Commentary: Quantifying the Impact of Maternal Influenza Vaccination—Beyond Laboratory-Confirmed Efficacy

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In many high-income countries, pregnant women have long been prioritized to receive influenza vaccine, based on expected benefits to the woman and the infant. In a global evaluation based on data collected in 2014, the World Health Organization reported that 75% of high-income countries had influenza vaccine policies that targeted pregnant women. Unfortunately, most low- and middle-income countries do not use influenza vaccine. In that same World Health Organization survey, of 49 low- and middle-income countries eligible for Gavi support, only 4 (8%) had any influenza vaccine policy and only 2 (4%) targeted pregnant women.[1]

A number of factors influence vaccine policy and uptake, including demonstrated disease burden and vaccine impact, financing mechanisms and logistic considerations. Particularly for low-income countries, with competing health priorities, demonstration of impact of the vaccine on severe disease is critical. Unfortunately, few definitive data exist for the vaccine-preventable burden of severe influenza illness in low-resource settings. Demonstrating such burden for influenza can be particularly challenging, given that influenza has substantial variability from season to season, and that most prospective studies are not conducted over multiple seasons or sufficiently powered for less common, more severe outcomes. Further, influenza diagnostics are not routinely used in low-resource settings. Even when diagnostics are employed, severe respiratory disease may occur as a consequence of earlier influenza infection and thus influenza virus may not be detectable at the time the severe illness occurs.[2]

Vaccine probe studies are an alternative way to establish disease burden.[2,3] The premise is that differences in outcomes identified in a randomized controlled vaccine trial can be assumed to be due to the disease targeted by the vaccine, even in the absence of a laboratory confirmation of the outcome. Probe studies have been instrumental in establishing the burden of all-cause pneumonia and deaths due to *Streptococcus pneumonia* and *Haemophilus influenzae* type b, and the burden of severe gastroenteritis attributable to rotavirus.[3,4] Such studies have influenced policy and financing decisions for those vaccines.

From 2011 to 2014, 3 randomized trials of maternal influenza vaccine were conducted in South Africa, Mali and Nepal. These landmark studies represented a major investment to understand the potential benefits of maternal influenza vaccine in preventing maternal and infant disease. While the prestated primary and secondary outcomes differed among the trials, in general the trials were powered to detect laboratory-confirmed influenza of any severity. Vaccine was well tolerated in all 3 studies, and all studies reported significant efficacy against laboratory-confirmed disease in mothers and infants, although results differed by setting and season.[5–7]

A study in this issue of the *Pediatric Infectious Disease Journal* reports on a pooled analysis of those 3 randomized controlled trials to determine the effect of maternal influenza vaccine on severe clinical pneumonia of any etiology in the infants.[8] Severe pneumonia was defined as hospitalization for any lower respiratory disease in South Africa and by Integrated Management of Childhood Illness criteria in Nepal and Mali. Overall, the authors report an adjusted incidence of 87.7 and 70.7 cases of severe pneumonia per 1000 infant-years, respectively, in maternal control and influenza vaccine groups for an overall efficacy of 31.3%. Efficacy estimates were greater during times of influenza circulation when compared with no circulation. In analyses by site, vaccine efficacy estimates in Nepal and South Africa were similar to the overall pooled estimate, while no effect of maternal influenza vaccination on infant pneumonia was demonstrated in the Mali site.

The inherent variability of influenza complicates execution and interpretation of clinical vaccine trials. This is true for this pooled evaluation as well. During the period of the trial, the sites had variability in influenza circulation (different circulating strains, different timing of peak season in relation to when vaccine was given), population (gestational age at receipt of vaccine, sociodemographic characteristics) and vaccine used (different formulations, different degree of "match" and different comparator vaccines). The trial size and multiyear design were strengths, but do not completely overcome these limitations. In addition, other differences in study design, including the definition of severe pneumonia, add to the heterogeneity of the data and cloud interpretation of the results. Unadjusted incidence rates are not provided and would be helpful in assessing the generalizability to other settings and comparability to other studies.

In spite of these challenges, these large randomized controlled trials provide a rich dataset that should be further explored. For example, Tapia et al[6] in Mali demonstrated that maternal influenza immunization provided protection that corresponded with infant age and level of maternal antibody. Protection was highest in the first 2 months of life. Thereafter, as influenza antibody titers diminished, efficacy decreased, until it was no longer evident at month 6 of follow-up. One would expect any vaccine protection against severe pneumonia to follow a similar pattern—with potentially a delay for pneumonia if the upper respiratory infection leads to subsequent lower respiratory viral or bacterial disease. Either way, looking at the magnitude of the effect by age of the infant would enhance the biologic plausibility for this finding.

Nunes et al[9] did evaluate the effect of maternal vaccination on infant lower respiratory tract disease in a single-site analysis from the South Africa trial. In that study, the incidence of hospitalizations for acute lower respiratory infection was lower in infants born to influenza vaccine recipients (3.4/1000 infant-months) compared with placebo recipients (6.0/1000 infant-months) with a vaccine efficacy of 43.1% ($P = 0.050$). The full effect of maternal vaccination was seen in the first 90 days of life; the incidence of acute lower respiratory hospitalizations was similar for infants >3 months of age. These findings are highly supportive of an effect of maternal vaccination on infant lower respiratory tract disease, even in the absence of laboratory confirmation.

Only 4 randomized controlled efficacy trials of influenza vaccine in pregnant women have been conducted—all 4 have been conducted in Africa and Southeast Asia and funded by the Bill and Melinda Gates Foundation.[5–7,10] This is a remarkable public health effort that has generated much needed data to inform policy and financing decisions in low-resource countries. Influenza vaccines given to pregnant women are safe, well tolerated and immunogenic and prevent laboratory-confirmed disease in mothers and infants.

Importantly, there is a growing body of evidence supporting the impact of these vaccines on other important public health outcomes, including lower respiratory tract disease in infants. In addition to the direct health benefits of influenza vaccine, additional benefits of maternal immunization programs include strengthening antenatal vaccine delivery in preparation for other vaccines (eg, respiratory syncytial virus) and improving country pandemic preparedness efforts.[11] These data are timely and critical to inform upcoming global investment decisions on maternal influenza immunization.

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