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Investing in Immunity: Prepandemic Immunization to Combat Future Influenza Pandemics

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(See the Editorial Commentary by Treanor on pages 499–500.)

We are unlikely, with current technologies, to have sufficient pandemic influenza vaccine ready in time to impact the first wave of the next pandemic. Emerging data show that prior immunization with an immunologically distinct hemagglutinin of the same subtype offers the potential to "prime" recipients for rapid protection with a booster dose, years later, of a vaccine then manufactured to match the pandemic strain. This article proposes making prepandemic priming vaccine(s) available for voluntary use, particularly to those at high risk of early occupational exposure, such as first responders and healthcare workers, and to others maintaining critical infrastructure. In addition to providing faster protection and potentially reducing social disruption, being able, early in a pandemic, to immunize those who had received prepandemic vaccine with one dose of the pandemic vaccine, rather than the 2 doses typically required, would reduce the total doses of pandemic vaccine then needed, extending vaccine supplies.

Keywords. pandemic; influenza; vaccine; preparedness; priming.

The 2009 H1N1 influenza pandemic taught us much about both influenza and global pandemic preparedness and response capacity. Among the most important lessons is that, despite enhancements in surveillance and manufacturing capacity, we are extremely unlikely, until radically new vaccine technologies are available, to have enough vaccine ready in time to impact the first wave of infections in the next pandemic. Our scientific understanding of influenza vaccines has also evolved, and it is now appreciated that immunization well in advance of influenza exposure may prime the immune system to rapidly respond, even years later, to vaccines that can then protect against a related pandemic strain. This article proposes the targeted use of prepandemic vaccines—those developed in advance of the emergence of an influenza virus with pandemic potential—to help protect otherwise susceptible members of the population and better prepare for future pandemics.

Influenza viruses have multiple properties that keep them among the leading infectious causes of morbidity and mortality. Among these properties are the virus's genetic instability, which causes nearly continuous alterations of immunogenic portions of its hemagglutinin (HA) and neuraminidase (NA) surface proteins (antigenic "drift"), and its ability to easily recombine with novel influenza strains, including of animal origin, resulting in sudden transfer of entire or major portions of HA genes (antigenic "shift"). It is such a shift, with the creation of a virus to which the population has little or no prior exposure or immunologic memory, that poses the risk of global pandemics, with devastating public health, economic, and social consequences.

Although much progress has been made in surveillance to detect new influenza strains, and in understanding viral molecular determinants associated with their severity and transmissibility, we still lack the ability to predict if a given strain will cause a pandemic and how severe such a pandemic might be. However, the threat is with us all the time and improved surveillance means we will continue to detect new viruses that may pose a pandemic risk. Recent examples include the widespread emergence of new H5N2 avian influenza viruses in the United States, which have so far not been transmitted to humans (unlike H5N1 strains, which have infected nearly 800 individuals since 2003), and the H7N9 avian virus that, while highly virulent, like H5N1 has also, to date, been limited in its ability to transmit from human to human. H7N9 has also been concerning in both its acquisition of genes associated with human virulence and transmissibility and the finding of a variant resistant to available antiviral drugs [1, 2].

The 2009 H1N1 pandemic experience reinforced attention to efforts to speed vaccine availability through new technologies with the potential to accelerate vaccine production (eg, synthetic virus seeds and use of cell and recombinant-based manufacturing) and release (eg, rapid sterility and potency assays). However, while such technologies can shave weeks from the

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time between outbreak detection and vaccine administration, more must be done to be able to optimally protect people, reduce viral transmission, and potentially affect the trajectory of an emerging pandemic. The importance of new approaches is further reinforced by the limited effectiveness of available antiviral drugs, along with the specter of resistance. The difficulty of getting enough vaccine in time to impact the initial wave of a pandemic, as well as the challenges of annual seasonal vaccine administration, are driving efforts to develop so-called "universal," long-acting, vaccines directed at conserved viral elements to protect against diverse strains as they emerge. However, the ultimate success and timeframe of such approaches, and the breadth and duration of protection that may be achieved, are uncertain. These realities, and the desire to quickly protect both those at high risk of exposure during a pandemic response (eg, front-line healthcare workers) and those who support critical infrastructure (eg, power, law enforcement, emergency responders, military), have led to the development of prepandemic vaccine stockpiles, where bulk vaccine against a given strain is stored and kept ready to be mobilized if the virus, or a related one, begins to transmit efficiently in humans. The United States has created such stockpiles, largely of frozen bulk vaccine, against various H5N1 clades and H7N9. However, stockpiles will take significant time to fill, finish, and mobilize in an emergency and are expensive to maintain. In addition, truly novel HA subtypes, such as H5 and H7, have been poorly immunogenic, and it is anticipated that 2 doses will typically need to be administered to achieve protection, further slowing the response to a pandemic.

