Priming for Pandemic Influenza: Thanks for the Memories

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(See the major article by Talaat et al on pages 1860–9.)

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Pandemic influenza remains a continuing global threat, and in the past 10 years we have seen 2 avian influenza viruses spread into the human population and a pandemic of a novel triple-reassortment influenza A(H1N1). Since reemerging in 2003, avian influenza A(H5N1) is now widely dispersed among birds, and >600 human cases of infection with high case-fatality rates have been reported worldwide [1]. The most recent threat, and perhaps the most concerning to date, is an avian influenza A(H7N9) strain first reported from China in March 2013 [2]. Cases continue to accumulate in China, and most illnesses are severe, with a death rate of approximately 33%. Infection is believed to be due to contact with infected poultry, and at the present time there is no evidence of sustained human-to-human transmission, although limited person-to-person spread has been noted.

Vaccination remains the cornerstone of any pandemic preparedness plan. The speed at which the pandemic influenza A (H1N1) strain spread across our interconnected world in 2009 clearly illustrates the need for rapidly deployable, effective vaccines. There are now global networks in place to identify new threats as early as possible, and methods to hasten and improve the efficiency of vaccine production have been developed. However, the time it takes to develop a protective immune response remains a key issue. Mathematical modeling indicates that the maximum reduction in viral transmission would be achieved by a vaccine capable of inducing a protective immune response within 2 weeks after the outbreak of the pandemic [3].

Unfortunately, the primary immune responses to novel antigens in the form of inactivated subvirion influenza vaccines (ISIVs) have been poor, requiring high doses of antigen and repeated immunizations [4]. The use of adjuvants can improve the primary immune response in virus-naive persons; however, multiple doses and time to develop protective immunity are still usually required [5, 6]. Of note, the immune response to primary immunization with 2009 influenza A(H1N1) was substantially better than what had been previously observed in influenza A(H5) vaccination trials. During the initial influenza A(H5) vaccine trials, two 90-μg doses of influenza A(H5N1) ISIV were found to be only modestly immunogenic in virus-naive subjects, whereas, a single 15-μg dose of 2009 influenza A(H1N1) ISIV induced protective titers of >1:40 in 95% of subjects [4, 7]. In addition, individuals born prior to 1957 were relatively protected from the 2009 pandemic influenza A (H1N1) strain [8]. Although the 2009 influenza A(H1N1) strain was very antigenically distinct from the previously circulating seasonal influenza A(H1N1) strain, these observations suggest that the population possessed some degree of immunologic memory to this new strain of influenza from prior influenza A (H1N1) infections or vaccinations.

It is well known that memory responses to previously encountered pathogens are quantitatively and qualitatively different than primary antibody responses. Switching to mature isotypes with higher affinity occurs, and a greater diversity of antibody is typically produced. Increased affinity for antigen and increased expression of major histocompatibility class II and costimulatory molecules facilitate antigen uptake, allowing memory B cells to initiate critical interactions with helper T cells at lower doses of antigen. However, the precise mechanisms involved and the specific cell types that are important for the successful development of memory are not well defined. Since memory immune responses are clearly superior to primary responses, an understanding of

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the biology of this phenomenon may be critical to successful pandemic influenza vaccine development. Yet, this concept presents a clear conundrum: memory responses are ideal, but pandemics occur when antigens shift and the population is immunologically naive.

In this issue of the *Journal,* Talaat et al describe a notable phenomenon of so-called subclinical priming, using a live attenuated influenza A(H5N1) vaccine (LAIV) [9]. This study may provide new insights on how immunologic memory can be harnessed to develop pandemic influenza vaccines. Using a small number of subjects, Talaat et al demonstrated a robust immune response after a 45-μg dose of ISIV given 4 years after an initial vaccination with an antigenically matched LAIV. One of the surprising aspects of the study was the clear priming of the immune response with development of a long-lasting memory response despite the fact that most subjects had little or no detectable viral replication, nor did they have any discernable primary humoral immune response after the initial LAIV immunization. Despite a small sample size, the frequency and the magnitude of the antibody responses were significantly greater when compared to those of unprimed subjects or those who received antigenically unmatched vaccines. In the LAIV-primed group, the antibody responses were very rapid, with 64% and 40% of subjects reaching titers of ≥1:40 and 1:256, respectively, by day 7 after immunization. Importantly, antibody had high affinity and exhibited cross-clade reactivity. As with seasonal influenza, there are no precise correlates of protection for pandemic influenza; however, one could reasonably expect some degree of protection if natural infection was subsequently encountered.

