Is a universal influenza vaccine feasible?

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***Abstract*:** The influenza virus causes significant human morbidity and mortality annually and poses a pandemic threat. In addition, the virus frequently mutates, contributing to thousands of identified strains. Current influenza vaccine solutions are strain specific, target existing strains, and achieve only approximately 40% vaccine effectiveness (VE). The need for broadly protective Universal Influenza Vaccines (UIVs) is clear. UIV research and development efforts focus on widely conserved (i.e. not strain specific) influenza epitopes. The most clinically advanced UIV candidate, the Multimeric-001 (M-001), is currently undergoing a pivotal, clinical efficacy, phase III trial. Completed clinical trials indicate M-001 is safe, well tolerated, and immunogenic to a broad range of influenza strains. Additional candidates are also under development, supported by public and private funding. Research results suggest that it is only a matter of time until a broadly protective influenza vaccine is approved for licensure.

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Introduction

Each year influenza (flu) viruses infect up to 20% of the global population,[1] causing severe illness in 3–5 million people and killing up to 650,000.[2,3] In the USA, flu and pneumonia are the eighth leading cause of death,[4] with influenza's costs to the national economy of over US $87 billion.[5] The flu virus mutates rapidly and unpredictably, contributing to potentially 144 different subtypes of influenza viruses and thousands of influenza strains. Consequently, each flu season features new flu strains that our immune systems have not previously encountered and therefore are not primed to fight. In addition to seasonal epidemics, a pandemic occurs when a shifted strain that is significantly different from previous seasonal strains emerges, causes illness, and is capable of human-to-human transmission. Infection with a pandemic strain usually results in relatively severe and widespread disease. Pandemics incur high human and financial costs. For example, the 1918 pandemic is estimated to have killed between 50 million and 100 million people. The most recent pandemic was the outbreak of A/H1N1 swine flu in 2009.

Seasonal flu

Seasonal flu is generally characterized by antigenic drift, slight mutations resulting in virus strains that are sufficiently different that a previous flu infection or vaccination does not provide sufficient protection, leading to illness and epidemics. Young children and older adults tend to be disproportionately affected in terms of severe morbidity and mortality. Indeed, approximately 90% of seasonal flu-related death occurs in the elderly. It is estimated that the annual cost of flu in the elderly in the US is $56 billion, out of the $87 billion total cost per year,[5] including hospitalization, mortality, and lost earnings.

Pandemic flu

Pandemic flu appears following antigenic shift. When and where pandemics emerge is unpredictable, although they have historically occurred approximately four times per century. A pandemic occurs when a new strain is capable of efficient human-to-human infection and exhibits high virulence due to the animal strain components being novel to the human immune system. In addition to the unfortunate human toll, the

potential economic costs of pandemics are massive and widespread, with reverberations impacting tourism, business, and regional and international trade.

Challenges with current flu vaccines

Many countries recommend that their citizens receive an annual seasonal flu vaccine, since the vaccine provides some protection against flu infection. However, according to the US Centers for Disease Control and Prevention (CDC), over the past 14 years, seasonal flu vaccine effectiveness (VE) averaged only about 40% in the general population.[6] In the elderly, the demographic most susceptible to flu-related illness and death, VE is as low as 9%.[7]

Currently approved influenza vaccines target specific viral proteins, in particular the surface protein hemagglutinin, of three or four specific strains. A possible reason for poor VE is the process by which flu vaccine strains are currently selected and produced: each year, World Health Organization (WHO) experts decide which existing flu strains to include in the following season's vaccine in the hope that it will match the circulating viruses.[8] All current influenza vaccine manufacturers base their vaccine on the WHO's recommendation, such that manufacturers produce essentially the same vaccine. Due to the long (4–6 months) production process, the WHO experts' decision must be made months in advance of flu season. And since the flu virus mutates constantly, rapidly, and unpredictably, the decision is not always correct, resulting in a mismatch between the vaccine strains and the circulating viruses.

Furthermore, most influenza vaccines are produced in eggs, and it has been noted that egg-based manufacturing techniques apparently lead to egg-based adaptations that result in a vaccine strain that is different from the selected wildtype virus strain, thus also contributing to low VE.[9]

A common denominator to influenza strains

To design a broadly protective flu vaccine, one should target the conserved, common regions in the virus. Indeed, there are influenza virus peptides (epitopes) that are widely conserved. Furthermore, the human immune system is conditioned to target these short peptide sequences. Various vaccination studies have demonstrated cumulative evidence supporting employment of synthetic peptides as a means to successfully increase immunity against influenza infection.[10–12] For example, integration of several conserved, linear T and B-cell epitopes common to the vast majority of influenza strains is predicted to directly elicit cellular immunity that will further lead to elevated humoral response, resulting in enhanced protection. Viruses replicate only within host cells and therefore, activation of cell-mediated immunity is essential in limiting viral shedding and illness duration. Studies have revealed more robust immune responses by mice immunized with both B- and T-cell epitopes than by mice immunized with either B- or T-cell epitopes.[13]

