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Considerations for Future Vaccine Development

Influenza Virus: Dealing with a Drifting and Shifting Pathogen

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Abstract

Numerous modern technological and scientific advances have changed the vaccine industry. However, nearly 70 years of influenza vaccine usage have passed without substantial changes in the underlying principles of the vaccine. The challenge of vaccinating against influenza lies in the constantly changing nature of the virus itself. Influenza viruses undergo antigenic evolution through antigenic drift and shift in their surface glycoproteins. This has forced frequent updates of vaccine antigens to ensure that the somewhat narrowly focused vaccine-induced immune responses defend against circulating strains. Few vaccine production systems have been developed that can entertain such constant changes. Although influenza virus infection induces long-lived immunologic memory to the same or similar strains, most people do not encounter the same strain repeatedly in their lifespan, suggesting that enhancement of natural immunity is required to improve influenza vaccines. It is clear that transformative change of influenza vaccines requires a rethink of how we immunize. In this study, we review the problems associated with the changing nature of the virus, and highlight some of the approaches being employed to improve influenza vaccines.

Keywords: influenza virus, antigenic drift, antigenic shift, vaccine

Introduction

Influenza virus produces a conundrum when it comes to successful vaccination. From a purely immunologic standpoint, it is clear what form of immunity has the most protective ability, which is antibody to the globular head of the viral surface protein hemagglutinin (HA). While other forms of immunity, both humoral and cellular, have been shown to be protective, the HA head-specific antibodies interfere with the attachment of viruses to their cellular surface receptors and are solely capable of neutralizing infection (11,16,20–22,45,51,91,92,102).

Current influenza vaccine production is based on this understanding, and vaccines are routinely designed to elicit protective neutralizing antibody responses. The flipside of this conundrum is that the HA globular head is the most variable part of the virus. As such, the virus can evolve to evade immunity generated by prior vaccination, and the targeting of HA using conventional approaches provides little hope for substantive improvements in how we vaccinate. Unfortunately, this flipside has proved to be a formidable obstacle to overcome. The inactivated influenza vaccines that are the mainstay of our current influenza vaccination programs generate a relatively narrow immune response that is short-lived. Instead of driving different vaccination approaches, the obstacle of antigen diversity has historically driven the development of a truly remarkable system of global virus tracking and annual vaccine reformulations to ensure vaccine/virus matching.

Both influenza A and B viruses, two genera of the *Orthomyxoviridae* family, are causes of substantial morbidity and mortality in humans and are targets for our current influenza vaccines. Two subtypes, classified based on the antigenic properties of their surface glycoproteins HA and neuraminidase (NA), of influenza A viruses currently circulate in humans, A(H1N1) and A(H3N2). While influenza B viruses are not further categorized into subtypes, two genetically and antigenically distinct lineages of virus, B/Victoria/2/87-like and B/Yamagata/16/88-like viruses, are also found in humans (81). The World Health Organization (WHO)-led tracking system traces the evolution of these viruses through epidemic seasons and selects the most appropriate virus antigens to be included in the seasonal influenza vaccine.

Concomitant with the development of the WHO tracking system has been the development of a regulatory framework that allows for antigen changes within the context of an approved vaccine process. So instead of overcoming the problem of antigenic change of the target virus by clever antigen and/or vaccine design, our most successful approach to date has been to develop a system that can rapidly

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respond to the virus change itself. It is, however, clear that this approach, while remarkable and a poster child for a global surveillance program, is not optimal and the search for better target antigen(s) and/or ways to deliver them is a priority. Fueled, in part, by improvements in analysis of single B cells and the spread of programs to estimate seasonal vaccine effectiveness, there has been a resurgence in the drive to improve influenza vaccines. A number of novel approaches are in various stages of preclinical and clinical development, offering hope that improvements could be on the way. There is little consensus, however, on what direction the field should take to offer the most improvements and this is reflected in the multiple strategies being employed. While none of these approaches appears to fulfill all requirements for an optimal influenza vaccine, the combined experiences and knowledge gained will be invaluable. In this review, we focus on the problem facing influenza vaccines and highlight some improvement strategies being explored.