Other approaches for priming the immune response to pandemic influenza vaccines have been evaluated and include adjuvanted ISIV and DNA vaccines. Both MF59 and AS03 have been used with influenza A(H5N1) and influenza A(H1N1) vaccines to improve the initial response in virus-naive individuals [5, 6]. One of the earliest attempts to develop an influenza A(H5) vaccine was an inactivated influenza A(H5N3) vaccine in which the addition of MF59 significantly increased the mean titer of antibody when compared to that of nonadjuvanted vaccine [6]. When some individuals from the original 1999/2001 cohorts were revaccinated up to 8 years later with two 7.5-mg doses of MF59-adjuvanted influenza A (H5N1) ISIV, a brisk and robust memory response could be demonstrated, similar to the observations in the current study [10]. Primed subjects had significantly better responses than unprimed individuals, and those who received MF59-adjuvanted ISIV in priming and boosting phases demonstrated the most rapid and longest-lasting responses, with induction of cross-clade reactive antibody. In addition to LAIV and adjuvanted ISIV, DNA vaccines have been explored as a way to boost antibody responses to influenza A(H5) vaccines [11]. In a study by Khurana et al, responses to DNA prime followed by ISIV boost were superior to an ISIV prime and ISIV boost series, and DNA priming led to enhanced avidity and an expanded antibody repertoire [12]. Of note, optimal prime-boost intervals were explored in this study and demonstrated that intervals of ≥12 weeks were required for optimal boosting responses.

Where do these data lead us in our goal to have a rapidly deployable, effective influenza vaccine in the face of an influenza pandemic? The concept of prepandemic priming with influenza A(H5) or influenza A(H7) vaccines for the general population is generally dismissed because of concerns for vaccine-related adverse events. Rare adverse events are deemed unacceptable in the setting of only a theoretical benefit for a pandemic that may never come to pass. Thus, mass immunization for prepandemic priming is not considered a feasible approach. However, prepandemic priming might be considered for special at-risk groups, such as healthcare workers, first responders, and certain high-risk occupations with frequent bird or swine exposures.

The prime boost approach might be most useful in the early stages of a pandemic if we have already identified the optimal vaccines and adjuvants to be used and the shortest possible interval that results in a robust memory response. However, there is much to learn. The optimal adjuvants, intervals, tolerance of prime-boost mismatch, and vaccine types have yet to be determined. As pointed out by Talaat et al, during a pandemic, different types of vaccines may become available at different times, and it could be important to know whether ISIV followed by LAIV achieves the same type of memory response. Another important issue that is raised in the present study is that not all subjects demonstrated priming. Three of the 11 persons given antigenically matched ISIV did not develop a memory response, presumably because subclinical infection with LAIV did not occur. Thus, biomarkers or transcriptional profiling will be needed to identify those who will respond to the priming immunization. Finally, because persons who had received seasonal LAIV in the past were excluded from the current study, it might be worthwhile to explore whether seasonal LAIV is capable of inducing some degree of cross-reactive immunologic memory.

Any pandemic vaccine strategy needs to consider how to provide coverage for the maximum number of people, including those in resource-poor settings. Thus, the ideal pandemic vaccine should be inexpensive; be capable of inducing a rapid, broadly cross-reactive, neutralizing immune response after a single immunization; and be amenable to immediate large-scale production. While this may seem like an impossible undertaking, the findings presented by Talaat et al open up new potential strategies as well as opportunities for future research to explore the mechanisms involved in the development of long-lasting B-cell memory. For it is only through a better understanding of immunologic memory that we can hope to manipulate the process

so that it might be used it to develop better pandemic vaccines.

Note

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