowledge and technical gaps that remain.

In 1918, there were approximately 1.8 billion persons living on earth; today, there are more than 7 billion [21]. If a pandemic similar to that of 1918 occurred today, how would the devastation compare? Because of rapid international travel, the spread of a new virus would be faster than it was in 1918, when spread was largely related to the movement of troops at the end of World War I. Today, population density is higher and cities are larger, providing a more favorable environment for a rapidly spreading virus. Although we now have more sophisticated medical care, the availability of hospital beds and life support equipment would probably not be sufficient to manage an outbreak equivalent in magnitude to that of 1918.

If there were sentinel events as in 1918 and in 2009—a small spring epidemic preceding the fall pandemic—current vaccine manufacturing approaches would not be sufficiently fast or scalable for worldwide distribution to preempt pandemic spread. Therefore, development of a universal influenza vaccine that can reliably protect against drifted seasonal strains and pandemic strains without biannual reformulation is imperative. Ideally, this vaccine would not need to be given every year; however, even if annual vaccination was required but antigenic components needed updating only every 5–10 years, it would still be a significant advance over the current system.

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The Journal of Infectious Diseases® 2019;219(S1):S107–9

DOI: 10.1093/infdis/jiz043

There are some clear pathways to explore and knowledge gaps to fill in the immediate future using currently available technology, as described in the accompanying commentaries, outlined here:

1. By harnessing high-throughput sequencing and computational biology, more sophisticated algorithms based on sequence analysis, glycan patterns, and other features that may anticipate high transmissibility can be developed for predicting the next dominant strain[4]. The prudent study of gain-of-function mutations would allow scientists to learn more about what molecular signatures to look for.
2. Improving strain selection for seasonal vaccines would increase the likelihood of an antigenic match between the vaccine and dominant circulating strains and thereby improve the utility of current vaccine technology[2]. The current vaccines could be further improved by better standardization of the neuraminidase content, adjustment of antigen doses, addition of improved adjuvants, and production in cell substrates that minimize the likelihood of viral adaptations and changes in protein sequences[2].
3. Precisely defining the B-cell repertoire and epitope-specific phenotypes involved in the response to influenza infection and vaccination would provide insight into the problem of "original antigenic sin" described by Thomas Francis in 1960 and the related phenomenon of immunodominance[22]. Prior influenza immunity and poorly understood antigenicity patterns make it difficult to reshape and broaden the antibody response using current vaccines[7]. Defining all the ways antibody can bind and neutralize influenza structurally and establishing a new nomenclature for describing antigenic sites across both influenza A groups as well as influenza B would reduce confusion and improve communication between scientists[5]. In addition, learning which features of vaccine-induced local or systemic immune responses result in sustained serum antibody responses may inform vaccine formulation and delivery approaches.
4. Understanding more precisely the B-cell and antibody responses would allow the application of protein engineering for antigen design and display using molecular targets and antibody lineage end points to guide iterative design modifications[14].
5. The role of $CD4^+$ T cells in determining the efficacy of a B-cell response is an area of active investigation; however, more work in this area may be required to solve the problem of durability and maintenance of antibody responses[6].
6. The direct role of $CD4^+$ or $CD8^+$ T-cell effector functions and whether those cells require localization in mucosal tissue or lymph nodes to effectively protect against respiratory viral pathogens are poorly understood. Optimizing vaccine formulation and delivery route and modality is dependent on acquiring this type of knowledge[6].
7. Defining the importance of including specific antigenic targets, such as the head or stem domains of hemagglutinin, neuraminidase, or the M2 ectodomain in universal vaccines, and determining whether they are more effective when used in combination or alone could be accomplished through both vaccine protection and natural history studies that provide a better understanding of protective immunity [9–12].
8. Understanding the mechanistic correlates of immunity generated by immunization with live attenuated vaccines may reveal the importance of secretory immunoglobulin A and intraepithelial T cells that require induction of immunity to occur at the mucosal surface[13].
9. Defining both the virological and host immune response patterns associated with transmissibility would allow better modeling of population dynamics and factors that could best interrupt transmission cycles[8]. This could be particularly important for identifying distinct vaccination strategies for different target populations, including in societal settings in which transmission dynamics and target populations vary[15].
10. Using human challenge studies and improving animal models of influenza infection and transmission may help answer some of these questions[3]. However, the utility of animal models hinges on selecting those that are most relevant to human pathogenesis and immunity. Improving the characterization of and expanding the reagents for these models would not only benefit influenza vaccine development but would also provide answers to immunological questions relevant to other respiratory virus infections and emerging infectious diseases in general.

Recent estimates place the cost of influenza pandemics at upward of $500 billion per year [23]. In this context, an investment of at least $1 billion per year in the biomedical research effort to achieve a solution for protection against pandemic influenza seems justified. In addition, efforts to develop a universal influenza vaccine, even before reaching this goal, will likely lead to improved seasonal vaccines, with the potential to reduce morbidity rates and save tens of thousands of lives each year. Solving this problem is potentially achievable with today's technology, and with an organized and sustained focus on interventions for influenza and other potential emerging infectious threats, more advanced approaches could be rapidly developed.

Finally, gaps remain in our understanding of influenza biology and immunity and methods to produce highly effective vaccines. To close those gaps, it will be important to align the interests of all the stakeholders preparing for the next pandemic. Priorities of public health officials in lower-, middle-, and high-income countries, academic researchers, regulatory bodies, major funders, and pharmaceutical companies must be understood and collectively addressed to face the logistical

and scientific challenges ahead [24]. Thanks to scientific and technological breakthroughs of the past decade, vaccinology is experiencing a revolution. May we find the resolve, political will, and new business plans to take full advantage of these new opportunities and prepare ourselves before the next pandemic arrives.

Notes

Acknowledgments. We thank our colleagues at the National Institute of Allergy and Infectious Diseases Vaccine Research Center and Anthony Fauci, MD, for critical comments and discussions.

Financial support. This work was supported by intramural funding from the National Institute of Allergy and Infectious Diseases.

Potential conflicts of interest. J. R. M. and B. S. G. are listed as inventors on patents related to influenza vaccines, including E-094-2014 & E-060-2015 (B.S.G.), E-061-2016 (J.R.M.), E-066-2014 (both), and E-228–2016 (both). M. C. C. certifies no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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