PREPANDEMIC IMMUNIZATION

Must we wait for a "universal" vaccine? Improved surveillance, identification, and characterization of potential pandemic "threat strains," and emerging science supporting prepandemic immunologic priming, mean we now have an opportunity to approach pandemics differently. Such an approach, instead of stockpiling vaccine in freezers, where it may never be used, would stockpile immunity directly, and for the long term, in the population.

Evolving data [3–7], to date from studies with a variety of H5N1 vaccines, show that prior immunization with a different, immunologically distinct vaccine of the same HA subtype not only may itself provide some cross-protection against other future viruses of the same subtype that emerge, but also offers the potential to "prime" recipients for subsequent protection with a single booster dose, months to years later, of a vaccine manufactured to match the pandemic strain, and administered, as soon as ready, during an emerging pandemic. Importantly, a measurable booster response has been observed even when there is a low or unmeasurable level of primed antibody, likely based on subtype-specific B cells [3] and CD4 T-cell help [8]. Although the response to poorly immunogenic HA subtypes (eg, H5 or H7) can be enhanced by novel adjuvants and whole virion approaches [3–5], nonadjuvanted split virion H5 vaccines can also prime for later boosters [3, 6, 7]. Such priming has resulted, months to years later (eg, [9, 10]), in a rapid, robust immune response to a single booster dose (as opposed to the 2 doses of pandemic vaccine typically needed in the absence of immune memory).

Although antibody levels drop rapidly after priming, it is possible, but unproven, that as observed in some animal studies, a single vaccine dose may afford partial protection against a different strain of the same HA type before or without boosting. More important, once the emergent pandemic strain-specific vaccine is ready, previously primed individuals are very likely to then achieve protective immunity more quickly than unprimed individuals, and to do so with a single booster dose. For first responders and healthcare workers, this may both provide protection that they might not otherwise have and enhance willingness to perform critical societal functions. Finally, in the event of a pandemic, being able to immunize those who received prepandemic vaccine with one rather than 2 doses of pandemic vaccine would not only shorten the time to protection of those individuals, but, by reducing the number of doses of pandemic vaccine needed, have the effect of extending the overall vaccine supply, allowing immunization of more people early in a pandemic. While nonadjuvanted HA-based vaccines can effectively induce immunologic priming, for poorly immunogenic HA subtypes, novel adjuvants may enhance the immune response and/or allow reduction in the antigen dose required. While this article focuses on prepandemic vaccine use, for a severe pandemic caused by a poorly immunogenic subtype, such adjuvants may offer the potential to help extend vaccine supplies more quickly to more people, if supported by immunogenicity and safety data and a careful risk/benefit analysis of the pandemic at hand.

Modeling studies suggest that early vaccine availability may help to blunt an emerging pandemic, mitigating its health, social, and economic effects [11], and that even vaccines of relatively low efficacy in terms of protection of individuals, if given early, and even to limited segments of the population, may have substantial effects in slowing population-wide pandemic spread [12, 13].

CONSIDERATIONS

While this approach is attractive, it has limitations and deserves thoughtful discussion and consideration. First, while future pandemics are a certainty, current tools are incapable of predicting the subtype that will spark the next one (eg, H5, H7, H2, H3) and therefore the subtype(s) that should be used for priming. Thus, costs and any potential risks of immunization are incurred with uncertain benefit. Second, like stockpiling, upfront investment is needed to produce and administer prepandemic vaccines and keep track of who has been vaccinated and

which vaccine(s) they received. Some of these costs are largely already incurred by stockpiling and would also be offset if a pandemic were to occur [13]. Third, current licensed seasonal vaccines, as well as the 2009 H1N1 pandemic monovalent vaccine, are very safe, with serious adverse events being extremely rare. However, there is considerably less experience with newer vaccine technologies, including novel adjuvants, or with vaccines against novel HA subtypes, and the risk that unexpected rare adverse events may occur cannot be ruled out even by clinical trials. The association of Guillain-Barré syndrome with administration of the 1976 "swine flu vaccine" and, more recently, the occurrence of narcolepsy in children following administration of one adjuvanted 2009 H1N1 vaccine used in Europe [14] illustrate that such possibilities and uncertainties must be considered in formulating policy and reinforce the importance of both robust vaccine safety monitoring systems and evidence-based communication so any recipients are fully informed of potential benefits, risks, and uncertainties.

