How Did the 2008–2009 Seasonal Influenza Vaccine Affect the Pandemic?

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(See the article by Cowling et al, on pages 1370–1379.)

A novel influenza A(H1N1) virus appeared in Mexico in March 2009 [1]. The prototype strain, A/California/09/2009 (H1N1), was identified in April 2009, and the virus was found to have surface antigens that are distinct from those of the circulating seasonal influenza A(H1N1) virus. An early survey of antibody prevalence suggested that many persons ≥60 years of age might be expected to have preexisting antibody titers to nH1N1 virus that could be protective and that a few younger persons had lower titers that may be boosted by immunization with seasonal influenza vaccines for both 2007–2008 and 2008–2009 [2]. This information suggested that seasonal trivalent influenza vaccine (TIV) might benefit some older adults but not children. In fact, early reports from Mexico found “partial protection” for persons who had received TIV [3]. Because several months would be required to produce a vaccine against the nH1N1 virus, vaccination with TIV was recommended as soon as it was available. This recommendation was questioned by a statement issued by the Canadian Agency for Drugs and Technologies in Health (CADTH) [4]. CADTH reported that the Canadian sentinel influenza surveillance system had found that persons who received the 2008–2009 seasonal TIV had higher rates of nH1N1 illness than did unvaccinated persons. The sentinel surveillance was an ongoing program that monitored the effectiveness of influenza vaccine in Canada annually [5]. Although the data supporting the CADTH report of increased risk of nH1N1 infection for those receiving TIV had not been published, some Canadian provinces altered their recommendations for the timing of administration of seasonal TIV and nH1N1 vaccines. With conflicting reports on seasonal TIV effectiveness from our neighbors to the South and to the North, the Centers for Disease Control and Prevention (CDC) examined available data for a case-cohort analysis [6]. The analysis used surveillance reports of persons aged ≥18 years with confirmed nH1N1 illness from 8 states. A survey of 2008 TIV uptake was used to estimate vaccine coverage for the population cohort. The overall vaccine effectiveness against nH1N1 virus infection was ~10% (95% confidence interval [CI], ~43% to 15%). The CDC’s conclusion was that current evidence did not suggest that seasonal influenza vaccine either decreases or increases the risk for acquiring nH1N1 illness; therefore, the recommendations were unchanged. The CDC report also cited experience in New York City schools that found an overall adjusted relative risk of 1.05 (95% CI, 0.91–1.20) for TIV-vaccinated students with proven nH1N1 infections [7]. A study of an outbreak of nH1N1 virus infections in military beneficiaries in San Diego, California, revealed a significantly higher proportion of individuals with laboratory-confirmed cases than of individuals with negative cases had received the 2008 seasonal vaccine (which was usually the live attenuated influenza vaccine [LAIV]) [8]. The authors considered this to be a consequence of the fact that almost all members of the military are vaccinated and that LAIV is the vaccine most commonly administered to military personnel. Examination of persons with cultures obtained in the Central Texas Field Trial found that the 2008 seasonal influenza vaccine did not prevent or enhance infection with nH1N1 virus; LAIV was administered to ~70% of >9000 seasonal vaccine recipients [9]. Canadian investigators published the results of 4 observational studies in April 2010 that purported to show an association between the 2008 TIV and nH1N1 illness [10]. The 4 studies were a test-negative case-control study based on the Canadian sentinel vaccine effectiveness monitoring system in 4 provinces, a conventional case-control design in Quebec.
that used population control subjects who were contacted by telephone about influenza vaccination, a test-negative case-control study in Ontario, and the Quebec household transmission study. The second (Quebec) and third (Ontario) studies included hospitalized as well as ambulatory patients. The sentinel vaccine effectiveness system estimated that the risk of nH1N1 infection was increased 1.4–2.5-fold by vaccination with seasonal 2008 vaccine after adjustment for comorbidities, age, and geography. A perspective on these studies was provided by Viboud and Simonsen [11]. They noted that TIV remained protective (53%) against seasonal viruses circulating in April and May 2009. The complementary studies in Ontario and Quebec confirmed the increased risk of nH1N1 infection attributed to TIV; however, this risk did not extend to the subsets of patients who were hospitalized. Hospitalized patients tended to have the same vaccination rates as did the control subjects. This inconsistency is difficult to explain if seasonal vaccine increased the risk of infection, because enhancement of disease might be expected. Furthermore, the household transmission study did not show increased risk of nH1N1 infection for 2008 vaccine recipients.

One variable that the previous observational studies had overlooked was the effect of natural infection by seasonal influenza virus. Cowling et al [12] had the advantage of a study structure in place at the time of the emergence of nH1N1 that allowed them to determine infection with seasonal viruses as a factor to compare with seasonal TIV vaccination and nH1N1 infection. They found that a recent seasonal influenza A infection protected against nH1N1 infection and that TIV administration did not affect nH1N1 infection rates. Persons who received seasonal TIV were protected against the seasonal viruses and, therefore, were less likely to benefit from the cross protection afforded by natural infection. Without knowledge of recent natural infection, observers might conclude that seasonal vaccine is the risk factor. At this time, the best hypothesis for explaining the distribution of nH1N1 infections by vaccine status is that natural seasonal influenza A infection provides cross protection against nH1N1. Persons with 2008 TIV vaccination were less likely to benefit from the protection afforded by natural seasonal virus infection because of the protection afforded by the TIV.

The novel H1N1 virus is so classified because it is antigenically distinct from previously circulating viruses. Perhaps, therefore, the protection provided by natural infection is mediated by innate or nonspecific mechanisms rather than by specific immunity. Examination of Figure 2 in the article by Cowling et al [12] shows that seasonal influenza viruses were co-circulating with the nH1N1 virus during the period May–October 2009. Infections with seasonal viruses of any type would stimulate production of interferon and other cytokines that might transiently prevent infection with nH1N1. Evidence for interference among the major respiratory viruses has been suggested by observations from Houston, Texas, and Chapel Hill, North Carolina [13]. LAIV infection mimics natural infection by stimulating immunity by multiple mechanisms [14, 15]. LAIV provides almost immediate protection against respiratory viruses, including influenza, that is evident for at least 14 days after administration, which allows time for specific immunity to develop [16, 17]. Experimental studies in animal models [18] and involving human volunteers [19] support this hypothesis. LAIV should be the vaccine of choice for healthy children and adults, especially when influenza is prevalent in the community [20, 21].

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References