The Problem, a Constantly Moving Target

The influenza virus is the classic example of a constantly evolving pathogen and its ability to evade the most potent immunity allows it to be a continual threat to its hosts, and to survive in populations with considerable prior exposure. The virus has two major mechanisms for antigenic change, antigenic drift, and antigenic shift. While both mechanisms have evolved to evade natural immunity, they also interfere with successful vaccination.

Antigenic drift is the process by which minor changes are introduced into key viral epitopes through point mutations in the viral genome (5). Frequent mutations are introduced into the influenza virus genome during the replication cycle due to the lack of proofreading mechanisms associated with the virally encoded RNA-dependent RNA polymerase (88). While many of the mutations lead to nonviable progeny or make minor changes to proteins or genes, some occur in antigenic regions of the HA and/or NA glycoproteins (27,50,93). When epitope-altering mutations occur, viruses containing them are rapidly selected by host immunity driving antigenic drift (99). Although there is no reason to suggest that the inherent mutation rates are different across viral RNA segments, the highest rate of drift appears in antigenic regions, because viruses with antigenic changes preferentially escape preexisting immunity (8,103).

A hallmark of influenza virus antigenic drift in humans is the replacement of older viruses by new drifted variants, although at rates dependent on subtype: antigenically variant populations have been shown to co-circulate for longer periods in A(H1N1) and influenza B viruses (24), whereas turnover is more rapid with A(H3N2) viruses (26). This succession of strains is what makes current vaccination strategies feasible, that is, diversity is limited at any given time. The challenge is of course for the WHO tracking system to correctly predict or detect the emerging lineages at an early stage. Due to the 6 or more months required to prepare a vaccine, the possibility exists that by the time a vaccine is manufactured to support a global campaign, it is no longer matched with circulating viruses (13). Any vaccination approach that targets the classic neutralizing responses to HA and/or NA must deal with antigenic drift effectively. It is also possible that novel vaccines that increase the potency of immunity to other viral proteins may lead to more rapid antigenic evolution.

The second form of antigenic change that influenza viruses have at their disposal is antigenic shift. Rather than the gradual changes seen with antigenic drift, antigenic shift results in a complete exchange of HA and/or NA genes (100). Antigenic shift only occurs among influenza A viruses due to their extensive animal reservoirs, the sources of antigenically distinct viruses (12). Influenza B viruses do not have a recognized animal reservoir [although there have been reports of virus presence in seals and horses (46,75)] and hence do not undergo antigenic shift (72). In humans, the result of antigenic shift is an influenza virus to which the population has limited immunity, leading to increased transmission, and a pandemic. To avoid pandemics, public health entities react with vigor to detections of novel subtypes, such as A(H5N1) and A(H7N9), in humans (112). As population immunity builds to a pandemic virus, the overall disease burden reduces and seasonality returns. The viruses present in humans today are all descended from prior pandemic strains that have evolved through drift in humans (90).

Pandemics have emerged infrequently, but repeatedly over the past 100 years. The emergence of the 1918 A(H1N1) pandemic virus occurred as a consequence of the transmission of an avian virus to humans (70). The 1957 A(H2N2) pandemic virus was derived from a descendent of the 1918 A(H1N1) virus that had acquired the HA, NA, and polymerase basic protein 1 (PB1) gene segments from an avian virus source (48). The 1968 A(H3N2) pandemic virus was similarly derived from an A(H2N2) virus that had acquired HA and PB1 genes from an avian virus (23). An A(H1N1) virus similar to viruses that had circulated in humans in the mid-1950s reemerged in 1977 (67). The 2009 A(H1N1) pandemic virus contained segments from avian, human, and swine viruses that had all been circulating in swine populations before virus emergence in humans (32,40). At present, descendants of the 1968 A(H3N2), 2009 A(H1N1), and influenza B viruses circulate in humans and all cause substantial morbidity and mortality; any successful vaccination approach must protect, at minimum, from these. To target a pandemic, new vaccines require months of production. An ideal seasonal influenza vaccine would induce immunity to seasonal strains as well as provide some immunity to pandemic viruses, but the diversity of viruses in animal reservoirs (Fig. 1) makes this an incredibly difficult proposition.

