ACS Infectious Diseases

Viewpoint

pubs.acs.org/journal/aidcbc

Universal Influenza Vaccines: To Dream the Possible Dream?

Jae-Keun Park and Jeffery K. Taubenberger*

Viral Pathogenesis Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, United States

ABSTRACT: Influenza viruses are a significant public health threat, causing both annually circulating epidemics and unpredictable pandemics. Vaccination is the best means of control against individual cases of influenza and also for decreasing epidemic spread in the population. However, rapid influenza virus evolution requires continual reformulation of vaccines for annual influenza epidemics, and because pandemics cannot be accurately predicted, no current vaccine strategy can induce broad protection against all subtypes of influenza viruses. Recent work has suggested that such broadly protective, or "universal", influenza virus vaccines might be achievable using vaccine strategies that target conserved B- and T-cell epitopes.

Influenza can be considered a "continuously" emerging infectious disease, and these diverse and rapidly evolving viruses are a significant public health threat. Around the world, many millions of influenza infections occur annually, mainly in the form of seasonal epidemics resulting in millions of severe infections and up to 500,000 deaths.[1] The unpredictable introduction of antigenically novel influenza viruses from animals can lead to the development of pandemics with even larger public health impacts. For example, the 1918 influenza pandemic resulted in ~50 millions deaths globally.

Influenza A viruses (IAV) are enveloped, negative sense, single-stranded RNA viruses with segmented genomes. IAV infect humans and also large numbers of animal hosts, including many bird and mammal species.[2] IAV are subtyped by antigenic characterization of the surface hemagglutinin (HA) and neuraminidase (NA) glycoproteins. Sixteen HA and nine NA subtypes are consistently found in avian hosts in various combinations, for example, H1N1 or H3N2, and this pool is the source of human pandemic viruses. IAV genome segmentation allows for viral reassortment following mixed infection, and novel subtypes can be generated (antigenic shift). IAV also have high mutation rates, and mutations that alter antigenic portions of HA and NA proteins allow strains to evade pre-existing immunity (antigenic drift). Seasonal influenza viruses rapidly acquire antigenic drift mutations. Future pandemics cannot yet be predicted, but human infections with avian H5N1, H7N9, and other subtypes have caused concern.[3]

Vaccination remains the best approach to control influenza. Current annual inactivated and live attenuated vaccines are intended to protect against circulating strains, but require a close antigenic match with circulating strains.[4] The key to the current vaccination strategy is selection of specific vaccine strains annually. Since 1973, WHO has made recommendations on vaccine stains each year based on which influenza viruses are circulating in the human population and how well current vaccine components protect against newly circulating viruses. Although this process has been effective and has contributed significantly to global influenza control, surveillance and strain prediction sometimes lag behind rapid viral evolution and antigenic drift, which may limit the protective efficacy of the vaccine, especially in at-risk populations. Moreover, occasional spillover infections from animal hosts to humans, and the potential of these zoonotic infections to lead to the development of a new influenza pandemic, are much harder to predict given our current state of knowledge. These two features of influenza—rapid evolution/antigenic drift and zoonotic infections that can lead to pandemics—necessitate a critical need for a new generation of vaccines that would protect against all influenza viruses, a so-called "universal" vaccine.

The term "universal" vaccine may be used to describe an influenza vaccine with broader protective efficacy than the typical strain-matched vaccines currently in use, such that vaccinees may be protected against a range of antigenically drifted seasonal influenza viruses or, alternatively, a vaccine with protective efficacy against potentially pandemic viruses with novel HA and/or NA subtypes or both.[5] Most recent approaches have focused on developing a prepandemic vaccine.[6,7]

Because influenza A viruses are very diverse genetically and antigenically, there are only a few highly conserved epitopes shared among influenza viruses.[2] Most of the strategies for developing a universal influenza vaccine have sought to develop protective immunity to these highly conserved "universal" epitopes. By inducing protective immune responses to these conserved epitopes, the primed immune system could in theory effectively abrogate infection or clinical disease even after encountering novel and unpredicted influenza virus strains. A small number of highly conserved regions found in various influenza viruses have been reported, and strategies for producing a broadly protective influenza vaccine have gained new traction in the past few years, including vaccines inducing antibodies against conserved epitopes in the HA, NA, or other viral proteins and vaccines that promote enhanced protective T-cell responses.[8,9]

The stalk region of the influenza HA protein, which is critical for fusion between the viral membrane and host cell endosomal membrane, is much more highly conserved than the globular head region of the HA protein, and as such there has been

Received: December 9, 2015
Published: December 18, 2015

DOI: 10.1021/acsinfecdis.5b00146
ACS Infect. Dis. 2016, 2, 5−7

renewed interest that the HA stalk could be an ideal target for a universal influenza vaccine.[5] However, because the HA head region is immunodominant, stalk antibodies are generally insufficiently induced after infection or standard vaccinations. Several strategies are being pursued to induce high levels of antibodies to the HA stalk region, including the engineering of stalk-only HA antigens[10] and a sequential immunization strategy with chimeric HAs containing the same stalk domains but different HA head domains.[5] Antibodies generated against the HA stalk confer protection by preventing membrane fusion and thus neutralizing viral infection. It is also thought that antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) may also play significant roles in broad protection.

