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Commentary

Maternal Influenza Immunization and Adverse Birth Outcomes: Using Data and Practice to Inform Theory and Research Design

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Maternal influenza immunization can reduce influenza-attributable morbidity and mortality among pregnant women and infants who are too young to be vaccinated. Data from empirical studies also support the hypothesis that immunization can protect the fetus against adverse outcomes if the mother is exposed to influenza. In their theoretical analysis in the *Journal*, Hutcheon et al. (*Am J Epidemiol*. 2016;184(3):227–232) critiqued the existing evidence of the fetal benefits of maternal influenza immunization by calculating the sample sizes needed to demonstrate hypothetical reductions in risk and concluded that the benefits observed in empirical studies are likely implausible. However, in their analysis, they did not take into account multiple fundamental characteristics of influenza epidemiology, including the time-variable effects of influenza illness and vaccination during pregnancy, or well-known differences in disease epidemiology between seasons, populations, and geographic regions. Although these and other factors might affect the magnitude of fetal benefit conferred by maternal influenza immunization, studies in which investigators have accounted for influenza circulation have demonstrated a consistent protective effect against a variety of adverse birth outcomes; those studies include the only randomized controlled trial designed a priori and adequately powered to do so. Only a comprehensive and nuanced assessment of the evidence base will allow for effective translation of these data into a global immunization policy.

birth outcome; birthweight; influenza; maternal immunization; pregnancy; preterm birth

Abbreviations: CI, confidence interval; RCT, randomized controlled trial.

Editor's note: *A response to this commentary appears on page 793.*

In their theoretical analysis, Hutcheon et al. (1) comment on the plausibility of the fetal benefits of maternal influenza immunization that have been observed in empirical studies by computing hypothetical risk ratios and the corresponding sample sizes needed to demonstrate these differences in risk. Unfortunately, their conclusions stand in stark contrast to biological evidence and data from the preponderance of published studies (2), including several well-designed randomized controlled trials (RCTs). We have multiple specific concerns about their conceptual piece, because critical issues relevant to influenza epidemiology have been overlooked.

First, influenza illness and vaccination are time-variable exposures. Their impact on adverse birth outcomes depends upon the time period of influenza circulation relative to the stage of pregnancy. Any analysis—theoretical or empirical—that fails to account for the timing and duration of potential influenza exposure (i.e., length of the influenza season and intensity of influenza circulation) is incomplete. Empirical studies with analyses of birth outcomes stratified by period of influenza circulation have yielded remarkably consistent findings despite differing settings (3–6). In these studies, the most extreme risk ratios associated with maternal vaccination applied only during the periods of highest influenza circulation,

which are typically only 2–8 weeks in duration. It is incorrect to draw conclusions about plausibility by comparing the magnitude of effect for this limited time period with that of other nonseasonal factors (e.g., maternal smoking). In fact, when the impact of maternal influenza immunization is assessed over the entire period of influenza circulation, the effect size is unsurprisingly much smaller. Assuming that the risk ratio observed during that at-risk period applies equally to all individuals over the entire study period leads to erroneous conclusions about the population-level impact of maternal immunization.

Similarly, the effect of maternal influenza illness or vaccination on birth outcomes will vary depending on the gestational age at the time of exposure, which introduces the potential for immortal time bias (7). This bias may lead to misleading estimates of the magnitude of effect of maternal influenza immunization on time-varying outcomes. For example, in a recent analysis of the impact of maternal influenza immunization on the risk of preterm or small for gestational age birth in a US cohort, Vazquez-Benitez et al. (8) found a protective effect of maternal vaccination against both outcomes when using an "any time during pregnancy" approach to classifying vaccine exposure status. After adjustment for time-dependent vaccine exposure during pregnancy (as well as some other potential confounders, including vaccine availability and baseline covariates), the magnitude and precision of this effect decreased for preterm birth, though the overall direction remained the same. Moreover, adjustment for time-dependent vaccine exposure had no effect on the risk ratio estimates for small-for-gestational-age birth (8).