The capacity for antigenic shift is a consequence of the segmented nature of the influenza virus genome. Upon coinfection of a single cell, gene segment exchange can occur between viruses (7,37). Although each functional virus must have a copy of each segment, 254 theoretical combinations of the eight gene segments are possible from a dual infection (56). In practice, not all combinations are seen and other factors limit the extent of viruses generated; these factors are poorly understood and the outcomes of mixed infections are unpredictable (57,97). Nevertheless, some patterns of reassortment have been identified, such as the associations of various matrix 2 (M2), HA, polymerase acidic protein (PA), and PB2 gene segments and/or proteins in avian viruses (15). Influenza B viruses also undergo reassortment in humans and can be accompanied by deletions and insertions (61,62). Reassortment between influenza virus genera

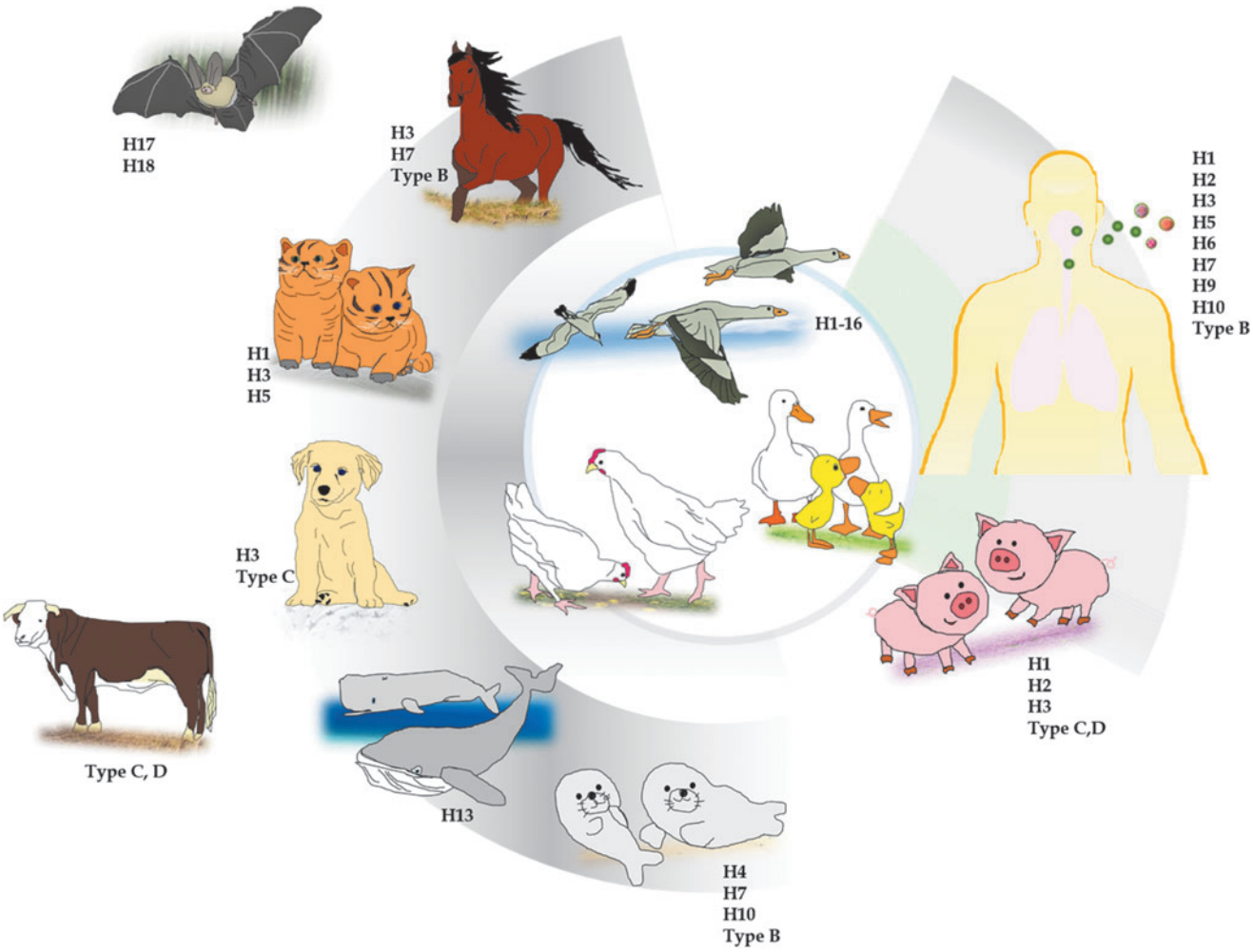

FIG. 1. Influenza viruses in different hosts. There are four genera of influenza viruses: A, B, C, and D, each with a distinctive host range as shown. Influenza A viruses are zoonotic pathogens that have a wide host range, which includes humans and other mammalian species. However, avian species are the primary hosts of influenza A viruses; currently, 18 HA and 11 NA subtypes are known, with most maintained in wild aquatic bird populations with sporadic transmission to other hosts. HA, hemagglutinin; NA, neuraminidase.

(i.e., between influenza A, B, C, and D) does not occur (33,60,66). However, reassortment between chimeric influenza A and B virus gene segments has been successful and it has shown that some of the incompatibility depends on terminal packaging and other noncoding regions (28,38).

Not only is reassortment important for the evolution of influenza viruses but is also harnessed for the current process of influenza vaccine manufacture. The influenza A seed viruses used to produce antigen for inactivated and live attenuated influenza vaccines are not the wild-type viruses themselves, but rather reassortant viruses containing the HA and NA gene segments for the target strain and the majority of remaining segments from a master strain generated to enhance yield and safety. The influenza B antigens in inactivated vaccines are variably derived from wild-type or reassortant viruses produced using a similar approach. Since the late 1990s, it has been possible to generate reassortant influenza viruses from cloned complementary DNA (cDNA) copies of the viral genomes by plasmid-based reverse genetics (29,69). The methods have taken some of the uncertainty away from the reassortment process and they are routinely used in the preparation of seed viruses for live attenuated seasonal vaccines and inactivated vaccines against zoonotic