Influenza Vaccine in the Red Zone Defense: A Game-Day Player

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(See the major articles by Ferdinands et al on pages 674–83 and Tsang et al on pages 684–92.)

Ultimate victory over influenza will rank among the great achievements of mankind because the defeats have been so bitter. The defense is growing stronger, and losses are less extreme. Incomplete successes against a lethal foe are great successes that fuel the determination for a shared and total victory. Studies reported in this issue of The Journal of Infectious Diseases invite consideration of the strengths and limitations of influenza vaccination, an especially important defense against life-threatening influenza disease and its transmission.

Influenza vaccination has not yet fulfilled the hope of complete protection against disease. Influenza vaccine effectiveness against all forms of influenza disease is variable. However, the prevention of influenza morbidity in all forms is less grave a need than prevention of mortality, and influenza vaccine performance is generally better in this regard. Consequently, persons at high risk for severe influenza disease benefit most from influenza vaccination, a conclusion that underpins the strongest recommendations for vaccination of this population [1].

Children who are older than 6 months, thus eligible for influenza vaccination, suffer high attack rates of influenza, though lower hospitalization rates than children younger than 6 months [2]. Children play an important role in the epidemic spread of influenza virus [3–6]. Childhood influenza deaths are devastating losses, and their ongoing prevention by vaccination would be a tremendous achievement; nowhere is the struggle with influenza more hard fought than in the red zone of our pediatric intensive care units (PICUs).

In this issue, Ferdinands and colleagues [7] examine the effectiveness of influenza vaccination in reducing the risk of severe childhood influenza disease requiring admission to one of 21 US pediatric intensive care units during the 2010–2011 and 2011–2012 influenza seasons. They prospectively enrolled children 6 months–17 years of age with acute, severe respiratory illness; those with influenza disease had endotracheal or nasopharyngeal aspirates positive by reverse transcriptase polymerase chain reaction analysis. The investigators enrolled 44 influenza-positive cases and 172 influenza-negative controls. They also enrolled 93 community control subjects matched by age group, comorbidities, and geographic region. Influenza vaccination status was determined for all children per the 2010–2011 recommendations and verified by contact with vaccine provider [8].

The median age of influenza-positive PICU cases was younger than PICU controls (4.3 vs 3 years), yet the proportions by age groups (0.5 to <2 years, 2 to <5 years, 5 to <9 years, and ≥9 years) were similar. Most PICU cases (55%) and PICU controls (69%) had underlying medical conditions, with over a third having respiratory or neuromuscular conditions. One-fifth of enrolled subjects had more than 3 chronic underlying conditions, and 3% died (9% cases and 2% of controls, P = .03). Sixty-eight percent of PICU cases were unvaccinated, 18% were fully vaccinated, and 14% were partially vaccinated. For PICU controls, 52% were unvaccinated, 31% were fully vaccinated, and 16% were partially vaccinated. Using unconditional logistic regression while controlling for confounding, full influenza vaccination was 74% (95% confidence interval [CI], 19%–91%) effective in preventing PICU admission with confirmed influenza as compared to no vaccination; partial vaccination was not protective. This vaccine effectiveness persisted in 2 sensitivity analyses. Studies in adults have shown that influenza vaccine effectiveness estimates can be susceptible to bias [9]. Thus, the investigators also tested all PICU specimens for respiratory syncytial virus (RSV) and determined if partial or full influenza vaccine status was...
The vaccination status for many community controls could not be confirmed, so parental report of influenza vaccination status was used in the analysis of cases and community controls. In contrast to the pattern seen in PICU enrollees, 51% of community controls were fully vaccinated, 16% were partially vaccinated, and 33% were unvaccinated. The vaccination status for community controls was determined at the time of enrollment for the matched case. Using a conditional logistic regression analysis while matching for age group, influenza risk category and geographic area and controlling for underlying chronic conditions, the vaccine effectiveness for full influenza vaccination was 82% (95% CI, 23%-96%) as compared to no vaccination; similar to the PICU controls, partial vaccination was not protective. The investigators conclude that “...influenza vaccination was associated with a three-quarters reduction in the risk of life-threatening influenza illness in children [7].”

This important work demonstrates that influenza vaccination prevents severe disease in children and reminds us of the importance of vaccination for children with risk factors for severe influenza. The 11 children included in this study who were fully vaccinated and admitted to the PICU with severe influenza disease remind us that the performance of influenza vaccines must continue to improve.