Second, Hutcheon et al. (1) did not take into account factors well known to influence influenza disease epidemiology, such as variability in viral pathogenicity within and between seasons and populations. These differences might be particularly pronounced when comparing findings between geographic regions because climate, socioeconomic and nutritional status, and the baseline risk of adverse outcomes may all influence disease epidemiology. For their sample size calculations, Hutcheon et al. used published estimates of influenza incidence and preterm birth rates (see Web Table 1 of their article), as well as measures of the association between maternal influenza illness and preterm birth calculated from previous observational studies (9). These estimates were derived almost entirely from studies conducted in temperate climates (predominantly the United States and Canada) with relatively short influenza seasons and low baseline rates of adverse birth outcomes. It is inappropriate to use these same assumptions to evaluate the plausibility of findings from low-income countries in the tropics (e.g., Bangladesh and Nepal), which have longer influenza seasons (more months of circulation with multiple peaks (10–12)) and significantly higher baseline rates of adverse birth outcomes, including not only preterm birth (13) but also small-for-gestational-age birth (when defined according to an appropriate referent) (14) and low birthweight (15).

Furthermore, there will always be variability in the magnitude of the observed benefit of maternal immunization on adverse birth outcomes between seasons. For example, in 2 separate studies of the effect of maternal influenza immunization on preterm or small-for-gestational-age birth in Georgia, overlapping groups of investigators used the same source of statewide surveillance data and determined odds ratios of varying magnitude in different surveillance periods (3, 5). These differences should be understood to reflect not only the influence of remaining confounding factors but also, more importantly, heterogeneity in the effect of the influenza vaccine. Indeed, heterogeneity in influenza vaccine efficacy/effectiveness is not limited to studies of maternal influenza immunization (16), and it may be attributable to vaccine, viral, and population factors. Moreover, it does not imply that the protective effect observed in some studies is spurious; in fact, it would be far more surprising to find that maternal influenza immunization exerted a protective effect of consistent magnitude across multiple seasons and between different populations.

Third, Hutcheon et al. also concluded that the observed fetal benefits of maternal influenza immunization are biologically implausible, and they supported this claim with a forthcoming (unpublished) systematic review in which minimal support for a strong association between maternal influenza illness and adverse birth outcomes was found (9). We disagree; not only is biological plausibility among the least important of the classic Bradford Hill criteria for assessing causality (17), but the conclusion reached by Hutcheon et al. ignores compelling empirical evidence to the contrary. There is in fact substantial evidence supporting the important role of infection and systemic inflammation in the causal pathway of preterm birth (18). Indeed, the authors of a recent systematic review of studies of the association between maternal influenza and birth outcomes (including several co-authors of the paper by Hutcheon et al.) reported adjusted odds ratios for preterm birth of 2.4 and 4.0 in 2 studies of severe 2009 H1N1 influenza during pregnancy; these studies were deemed in that analysis to be of the "highest methodological quality" (9). Furthermore, the results of multiple well-designed studies, including publicly available data from recent RCTs, have been excluded from their analysis, ostensibly because they are implausible on purely hypothetical grounds.

For example, in 2 independently conducted RCTs of maternal influenza immunization in Bangladesh and Nepal, influenza vaccination had a significant beneficial effect on birth outcomes (19, 20). In a secondary analysis of the RCT in Bangladesh, maternal influenza vaccination was associated with a 56% (95% confidence interval (CI): 1, 81) reduction in the odds of delivering a small-for-gestational-age infant, which translated to a difference of 193 g (95% CI: 9, 378) in mean birthweight during periods of influenza circulation (19). In the trial in Nepal, maternal influenza immunization was associated with a 15% reduction (95% CI: 3, 25) in infants with low birthweights, which translated to a difference of 43 g (95% CI: 9, 77) in mean birthweight between the influenza vaccine and control groups (20). Importantly, that study was the only RCT designed a priori with a (co-)primary outcome of low birthweight, and therefore the only trial powered to detect a difference in birthweight between the 2 groups. In addition to data from clinical trials, results from multiple recent observational studies have also demonstrated a consistent beneficial impact of maternal influenza immunization on a variety of fetal and infant outcomes (21–24).

Taken together, the available evidence supports the hypothesis that maternal influenza immunization can benefit the

fetus if the mother is exposed to influenza. Although multiple factors may influence the magnitude of this association—including residual confounding, heterogeneity in influenza vaccine effect, and baseline differences between study populations—studies in which investigators have accounted for influenza circulation have demonstrated a consistent protective effect against a variety of adverse birth outcomes, including the only RCT designed a priori with a (co-)primary birth outcome and thus adequately powered to do so. These data must be considered for translation into public health action globally.

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