viruses. Importantly, the reverse genetics systems also allow for directed mutagenesis of the viral genome. As the amount and speed of vaccine manufacture are directly related to the yields and growth kinetics of the seed viruses, attempts have been made to improve vaccine yield by introductions of mutations into the master virus (10,49,101). The current WHO-led system provides a relatively uniform set of seed viruses to manufacturers of inactivated vaccines. As mutations and/or genetic regions are identified, which increase desirable properties of these seed viruses, proprietary master strains may become more of the norm than the exception. Improving the yields of conventional and live attenuated seed viruses must remain a high priority and while not necessarily improving the breadth of immunity, such activities increase the speed with which manufacturers can respond to a changing virus.

Considerations for Improvements to the Current System

Currently available commercial influenza vaccines can be categorized into three groups:inactivated influenza vaccines, recombinant influenza vaccines, and live attenuated influenza vaccines. As the name suggests, the latter vaccines are replication-competent viruses attenuated in their ability to cause disease. The former two vaccines are administered by the intramuscular route and the live attenuated vaccines are administered by the intranasal route using relatively simple delivery systems. Various forms of inactivated vaccines have been deployed, including inactivated whole virus, split virion, and subunit.

Influenza vaccines were first commercialized in 1945 to help prevent or reduce diseases caused by epidemics and pandemics such as the pandemic of 1918, which killed an estimated 20–50 million people (43), or the most recent 2009 A(H1N1) influenza pandemic (74,76). However, vaccines are far from perfect. This is particularly true in the elderly where the inactivated vaccines (the mainstay of our current vaccination programs) rarely reach effectiveness estimates of 50%. The effectiveness of influenza vaccines has been found, in some studies, to reduce influenza illness by up to 70–95% in healthy adults, although vaccines are often less successful (71,82,89,105). The less than optimal effectiveness levels of inactivated influenza vaccines have been major political and scientific drivers for new vaccine development, but also dampen public opinion. Public expectation of vaccine effectiveness may be overly optimistic, and meeting or managing this expectation is challenging. Expectations may rise when protection is observed in small animal studies during the preclinical development of a vaccine, but disappointments may follow in clinical trials. Small animal models provide limited guidance as to true efficacy in either humans or larger animal models, such as ferrets.

