Evidence in a Cluster Randomized Controlled Trial of Increased 2009 Pandemic Risk Associated With 2008–2009 Seasonal Influenza Vaccine Receipt

To the Editor—The 2009 influenza A(H1N1) pandemic provided a unique opportunity to evaluate seasonal influenza vaccine effects on pandemic risk. When A(H1N1)pdm09 viruses arose in April 2009, the Canadian Sentinel Practitioner Surveillance Network (SPSN) was already well established for annual influenza vaccine effectiveness (VE) monitoring using the test-negative design (TND) [1, 2]. Without pause or protocol change, the SPSN extended its ongoing evaluation of the 2008/2009 trivalent inactivated influenza vaccine (2008/09-IIV3) to also capture effects on A(H1N1)pdm09 risk during the first 2009 spring–summer pandemic wave [2].

According to the SPSN, 2008/09-IIV3 significantly reduced the risk of laboratory-confirmed, medically attended seasonal influenza illness by more than half (VE, 56%; 95% confidence interval [CI], 41% to 67%) [2]. Conversely, 2008/09-IIV3 was associated with a significant 1.68-fold (95% CI, 1.03 to 2.74) increased risk of A(H1N1)pdm09 illness, corresponding to negative VE of –68% (95% CI, –3% to –174%) [2]. Among vaccinated participants aged <50 years, A(H1N1)pdm09 illness was increased by 2.23-fold (95% CI, 1.31 to 3.79), corresponding to a negative VE of –123% (95% CI, –31% to –279%) [2]. At least 4 other observational studies [2] and a randomized control trial (RCT) in ferrets [3] corroborated these findings in Canada. Elsewhere, however, observational studies gave mixed results, including negative VE against A(H1N1)pdm09 illness based on TND analysis of US military beneficiaries [4] but null VE in a case-cohort study by the US Centers for Disease Control and Prevention [5]. Although authors deemphasized their findings, a pilot RCT in Hong Kong that was ongoing during the pandemic also showed that children aged 6 to 15 years randomized in November 2008 to receive 2008/09-IIV3 vs placebo experienced higher rates of pandemic infection during the summer of 2009 (relative risk = 2.58; $P = .04$) [6, 7]. Conversely an Australian RCT that randomized adults to receive seasonal 2009-IIV3 or placebo beginning in March 2009 showed substantial cross-protection against A(H1N1)pdm09 illness during the pandemic wave that peaked in July 2009 (38%; 95% CI, 19% to 53%) [8].

In that regard, the cluster RCT recently published by Diallo et al [9], which was also conducted among children during the pandemic, merits greater attention. The authors randomized Senegalese villages so that between May 2009 and July 2009 children aged 6 months to 10 years received either 2008/09-IIV3 or inactivated polio vaccine (IPV). During the first pandemic wave that commenced 6 to 8 months later in January 2010, the A(H1N1)pdm09 risk among children who had received 2008/09-IIV3 was increased by more than half (VE, –54%) compared to IPV recipients but without reaching statistical significance (95% CI, –180% to 16%) overall.

In hypothesizing biological mechanisms, Canadian investigators had earlier cited a potential contribution by "original antigenic sin"—a phenomenon of immunological imprinting, with memory response to influenza viruses of original childhood priming preferentially recalled upon subsequent influenza virus exposures [2]. If seasonal influenza vaccine also preferentially back-boosts original (eg, heterologous, cross-reactive but sub-neutralizing) antibodies, and that negatively affects response to novel influenza viruses, then increased pandemic risk associated with seasonal influenza vaccine should be more pronounced in children previously primed to seasonal influenza viruses.

Virtually everyone has had an influenza A priming infection by age 6 years [10]. We therefore anticipate the negative effects of seasonal influenza vaccine on pandemic risk to be more pronounced in children aged ≥6 years. Consistent with this hypothesis, Diallo et al reported negative VE against A(H1N1)pdm09 among 2008/09-IIV3 recipients aged 6 to 35 months (–31%; 95% CI, –128% to 25%) and 3 to 5 years (–56%; 95% CI, –238% to 28%) that became substantially more negative in older children aged 6 to 8 years (–102%; 95% CI, –328% to 5%) and 9 to 10 years (–89%; 95% CI, –384% to 26%). To assess this hypothesis with greater statistical power, it would be valuable for Diallo et al to display their findings more simply dichotomized for children aged <6 years or ≥6 years. VE of 2008/09-IIV3 against A(H1N1)pdm09 illness in the latter group of previously primed children is likely to be statistically significantly negative.

