American Journal of Epidemiology

Vol. 184, No. 11
DOI: 10.1093/aje/kww111
Advance Access publication:
October 26, 2016

Response to Commentary

Hutcheon et al. Respond to "Maternal Influenza Immunization and Birth Outcomes"

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Initially submitted September 2, 2016; accepted for publication September 13, 2016.

We appreciate the opportunity to address the concerns of Phadke et al. (1) regarding our recent article (2). First, we agree that accounting for the time-dependent nature of influenza illness, immunization, and pregnancy outcomes is critical for obtaining unbiased estimates of the association between maternal influenza immunization and fetal health (3). The rates of influenza attack, vaccine uptake, and vaccine effectiveness used in our analysis were based on rates estimated during influenza season, not rates averaged across the calendar year. By design, our results therefore specifically apply to the limited time window of possible benefit from maternal influenza immunization.

Second, we accounted for seasonal and regional variability in influenza disease epidemiology by evaluating a broad range of plausible rates of influenza attack, vaccine effectiveness, and vaccine uptake. For example, the United States Centers for Disease Control and Prevention estimates influenza attack rates of 5%–20% (4), whereas attack rates in the control arms of randomized trials of pregnant women from South Africa (with and without human immunodeficiency virus) and Mali were 17.0%, 3.6%, and <3%, respectively (5, 6). Our scenarios included an influenza attack rate as high as 40%. Likewise, the preterm birth rate in our primary analysis was the overall global estimate from a recent *Lancet* analysis (7), and our sensitivity analysis used a rate higher than the upper 95% confidence limit for the global region with the highest preterm birth rate (southeastern Asia, with an upper limit of 18.6% vs. 20% in our analysis).

We agree that biological pathways linking influenza illness, immunization, and adverse fetal outcomes are plausible. However, our concerns with respect to plausibility refer to the plausible *magnitude* of the observed associations in comparisons of vaccinated and unvaccinated women. Our key finding was that even during influenza season, rates of influenza attack, vaccine uptake, and vaccine effectiveness are all relatively low; therefore, only a small fraction of pregnant women have their influenza illness status altered by vaccination. When the causal effect of the intervention is experienced in only a small minority of pregnant women, any effects need to be extremely large to be detected in overall comparisons of vaccinated and unvaccinated women. Even under the more extreme scenarios covered by our simulations, effects remained difficult to detect. This does not imply that biological associations cannot exist, only that it is highly unlikely that they could be detected using standard epidemiologic research designs.

We agree that randomized trials offer the important strength of control for unmeasured confounding, but the same concerns about magnitude of plausible effects would apply. Moreover, data from the trial in Nepal remain unpublished, and the post-hoc analysis of births during the circulating influenza period in the Bangladesh trial had a total of only 6 preterm births (8). For these reasons, we did not emphasize those trials in our discussion; however, we did note that neither study found a significant effect of maternal vaccination on our study's outcome of preterm birth (9). Most recently, in the largest randomized trial of maternal influenza immunization published to date, Tapia et al. (6) found no significant differences in neonatal outcomes between study groups.

Finally, we disagree with the commentary authors' interpretation of the current literature on the fetal benefits of maternal influenza immunization. Citing an opinion article written by their group (10), Phadke et al. suggest that a protective effect of maternal influenza immunization on