The development of influenza vaccines is also challenged by poor immunologic correlates of protection. The only currently accepted correlate is hemagglutination inhibition (HI) serum antibody titers of 1:32 to 1:40, although there is far from robust experimental support for this (14). It is still, however, an important benchmark for vaccines that elicit protection primarily through the generation of neutralizing antibodies targeting the HA. The development of next generation influenza vaccines that may function through different mechanisms is hampered by a complete lack of other convincing protective immunologic correlates. Indeed, the live attenuated vaccines have shown efficacy without generating serum HI titers of 40, demonstrating that protection is afforded by other mechanisms. As newer targets are identified and different components of the immune response are triggered, the lack of known correlates becomes more problematic. A better understanding of the hallmarks of a successful immune response to natural infection will help guide the optimization of vaccine platforms. Animal models are critical in this discovery path, but it is near impossible to mimic the repeated exposures and considerable preexisiting immunity that exist in the human population.

Incremental improvements to overcome the limitations of the current influenza vaccine platforms have included exploring a shift away from the egg-based manufacture to cell-based systems. There are theoretical improvements afforded by this shift, some relating to the increased flexibility of the supply chain of cells compared to eggs. There are, however, other reasons to move toward a cell-based product. One of the most important is the fact that some influenza viruses acquire adaptations in the HA upon growth in eggs and a subset of these changes can impact antigenicity resulting in a mismatch between vaccine antigen and circulating strain. While the effect of growth substrate choice on virus antigenicity has been long recognized (47), the true impact on vaccine effectiveness in humans is becoming more apparent [for example, Skowronski *et al.* (85)].

While substantial resources and effort have been utilized in this area, the lower yields of most cell-based systems have offset any positive gain in terms of speed and flexibility of production. Cell-based platforms are still an important component of a global vaccine response, particularly to pandemic influenza. An alternative approach to the egg issues has been to remove the need for growth of virus altogether. As current inactivated vaccines are enriched for HA, recombinant HA approaches have been explored. The most commercially successful approach to date has utilized the baculovirus system (94). These vaccines have been shown to be protective in different animal models (6,42,44) and a baculovirus expressed HA protein-based influenza vaccine is licensed in the United States (18). Studies have shown that the recombinant HA vaccines can be protective in immunologically primed healthy adults and the elderly (19,94). A more widespread switch to recombinant platforms, however, will be challenged by a high capital investment necessitated by the need to phase in a new system. In addition, a switch in manufacturing process without a substantial change in antigen, still, only provides solutions for some of the influenza vaccine issues and does not address the primary concern of matching vaccine HA antigen with a constantly moving target.

So, are there ways to tweak current systems to improve the breadth and longevity of the induced response? Potential strategies to improve the breadth of responses to vaccination have included the addition of the other immunogenic surface antigen, the NA. Studies have suggested that the addition of the NA to HA-based vaccines can improve the breadth of protection (6,59). In addition, recent data from both human challenge and clinical vaccine trials have shown that antibodies to the NA are independent correlates of protection. In influenza human challenge models, it was shown that baseline NA inhibition antibody titers correlated with reduced measures of disease severity (64). Similarly, analysis of data from vaccine efficacy studies showed that increased NA inhibition antibody titers following inactivated influenza administration was correlated with a reduced frequency of subsequent influenza virus infection (65). As all inactivated products start with whole viruses, there is a probability that available products contain NAs; however, there are no specific regulations on controlling NA concentration. NA content is generally unknown and likely varies from manufacturer to manufacturer and probably from batch to batch. How difficult altering the current production systems to include standardized amounts of the NA would be is unclear, but should be explored.