Although not as conserved as HA stalk, the NA protein, the other major surface glycoprotein of influenza viruses, is likely a good target to broaden the protective efficacy of influenza vaccines.[11] Furthermore, NA is subjected to less antigenic drift in seasonal virus strains than HA. NA functions to cleave host cell sialic acids facilitating the release of newly formed virions from the infected cell.[5] The enzymatic active site itself is highly conserved even among different NA subtypes, making it an attractive target for universal influenza vaccination. Immunization with NA antigens has been shown to decrease influenza symptoms and virus shedding. The protective mechanisms of anti-NA antibodies include reductions in virus release, along with ADCC, ADCP, and CDC. Supplementation of vaccines with NA antigens broadened the protective efficacy of inactivated vaccines. However, currently available influenza vaccines are standardized only by HA content, resulting in variable amounts of immunogenic NA in vaccine formulations. Inclusion of standardized and immunogenic amounts of NA to current vaccine formulations would be expected to broaden current vaccines.

M2 is a transmembrane ion channel required for uncoating the virus after entry into the host cell.[5] The small M2 ectodomain (M2e) protrudes from the viral surface and is conserved, especially among human influenza A viruses. Anti-M2e antibodies, although not neutralizing, could increase the protective efficacy of vaccines. Vaccines inducing anti-M2e antibodies could induce ADCC, ADCP, and CDC because infected host cells express abundant quantities of viral M2e.

Whereas vaccines targeting the HA stalk, NA, and M2e have been generally designed to induce broadly reactive antibodies that would confer protection, it has been demonstrated that vaccines inducing T-cell responses might also be good candidates for a universal vaccine. Vaccines stimulating T-cell immunity could have advantages over antibody-based vaccines because T-cells recognize linear epitopes presented by host MHC molecules, and many of conserved peptides from influenza proteins could be targeted (e.g., conserved regions of HA, nucleoprotein (NP), and matrix1 (M1) proteins).

Although much more research is needed to evaluate different universal vaccine strategies in experimental systems, a number of specific research questions will need to be addressed to advance this research, whichever vaccine candidates emerge for clinical use.

Improving immunoassays: Reliable immunoassay following vaccination is essential to assess the performance of vaccines. For example, hemagglutination inhibition (HI) assays have long been the gold standard to demonstrate influenza vaccine efficacy. However, different universal vaccine candidates have different correlates of protection that have not yet been fully characterized. Developing reliable and standardized immunoassays showing clear correlates of protection is critical for universal vaccine development and further assessment of its performance in clinical trials.

Evaluation of "universal" protection in people: What is the most likely achievable goal for new-generation influenza vaccines in people? Would it be to expand the protective efficacy and breadth of protection against antigenically drifting seasonal viruses, or is the major public health goal to develop an effective prepandemic vaccine, or both? Experimental animal model systems can be used to evaluate universal vaccine efficacy against a wide variety of challenge viruses, including past pandemic viruses, pathogenic avian viruses, and other influenza strains that could not be evaluated ethically in clinical trials. In people, experimental vaccines could be evaluated by immunologic responses, in volunteer challenge studies using circulating seasonal viruses[12] and eventually in prospective field studies, possibly including regions with ongoing influenza epizootics (e.g., areas with avian H5N1 or H7N9 circulation).

Increasing immune responses in the elderly, infants, and immune-compromised: Whether a universal vaccine is used to broaden protection against seasonal influenza or for prepandemic protection, inducing adequate protective immune responses in the elderly, infants, and other immune-compromised populations is also an important consideration.[4] Current influenza vaccine efficacy in these individuals is known to be inferior to that in healthy young adults, and efforts to enhance vaccine efficacy in the elderly especially is a crucial public health goal.

Achieving longevity of immune responses: Administration of broadly protective vaccines may remove the need for annual updating of influenza vaccine formulations. It is not known, however, whether any proposed universal vaccine strategy would induce long-term protective efficacy following immunization in people, whether exposure to different influenza viruses by natural infection or vaccination prior to receiving a universal vaccine would enhance or inhibit development of broadly protective immunity, and how long immune protection would last without boosting.