A STAGED APPROACH

The simplest short-term approach would be to develop monovalent vaccines against subtype(s) of highest concern (such as currently stockpiled) for voluntary and carefully targeted use. Vaccine could be offered to segments of the population with the highest risks of potential exposure (eg, first responders, healthcare workers, those with occupational exposures such as to swine or fowl) and to individuals who maintain critical infrastructure [15]. Such an approach would, ideally, utilize a licensed formulation of vaccine and be well supported by clinical studies that inform the best dose for priming (including whether or not adjuvant is needed). There are a number of knowledge gaps that can and should be further addressed. The data to support heterologous priming should be augmented to evaluate important HA subtypes beyond H5, such as H7. There should be robust data supporting that candidate prepandemic vaccines prime broadly, and for a substantial duration, against divergent viruses of the same subtype and are, therefore, likely to be effective in priming against a future pandemic strain. We need to further understand the basis and correlates of vaccine-induced protection against disease, or reduction in disease severity, including whether a single priming dose of prepandemic vaccine may have benefits. The potential role of adjuvants in priming, as well as boosting, for specific subtypes and against divergent clades should be further studied. Additional clinical data on both the safety and effectiveness of adjuvanted vs nonadjuvanted influenza vaccines are becoming available and can also help inform preparedness and response strategies. The regulatory pathway and data needed to support prepandemic vaccine use for priming immunity, and potentially, licensure, require further consideration. While at present, use of such a prepandemic vaccine in the United States would most likely be as an investigational new drug, it may be possible to define an approval path based on documented priming against a broad range of viruses of the same subtype and the potential to protect individuals at risk of exposure to future pandemic strains.

Clear, well-designed communication about both the rationale for this approach and what is known and not known about potential benefits and risks would be essential. Although it is difficult to assess the degree of vaccine uptake that may occur, and it is likely to be highest for a licensed product [16], there may well be interest among populations more likely to have exposure risk [17, 18]. Voluntary use of monovalent vaccine(s) offered to such populations could also provide additional data on longer-term immunogenicity, priming, and safety. Such data would be helpful both in considering broader prepandemic use and in informing future vaccine use in a pandemic.

If initial experience is positive, prepandemic monovalent vaccine(s) could be offered more broadly in an effort to anticipate the range of influenza viruses with pandemic potential that may emerge. To that end, it may be possible to provide individuals with different vaccine subtypes, either with individual antigens over time or as a "combination" multiantigen prepandemic vaccine, thus building priming immunity to a spectrum of known threats, so long as they are immunogenic, safe, and supported by evolving science. Such approaches could potentially be extended to provide immunity against influenza subtypes (eg, H2) not currently circulating but where historical inference and lack of population immunity present a substantial vulnerability [19]. Ultimately, it may be possible to build on the pathway of the recent development and approval of quadrivalent seasonal vaccines (which contain a second influenza B antigen added to reflect the diversity of circulating strains) to develop a multiantigen vaccine that includes both seasonal and pandemic threat antigen(s) [20, 21].

In summary, despite the tremendous efforts to have more pandemic vaccine available sooner when the next pandemic strikes and the ongoing efforts to develop a "universal vaccine," we are still faced with the challenge of producing and administering sufficient pandemic vaccine to impact the first wave of a pandemic. Emerging science supports a new approach that could help to dampen the next pandemic—judiciously making prepandemic monovalent vaccine(s) available for voluntary use, particularly to those at high risk of early exposure. Advances in understanding immunologic priming, along with enhanced manufacturing capacity and existing stockpiles, can allow us to better protect those most at risk and may help speed our response, even as we wait for broadly protective universal influenza vaccines.

Notes

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