As might be expected, adjuvant technology has also been used with influenza vaccines in the hope of increasing immunogenicity and breadth of immunity with mixed success. Alum (aluminum salts) has been licensed as an adjuvant for human use; however, it has had mixed results with

influenza vaccines and does not promote cell-mediated immunity (53). The oil-in-water emulsions AS03, MF59, and AF03 have demonstrated a significant dose-sparing effect when used in conjunction with influenza vaccines and have been shown to increase the breadth of the immune response when compared to unadjuvanted formulations (3,35). Other approaches such as ISCOMATRIX (83) and immunopotentiating reconstituted influenza virosomes (IRIVs) (34) have also been studied. However, there may be perception and possibly regulatory issues associated with adjuvant use in vaccines requiring frequent boosting.

Toward a More Universal Influenza Vaccine

What have been discussed to date are issues and some possible solutions to overcoming the shortfalls of current vaccines, the most important of which is matching vaccine HA antigens to the HA of circulating viruses. So long as the globular head of HA remains the vaccine target, it is difficult to imagine this ever being overcome. The search for more conserved epitopes and antigens is critical to truly advancing influenza vaccinology and heading it in the direction of a universal influenza vaccine.

What should a more broadly reactive influenza vaccine target? The influenza virus was initially classified as a myxovirus (1) with later reclassification within the family of *Orthomyxoviridae* (63). There are seven genera within the *Orthomyxoviridae* family: influenza A, B, C, and D virus, tick-borne Thogotovirus, infectious salmon anemia (ISA) virus (52), and Quaranjavirus (39). Orthomyxoviruses are segmented, single-stranded, negative-sense RNA viruses (109). The influenza viruses are classified on the antigenic properties of their matrix (M) and nucleoprotein (NP) (106) with influenza A and B viruses first isolated in 1933 and 1940, respectively (30,68); influenza C virus was first isolated in 1949 (31). An influenza virus with moderate homology to human influenza C viruses was isolated from swine in 2011 and has been proposed as a new genus of influenza virus named influenza D virus, and a new member of the family *Orthomyxoviridae* (36). Due to their distinct characteristics and limited impact as human pathogens, influenza C and D viruses are not vaccine targets of high importance. Therefore, although universal influenza vaccines should provide protection against all influenza viruses, when it comes down to vaccine development, coverage of influenza A viruses and influenza B viruses is most important.

With this in mind, searches for more conserved sequences within the influenza virus proteome have been explored. The most extensive endeavors have targeted various epitopes within the HA (Fig. 2), the ectodomain of matrix 2 protein (M2e), and the NP. Some of the earliest hopes for a more broadly reactive vaccine were focused on M2e. The M2 protein is a transmembrane ion channel that acts during the influenza virus lifecycle to regulate the pH of various cellular and viral compartments. M2e contains an N-terminal sequence highly conserved in influenza A viruses (25). Vaccines based on this conserved domain are protective in small animal models, particularly mice, and can induce broadly reactive immune responses (17,80,84). The mechanism of protection with M2e approaches is antibody based, but involves mechanisms beyond simple neutralization effects. While there is still some uncertainty about the exact mechanisms of protection afforded by M2e-based vaccines, antibody-dependent cell-mediated cytotoxicity has been implicated [reviewed in Lee *et al.* (55)]. Some of the M2e approaches have not shown as much promise past murine