Possible emergence of vaccine escape mutants: Even after successful introduction of universal influenza vaccines to humans, there is another critical point that will need to be addressed. It is possible that highly conserved viral epitopes may subsequently be targets of antigenic drift pressure different from that seen in natural infections or current vaccination strategies and that even broadly protective "universal" vaccines might need to be updated to keep pace with viral evolution.

Despite the above caveats and uncertainties, development of new generations of influenza vaccines that would offer broader protection than specifically strain-matched vaccines would be greatly beneficial. New insights into influenza virus biology and host immune responses, coupled with new technologies, have opened an exciting new chapter in our long quest to prevent and/or mitigate the significant public health consequences of influenza epidemics and pandemics.

AUTHOR INFORMATION

Corresponding Author

*(J.K.T.) E-mail: taubenbergerj@niaid.nih.gov.

DOI: 10.1021/acsinfecdis.5b00146
ACS Infect. Dis. 2016, 2, 5−7

Funding

This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) WHO. Influenza (seasonal); http://www.who.int/mediacentre/factsheets/fs211/en/ (accessed Feb 19, 2015).

(2) Taubenberger, J. K., and Kash, J. C. (2010) Influenza virus evolution, host adaptation, and pandemic formation. *Cell Host Microbe* 7 (6), 440−451.

(3) Morens, D. M., Taubenberger, J. K., and Fauci, A. S. (2013) Pandemic influenza viruses − hoping for the road not taken. *N. Engl. J. Med. 368*, 2345.

(4) Osterholm, M. T., Kelley, N. S., Sommer, A., and Belongia, E. A. (2012) Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect. Dis. 12* (1), 36−44.

(5) Krammer, F., Palese, P., and Steel, J. (2014) Advances in universal influenza virus vaccine design and antibody mediated therapies based on conserved regions of the hemagglutinin. *Curr. Top. Microbiol. Immunol. 386*, 301−321.

(6) Schultz-Cherry, S., Is it possible? A different approach to creating a universal influenza vaccine. *mBio* 2015, *6* (5), e01580-1510.1128/mBio.01580-15

(7) Schwartzman, L. M., Cathcart, A. L., Pujanauski, L. M., Qi, L., Kash, J. C., and Taubenberger, J. K. (2015) An Intranasal virus-like particle vaccine broadly protects mice from multiple subtypes of influenza A virus. *mBio 6* (4), e01044.

(8) Lee, Y. T., Kim, K. H., Ko, E. J., Lee, Y. N., Kim, M. C., Kwon, Y. M., Tang, Y., Cho, M. K., Lee, Y. J., and Kang, S. M. (2014) New vaccines against influenza virus. *Clin. Exp. Vaccine Res. 3* (1), 12−28.

(9) Quinones-Parra, S., Loh, L., Brown, L. E., Kedzierska, K., and Valkenburg, S. A. (2014) Universal immunity to influenza must outwit immune evasion. *Front. Microbiol. 5*, 285.

(10) Impagliazzo, A., Milder, F., Kuipers, H., Wagner, M. V., Zhu, X., Hoffman, R. M., van Meersbergen, R., Huizingh, J., Wanningen, P., Verspuij, J., de Man, M., Ding, Z., Apetri, A., Kukrer, B., Sneekes-Vriese, E., Tomkiewicz, D., Laursen, N. S., Lee, P. S., Zakrzewska, A., Dekking, L., Tolboom, J., Tettero, L., van Meerten, S., Yu, W., Koudstaal, W., Goudsmit, J., Ward, A. B., Meijberg, W., Wilson, I. A., and Radosevic, K. (2015) A stable trimeric influenza hemagglutinin stem as a broadly protective immunogen. *Science 349* (6254), 1301−1306.

(11) Easterbrook, J. D., Schwartzman, L. M., Gao, J., Kash, J. C., Morens, D. M., Couzens, L., Wan, H., Eichelberger, M. C., and Taubenberger, J. K. (2012) Protection against a lethal H5N1 influenza challenge by intranasal immunization with virus-like particles containing 2009 pandemic H1N1 neuraminidase in mice. *Virology 432* (1), 39−44.

(12) Memoli, M. J., Czajkowski, L., Reed, S., Athota, R., Bristol, T., Proudfoot, K., Fargis, S., Stein, M., Dunfee, R. L., Shaw, P. A., Davey, R. T., and Taubenberger, J. K. (2015) Validation of the wild-type influenza A human challenge model H1N1pdMIST: an A(H1N1)-pdm09 dose-finding investigational new drug study. *Clin. Infect. Dis. 60* (5), 693−702.

DOI: 10.1021/acsinfecdis.5b00146
ACS Infect. Dis. 2016, 2, 5−7