An influenza vaccine that provides broad protection against most influenza strains is popularly referred to as a Universal Influenza Vaccine (UIV). Since a UIV formulation does not change, it can be stockpiled by healthcare authorities for proactive epidemic and pandemic preparedness. In addition, a UIV could be produced and administered year-round, thereby breaking the current linkage of flu season to flu vaccination campaigns; vaccinations could be administered year-round, rather than prior to flu season or sometime after a pandemic outbreak.

Current UIV approaches

There are a number of UIV candidates at various development stages, ranging from concept to preclinical to human clinical trials. The most clinically advanced UIV candidate is the Multimeric-001 (M-001), which entered a pivotal, clinical efficacy, phase III trial in Europe in 2018 (ClinicalTrials.gov identifier: NCT03450915). In contrast to currently licensed seasonal influenza vaccines, which induce predominantly humoral immunity, M-001 is designed to directly activate cellular immunity and indirectly enhance humoral immunity. Indeed, when used ahead of a hemagglutinin (HA)-based influenza vaccine, M-001 enhances and broadens the immunity offered by the HA-based vaccine.[14,15]

M-001 is a recombinant 45 kDa protein produced in *Escherichia coli*. The M-001 vaccine consists of three repetitions of nine linear, conserved influenza A and B epitopes to form a single recombinant protein. The epitopes were derived from the M1 matrix

protein [B and cytotoxic T lymphocyte (CTL) epitopes of both influenza type A and type B strains, Victoria and Yamagata lineages], from the nucleoprotein (two CTL and one Th epitope), and from conserved regions of the hemagglutinin (B and Th epitope), which have all demonstrated induction of cellular immunity.

Following evidence of cross-strain efficacy in animal models,[16–18] M-001 progressed to human clinical trials beginning in 2009. Prior to the ongoing pivotal, clinical efficacy phase III trial, M-001 demonstrated safety and immunogenicity in 698 participants in six completed phase I/II and Phase II clinical trials.[15,17,19] Since there is no correlate of protection for new cell-mediated immunity (CMI)-based vaccines such as M-001, a clinical efficacy trial is required by the authorities to show the protection conferred by the vaccine in appropriate populations.[20] In view of this requirement, in August 2018 BiondVax Pharmaceuticals Ltd., the developer of M-001, initiated a pivotal, clinical efficacy phase III trial titled 'A pivotal, multicenter, randomized, modified double-blind, placebo-controlled phase III trial to assess the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (⩾50 years of age)'. The trial (ClinicalTrials.gov identifier: NCT03450915) aims to assess the safety of M-001 and its capacity to protect against influenza infection by measuring reduction in influenza illness incidence (as a primary endpoint) and in influenza illness severity (as a secondary endpoint).

The pivotal, clinical efficacy phase III trial design calls for approximately 12,000 participants, aged ⩾50 years old, at least half of whom are ⩾65 years old, to receive either M-001 or placebo. Over 4000 participants were enrolled prior to the Northern Hemisphere 2018/2019 flu season, and approximately 8000 are being recruited prior to the 2019/2020 flu season. The proportion of confirmed influenza cases in both groups will be evaluated to assess efficacy of M-001 as an unadjuvanted standalone UIV.

While M-001 is the only UIV currently in phase III trials, there are other candidates in earlier stage clinical and preclinical studies that are also designed to provide broadened protection. Among those in phase II trials are MVA-NP+M1, an adenovirus vector expressing Influenza A conserved NP and M1 proteins (ClinicalTrials.gov identifier: NCT03880474),[21] and Flu-V, an adjuvanted formulation of four conserved T-cell peptides targeting T cell responses to NP, M1 and M2 (ClinicalTrials.gov identifier: NCT02962908).[22] Candidates currently in phase I trials include the OXV836, a recombinant poly-arginine NP (H1 strain) in VLP and produced in *E. coli* (ClinicalTrials.gov identifier: NCT03594890); and the H1ssF_3928, an H1 HA stem and ferritin nanoparticle (ClinicalTrials.gov identifier: NCT03814720).[23,24] A number of groups are exploring conserved HA, NA, and M2 domains in preclinical studies.[25]