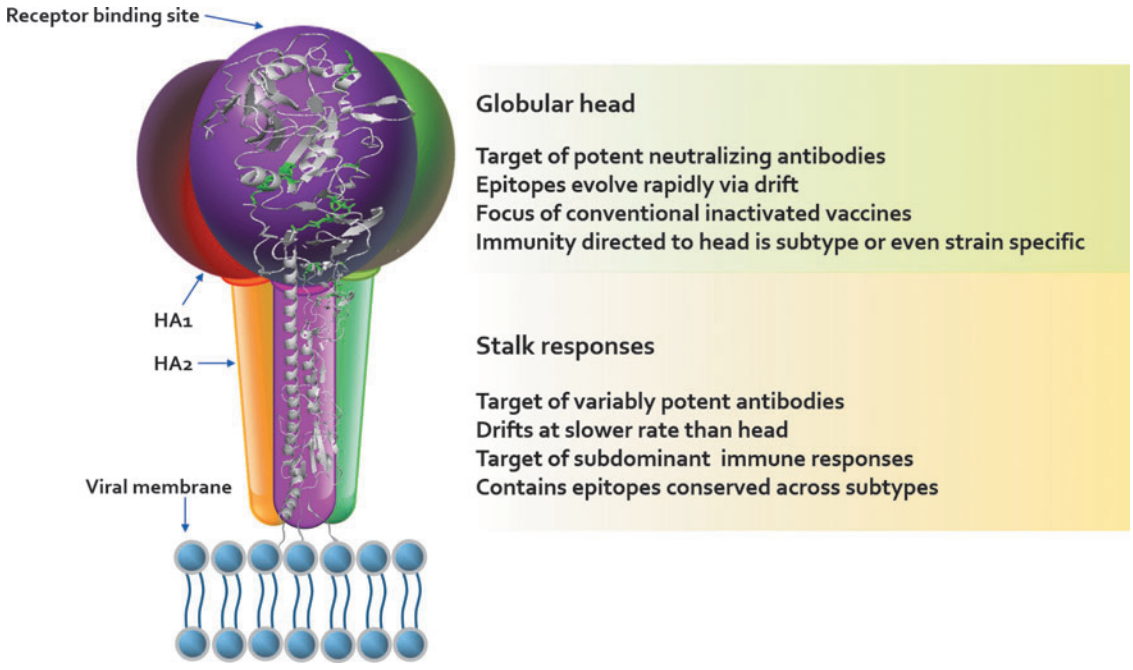

FIG. 2. HA as a vaccine target. Representation of HA trimer showing the two major domains (globular head and stalk) and their antigenic and immunologic characteristics.

studies, although others have advanced into clinical trials (95). Producing a vaccine based on a single peptide antigen is not a feasible standalone product, and the best promise for M2e approaches is to supplement other viral antigens/vaccines. While the M2e epitope is relatively well conserved, focusing the immune response on it will undoubtedly lead to issues of viral escape. Determining the best way to harness the expanded breadth of M2e immunity warrants further investment.

The approaches to influenza vaccines discussed to date have primarily relied on generating humoral immunity (with the exception of live attenuated platforms, for which the primary means of protective immunity is unclear). Other more conventional approaches to expanded breadth of influenza vaccines have focused on eliciting cellular, particularly cytotoxic $CD8^+$ T cell, immunity; such cells often target epitopes on more conserved viral proteins typically not exposed to antibody-driven selection. One example of this is a recombinant pox vaccine expressing the NP. This vaccine induced strong immune responses that protected against multiple influenza virus challenges (96). Similarly, other approaches designed to induce $CD8^+$ T cell immunity have been shown to be broadly protective against various influenza viruses in animal models (77,79).

While these are but just two examples of the many that have gone down the T cell path, most have targeted the immunodominant epitopes present in the NP and M1 in the context of generating heterologous immunity mediated by cross-reactive T cells (9,54). It is somewhat unclear as to what the future of T cell -directed influenza vaccines holds. While animal models clearly show that $CD8^+$ T cells can play a critical role in protection from influenza virus infection, the role of T cell protection in influenza disease in humans [even though there has been some rapid progress (86,104)] is less clear. Some of this is due to the difficulty in examining the T cell response at the site of infection as well as the high cost and technical challenges of conducting immunologic studies in naturally infected individuals. It is very difficult to imagine, however, that T cells do not have a substantial influence on the outcomes of human influenza. The development of methods to induce memory $CD8^+$ T cell populations through vaccination should be encouraged. A better understanding on the protective effects of targeting different epitopes/proteins in the context of human immunity would help push these approaches forward.