The process of improving influenza vaccines depends on both a nuanced understanding of the complex immune response to influenza virus infection, and methods to reliably measure the protective capacity of that response following vaccination. The human immune response that controls influenza virus replication, prevents or limits transmission and disease, and clears infection involves many components of both the innate and adaptive immune system including T-cell and B-cell responses. Vaccines in current use provoke production of protective antibodies specific to the influenza surface glycoproteins hemagglutinin and neuraminidase, and improvements in vaccine performance require reliable ways to determine whether these antibodies are present at levels sufficient for protection. The hemagglutination-inhibiting (HAI) assay has been widely used to measure levels of antibody present in a serum sample that bind to influenza virus surface proteins to prevent the virus from attaching to red blood cells. An HAI antibody titer of 1:40 correlates with 50% protection from influenza disease in community-based and experimental challenge studies of healthy adults, referred to as a “correlate of protection” [1, 10–13]. The related influenza microneutralization (MN) assay measures levels of serum antibodies that can block viral infection and killing of tissue culture cells, but the antibodies measured are different than those detected by an HAI assay, and the true correlates of protection are not known. Whether an HAI antibody titer of 1:40 will also correlate with influenza protection following the potentially more extreme influenza exposure of a household contact with disease is an important question.

In another article in this issue, Tsang and colleagues [14] explore influenza transmission in Hong Kong households with confirmed influenza. Over 2 years, the investigators prospectively enrolled children and adults with influenza disease diagnosed by rapid influenza antigen test and confirmed by polymerase chain reaction (PCR) assay. The household contacts of index cases were asked to complete symptom diaries for 7–10 days, and twice during this time nasal/throat swabs were obtained for RT-PCR influenza assay. A subgroup of index cases and household contacts also consented to provide serum specimens for antibody assays.

Of the 297 index cases with PCR-confirmed influenza, about two-thirds were infected with seasonal A(H1N1) and about one-third with seasonal A(H3N2) influenza. Influenza vaccination rates among the 297 index cases (11%–14%) and 895 household contacts (18%–21%) were relatively low. Household contacts who had higher antibody titers specific for the influenza A subtype infecting the household index case were found to be at significantly lower risk of PCR-confirmed influenza disease than those with antibody titers <1:10. Interestingly, the investigators found that HAI-determined antibody titers of 1:40 were associated with just 31% protection against PCR-confirmed seasonal influenza A(H1N1) or influenza A(H3N2) for household contacts, in contrast to previous studies conducted in healthy adults in other settings [10]. Computational analysis was used to estimate that HAI titers of 1:255–1:260 would be associated with 50% protection against seasonal A(H1N1) and A(H3N2). The investigators also examined microneutralization (MN)-determined influenza antibody titers (for strain A(H3N2) only), and found that a 1:40 titer was associated with 49% protection against PCR-confirmed influenza in household contacts. Although this study was not designed to assess vaccine effectiveness, the authors note that influenza vaccination (well matched to circulating virus) provided children and adult household contacts with measurable protection against seasonal influenza A(H1N1) infection. Despite its limitations, this important study shows that the type and extent of exposure to influenza virus may significantly alter the likelihood of disease acquisition, as well as the threshold of influenza immunity required for protection.

These findings underscore the importance of further research to understand the complex interplay of factors that determine the efficiency of person-to-person influenza transmission. The finding that children are more likely to acquire influenza following household influenza exposure than adults, and that levels of influenza-specific humoral immunity must be higher to provide protection from household influenza exposure, are perhaps not surprising. But
why is this the case? To say that current best explanations are “lacking in detail” is an understatement. Spectacular scientific work has led to a better understanding of influenza virus cellular replication and has driven the development of effective drugs to treat and prevent disease. Similarly, discoveries that will illuminate the path taken by influenza virus following egress from cellular replication sites to begin productive virus replication in a new host should reveal successful new approaches to prevent disease. For now, the understanding that household influenza exposure results in higher risk of disease, that influenza vaccination can reduce this risk in household contacts, and that vaccinated children are less likely to suffer very severe disease, is actionable. Clinicians are urged to encourage influenza vaccination in all eligible persons living with patients at especially high risk for severe influenza disease [1]. Clinical practices that meet the significant challenge of successful influenza vaccine cocooning will lead in protecting against severe disease in patients and communities [15–18].

Influenza virus vaccine holds an especially important position in our defense against influenza disease in its most severe manifestations. The 11 children requiring PICU care for severe disease despite full influenza vaccination, reported by Ferdinands and colleagues [7], call on us to important work ahead to improve every aspect of our defense. We borrow inspiration from Coach Vince Lombardi who once said to his team, the Green Bay Packers, “...we are going to relentlessly chase perfection, knowing full well we will not catch it, because nothing is perfect. But we are going...”

Notes

Financial support. The authors have received research support from National Institutes of Health (R01 AI079226), BD Diagnostics and Medimmune.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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