While currently applicable to strain-specific vaccine candidates, an additional promising approach for improved influenza vaccines is the use of nucleic acid therapeutics, in which gene mRNAs lead to production of its respective protein. Development of this approach was delayed, apparently due to concerns associated with mRNA instability, high innate immunogenicity, and inefficient *in vivo* delivery. These obstacles were recently resolved by stabilizing the mRNA and formulating it into carrier molecules for efficient delivery. mRNA is apparently safe, as it is the minimal genetic vector, and therefore anti-vector immunity is avoided, and mRNA vaccines can be repeatedly administered. mRNA vaccines have the potential for rapid, inexpensive, and scalable manufacturing, owing mainly to the high yields of *in vitro* transcription reactions.[26] Indeed, phase I trials were conducted to confirm the safety and immunogenicity of H10N8 or H7N9 strain-specific pandemic influenza antigen mRNA in healthy adults.[27] The trials showed that the mRNA vaccines induced hemagglutination-inhibiting (HAI) and neutralizing antibodies and were well tolerated. Further research and development aim to use this approach also to design a UIV. One such development is self-amplifying mRNA (SAM technology) encoding M1 and NP of influenza that elicited both B and T cell responses in preclinical models.[28]

While this paper concerns the potential for broadly protective influenza vaccines, there are parallel efforts to improve upon current strain-specific influenza vaccines through improved production processes and delivery methods. Strain-specific vaccines featuring faster production

processes as compared with egg-based manufacturing techniques include Flublok, a recombinant protein, and Flucelvax, which is manufactured in animal cells. Other candidates are in development. In additional to faster production time, these vaccines potentially offer more scalable production and avoid egg-based adaptions. While most currently marketed flu vaccines are injected intramuscularly, FluMist is delivered intranasally. Other alternative delivery methods, including oral, are under development. (Note that Flublok, Flucelvax, and Flumist are trademarked names).

Challenges in universal flu vaccine development

Currently available HA-based strain-specific vaccines use HAI as a correlate of protection. It is likely that UIVs will not be HA-based, and consequently a new correlate of protection will be required. Further, since the mechanism of action of each UIV candidate will likely differ, each candidate will require its own correlate of protection. Alternatively, large clinical efficacy trials may be required to achieve regulatory and marketing approval. In such a trial, the statistical power relies on sufficient flu attack rates, and the need for a large sample size may pose a significant barrier to UIV developers.

An additional challenge is to show that a UIV will protect against strains that do not yet exist. As M-001 consists of broadly conserved influenza A and B epitopes, it is postulated that these particular epitopes are inherent to influenza viruses, and therefore will be conserved in any new viable drifted (seasonal) or shifted (pandemic) influenza strains. Indeed, sera of participants from a trial conducted in 2011 contained HAI antibodies to another strain that only appeared a few years later (A/Switzerland/9715293/2013). These data indicate that M-001 can provide broadened enhanced immunity extending even to influenza strains destined to circulate in the future.[29]

Other factors to be considered in developing a UIV include determining the required VE strength. A UIV that achieves a specific VE against all strains is clearly superior to current strain specific vaccines with the same VE. Furthermore, while current flu vaccines provide coverage for one flu season, a UIV should ideally provide longer coverage. Based on preclinical studies, M-001 is expected to protect for 3–5 years.

Support for UIV development

Further indication of the feasibility of a UIV is suggested from the broad and increasing support for the development of a UIV among governments and nongovernmental organizations. For example, in 2018 the Bill and Melinda Gates Foundation offered US$12 million 'aimed at stimulating research' into UIVs.[30] In 2019, the *Flu Vaccine Act* (*S.2438*/*H.R.5092*) bill, which calls for US$1billion over 5 years to support the development of a UIV was introduced in the US Senate.[31,32] Also in 2019, The Sabin-Aspen Vaccine Science and Policy Group published a thorough report that 'explores challenges and opportunities to develop a universal influenza vaccine'.[33] The general consensus is that development of a UIV, while challenging, is certainly worthwhile and ultimately achievable.

In 2018, the National Institute of Allergy and Infectious Diseases (NIAID) published a strategic plan for development of a UIV, noting that 'one of its highest priorities (is) the development of a universal influenza vaccine that would provide long-lasting protection against multiple strains of the virus, including strains with the potential to cause a pandemic'.[34] The same year, NIAID began a phase II clinical trial of M-001.[35] Behind the ongoing M-001 pivotal, clinical efficacy, phase III trial, public and private funding and research are lining up to develop a universal flu vaccine. Research results strongly suggest that it is only a matter of time until a broadly protective influenza vaccine is approved.

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The authors are employees of BiondVax Pharmaceuticals Ltd. JEP is Head of Business Development. RB is CEO, President, and a member of the Board of Directors. TBY is Chief Scientific Officer (CSO). RB, TBY, and JEP may also hold BiondVax shares and stock options.

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