Much of the recent activity in universal influenza vaccine approaches has centered on focusing the immune response to more conserved domains of the HA. While it has been recognized for some time that more conserved antibody epitopes exist on the HA, particularly in the stalk domain, the development of single-cell B cell analysis tools has uncovered an underappreciated role B cells play in response to infection and vaccination. B cell responses to the HA stalk domain are substantially less dominant than those to the globular head, but they do exist and are variably neutralizing (2,20,73). An important clinical advance is the development of broadly reactive antibodies to the HA stalk as treatment options (78,87). Anti-influenza HA stalk-specific broadly neutralizing antibodies, such as CT149, SFV005-2G02, and MEDI8852, have been developed and are capable of recognizing structurally constrained epitopes (45,58,110). The challenge is to utilize this knowledge to design vaccine antigens able to induce broadly neutralizing antibodies. Studies conducted during the 2009 pandemic showed that under certain circumstances, exposure to novel antigens induced stalk-directed antibody responses, providing more useful guidance on how to stimulate broadly reactive responses (108). Encouraging early results from mice immunized with stable HA stalk vaccines (which lacked the immunodominant globular head domain) showed that the HA stalk could induce broad protection (41,111). Currently, a number of other approaches are in development and clinical data should be available in the coming years. It should also be noted that studies looking at the individual human B cell response have identified rare antibodies that are broadly reactive across influenza virus subtypes; these antibodies bind near the receptor binding site of the HA (22,102).

While there is considerable research effort ongoing, directing the immune response to target the conserved HA stalk domain, other approaches have taken a somewhat different route to induce more broadly reactive HA-focused immunity by generating computationally derived ''consensus'' antigens. While there are several slight variations on the theme, the basic approach has been to utilize the sequence of circulating strains and generate an artificial sequence that is most representative of the group. The theory behind this is that this should minimize the average genetic, and by inference antigenic, distance between the vaccine antigen and circulating viruses. In animal models, this has been shown to be an effective approach against numerous influenza virus subtypes including, but certainly not limited to, A(H1N1) (98) and A(H3N2) (107) viruses.

While most of the more universal approaches have concentrated on influenza A viruses, where the most genetic and antigenic diversity exists, universal influenza B vaccines are also being developed. An example of one approach targets the highly conserved influenza B HA cleavage site located within the stalk domain. Three doses of this conjugated vaccine protected from multiple influenza B virus challenges (4). Similar to what has been explored with influenza A viruses, conserved epitopes from influenza B viruses have been discovered and tested in mice (16).

Concluding Remarks

While the long-term goal for influenza vaccination must remain on a more universal vaccine, there is some debate on exactly what the traits of such a vaccine should be. We can all agree that a single dose of vaccine capable of protecting against all epidemic and pandemic viruses would be ideal, but is likely unrealistic. What then is realistic? The current approaches suffer from narrowness and short duration of induced immunity. Improving either of these, either in tandem or alone, would be a major step forward and is not outside the realm of possibility. Having a vaccine that would cover more drift variants might mean less vaccine updates and a reduced need for yearly vaccinations. Such vaccines may not cover the gamut of influenza A subtypes, but would still constitute a significant public health achievement. Of course challenges remain even for these relatively minor improvements. The challenges include inducing responses to epitopes other than the immunodominant HA head, and the tradeoff between immunity potency and breadth. Even with a current vaccine that induces the most potent form of

immunity, neutralizing antibodies to the HA globular head, vaccine effectiveness measures can be disappointing. In the context of pandemic vaccination where the initial end goals of vaccination might be to reduce mortality, a less robust protective immunity might be tolerated, but in the context of seasonal epidemic influenza viruses, there is little room for loss of potency. Another major focus of influenza vaccine improvements, whether in terms of breadth, duration, or immunogenicity, concerns the elderly. This sector of the population is hardest hit by the severe consequences of influenza infection and is recognized as a priority vaccination target, but has the most disappointing responses to conventional vaccines. The full-throttle forward approach to a more universal vaccine should not come at the expense of improving vaccines for the elderly; the improvements here may be more readily achieved and the public health impacts just as significant.

While there is still clearly work to do, there has been a marked progress in influenza vaccine research over the past decade, and vaccination has become an important means of protection against influenza. In addition to taking steps forward to realize a perfect vaccine, overcoming the social atmosphere is also a challenge for vaccine developers and cannot be ignored. The erosion of public trust in vaccination could cause an important global health issue; the variable efficacy of influenza vaccines does not help this problem. Current approaches to improve influenza vaccines are diverse and at various stages of development. While some will undoubtedly fail, the data that each will generate will be invaluable and it is likely that different options for influenza vaccination will be available in the coming future. Watch this space.

Author Disclosure Statement

No competing financial interests exist.

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