fetal outcomes is supported by "data from the preponderance of published studies" (1, p. 789). However, this is not supported by the findings of 2 recent systematic reviews that found inconsistency in the evidence and concerns about bias and other methodological shortcomings (11, 12). Phadke et al. also claim that the study by Vazquez-Benitez showed that after controlling for biases, "adjustment for time-dependent vaccine exposure had no effect on the risk ratio estimates for small-for-gestation-age birth" (1, p. 790). That claim is not supported by the conclusions of the cited paper, however, in which the authors state that they "found a strong protective effect of vaccination on preterm birth (relative risk: 0.79; 95% [confidence interval]: 0.74, 0.85) when ignoring potential biases and no effect when accounting for them (relative risk: 0.91; 95% [confidence interval]: 0.83, 1.0)" (13, p. 176). Likewise, of the 4 studies used to support the claim that "[e]mpirical studies with analyses of birth outcomes stratified by period of influenza circulation have yielded remarkably consistent findings" (1, p. 789), 2 (from the same population) are highly prone to immortal time bias due to their use of a time-fixed exposure variable (immunization at any point in pregnancy (ever vs. never)) (14, 15), and the third reported null associations between maternal immunization and fetal outcomes (for preterm birth, adjusted hazard ratio = 1.03, 95% confidence interval: 0.84, 1.25; for fetal death, adjusted hazard ratio = 0.88, 95% confidence interval: 0.66, 1.17) (16). In the absence of consistent, high-quality evidence of fetal benefits from maternal influenza immunization and with practical constraints on the detection of such benefits, we believe that immunization policies should be based on the strong evidence that immunization protects both mothers and their infants against influenza illness (5, 6, 17).

ACKNOWLEDGMENTS

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J.A.H. is the recipient of New Investigator Awards from the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research. R.W.P. holds a Chercheur-National award from the Fonds de la Recherche du Québec - Santé.

J.R.O. works for the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the World Health Organization.

Conflicts of interest: none declared.

REFERENCES

1. Phadke VK, Steinhoff MC, Omer SB, et al. Maternal influenza immunization and adverse birth outcomes: using data and practice to inform theory and research design. *Am J Epidemiol*. 2016;184(11):789–792.
2. Hutcheon JA, Fell DB, Jackson ML, et al. Detectable risks in studies of the fetal benefits of maternal influenza vaccination. *Am J Epidemiol*. 2016;184(3):227–232.
3. Hutcheon JA, Savitz DA. Invited commentary: Influenza, influenza immunization, and pregnancy-it's about time. *Am J Epidemiol*. 2016;184(3):187–191.
4. Centers for Disease Control and Prevention. Seasonal Influenza Questions & Answers. Atlanta GA: Centers for Disease Control and Prevention; 2015. http://www.cdc.gov/flu/about/qa/disease.htm. Accessed November 1, 2015.
5. Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med*. 2014;371(10):918–931.
6. Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. *Lancet Infect Dis*. 2016;16(9):1026–1035.
7. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet*. 2012;379(9832):2162–2172.
8. Steinhoff MC, Omer SB, Roy E, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. *CMAJ*. 2012;184(6):645–653.
9. Steinhoff MC, Tielsch J, Katz J, et al. Evaluation of year-round maternal influenza immunization in sub-tropical SE Asia: placebo-controlled randomized trial. Presented at ID Week 2015, San Diego, California, October 7–11, 2015.
10. Phadke VK, Omer SB. Maternal vaccination for the prevention of influenza: current status and hopes for the future. *Expert Rev Vaccines*. 2016:15(10):1255–1280.
11. McMillan M, Porritt K, Kralik D, et al. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. *Vaccine*. 2015;33(18):2108–2117.
12. Fell DB, Platt RW, Lanes A, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. *BJOG*. 2015;122(1):17–26.
13. Vazquez-Benitez G, Kharbanda EO, Naleway AL, et al. Risk of preterm birth or small for gestational age after influenza vaccination during pregnancy: caveats when conducting retrospective observational studies. *Am J Epidemiol*. 2016; 184(3):176–186.
14. Adedinsewo DA, Noory L, Bednarczyk RA, et al. Impact of maternal characteristics on the effect of maternal influenza vaccination on fetal outcomes. *Vaccine*. 2013;31(49): 5827–5833.

15. Omer SB, Goodman D, Steinhoff MC, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. *PLoS Med*. 2011;8(5): e1000441.
16. Håberg SE, Trogstad L, Gunnes N, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. *N Engl J Med*. 2013;368(4):333–340.
17. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008;359(15):1555–1564.