Although the 2009 pandemic was relatively mild, such interactions and their mechanisms still remain critical to clarify. If real, a potential doubling of pandemic infection risk among prior seasonal vaccine recipients could be disastrous in the event of a more severe pandemic involving a higher per-case fatality risk.

Note

Potential conflicts of interest. D. M. S. has received grants from the Public Health Agency of Canada for influenza vaccine effectiveness estimation. G. D. S. has received grants for investigator-initiated studies unrelated to influenza vaccine from Pfizer and provided paid expert testimony for the Ontario Nurses Association, the Quebec Ministry of Justice, and GlaxoSmithKline. Both 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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Reply to Skowronski and De Serres

To the Editor—Skowronski and De Serres summarized evidence of increased attack rates with 2009 pandemic influenza A virus (A/H1N1pdm09) following receipt of 2008–2009 Northern Hemisphere trivalent inactivated influenza vaccine (IIV3) [1]. They postulated that exposure to previously circulating influenza A viruses may have modified the immune response to the IIV3 in a way that led to decreased or negative vaccine effectiveness (VE) against illness caused by A/H1N1pdm09. To further explore this hypothesis, they proposed that we collapse age groupings in analyses of total vaccine effectiveness from our trial in Senegal [2] to dichotomize children as having all had prior exposure to influenza A viruses or not. Skowronski and De Serres suggested age groupings based on a study from the Netherlands in which 100% of children had serologic evidence of prior infection with a previously circulating influenza A virus by the age of 6 years, as determined by hemagglutination inhibition (HI) assay [3].

At the beginning of our cluster-randomized trial we conducted a vaccine immunogenicity substudy among 217 children who were participating in the larger trial, although length considerations did not allow inclusion of those results in the primary publication. We tested sera collected before and after vaccination using the HI assay at the Institut Pasteur de Dakar using vaccine viruses as antigen. However, unlike in the Netherlands study, we did not test for antibodies against a panel of other previously circulating influenza A viruses. However, we believe prevaccination HI titer data from our substudy are most appropriate for determining age groupings for the requested exploratory analysis. Prevaccination serologic results indicate that by 4 years of age 100% of children in our study population had evidence of prior A/H1N1 or A/H3N2 exposure, as defined by an HI titer ≥1:10. Based on this, we reanalyzed total VE against H1N1pdm09 using identical statistical methods [2], dichotomizing age as <4 years or ≥4 years.

In our original per protocol analyses, we found consistently negative, albeit nonsignificant, total VE for 2008–2009 IIV3 against illness caused by A/H1N1pdm09. In this requested post hoc analysis, we demonstrate among children aged 4 through 10 years a highly negative total VE for which the 95% confidence interval excludes zero (Table 1). Although this result comes from a well-controlled, blinded, randomized trial, readers should take caution in interpreting these results, as we cannot exclude that some undetermined bias might be operating in this cluster-randomized trial with 20 villages. While similar to findings in Canada and elsewhere during the 2009 pandemic, described by Skowronski and De Serres, we also cannot determine

Table 1. Total Vaccine Effectiveness of Trivalent Inactivated Influenza Vaccine in Preventing Laboratory-confirmed Symptomatic 2009 Pandemic Influenza A (A/H1N1pdm09) by Revised Age Groupings

	Trivalent Inactivated Influenza Vaccine Villages			Inactivated Poliovirus Vaccine Villages			
Age Group	Cases (n)	N	Cumulative Incidence[a]	Cases (n)	N	Cumulative Incidence[a]	Per Protocol Adjusted Total Vaccine Effectiveness,[b] % (95% Confidence Interval)
6 months–47 months	64	1398	4.58	45	1381	3.26	−40.2 (−154.5 to 22.7)
4 years–10 years	134	2329	5.75	64	2329	2.75	−80.7 (−204.2 to −7.4)

Abbreviations: n, number of cases; N, number of children followed.

[a]Per 100 persons through the entire surveillance period (15 July 2009 through 28 May 2010).

[b]Estimated using a logistic regression model fit using generalized estimating equations, assuming an exchangeable correlation matrix to account for within-village correlation of participant observations.