3. Kharbanda EO, Vazquez-Benitez G, Lipkind H, et al. Inactivated influenza vaccine during pregnancy and risks for adverse obstetric events. *Obstet Gynecol*. 2013;122(3):659–667.
4. Vazquez-Benitez G, Kharbanda EO, Naleway AL, et al. Risk of preterm or small-for-gestational-age birth after influenza vaccination during pregnancy: caveats when conducting retrospective observational studies. *Am J Epidemiol*. 2016;184(3):176–186.
5. Savitz DA, Fell DB, Ortiz JR, et al. Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs. *Vaccine*. 2015;33(47):6430–6435.

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THE AUTHORS REPLY

In their letter (1), Drs. De Serres and Skowronski focused on the assessment of adverse fetal outcomes as a safety issue associated with maternal influenza immunization. In contrast, our study (2) dealt primarily with reductions in adverse fetal outcomes as a benefit of influenza immunization. We emphasized that the sample sizes presented in our study were intended only to inform the interpretation of studies in which fetal benefits of maternal influenza immunization were examined. In studies of immunization safety, all vaccinated women are at risk of experiencing an adverse outcome due to immunization (assuming the vaccine is received in a gestational-age window of fetal vulnerability to the adverse outcome). In contrast, only the small fraction of vaccinated women whose influenza illness is averted by immunization can experience a protective effect of vaccination on fetal outcomes (assuming that the fetal benefits of immunization occur by prevention of influenza illness) (3). Thus, for a given effect size, the overall sample sizes required to demonstrate fetal benefit will be considerably larger those required to identify adverse events after immunization.

Further, the approach we used to calculate sample size requirements for studies of fetal benefit may not be the best choice for studies of immunization safety. In studies of fetal safety, the goal is to demonstrate that risks in the vaccinated cohort are not meaningfully higher than risks in the unvaccinated cohort. As a result, our approach for calculating sample sizes based on testing the superiority of an intervention (vs. no intervention) is less relevant: Failure to detect a significant difference in risk between groups and retaining the null hypothesis of no difference does not "prove" that no true difference exists. Instead, in studies designed to evaluate the safety of maternal influenza immunization, investigators should determine sample size requirements using the methods used in noninferiority clinical trials, which are randomized trials meant to demonstrate that a new intervention (usually one with other desirable characteristics, such as lower cost or reduced side effects) is at least as effective as the standard intervention (i.e., is not associated with meaningfully increased risks of adverse outcomes) (4). In noninferiority trials, a noninferiority margin that reflects the point at which risks associated with a new intervention can no longer be considered clinically equivalent to the risks associated with the standard intervention is elicited from patients, clinicians, or policy makers. Sample sizes are derived to ensure that the upper limit of the 95% confidence interval for the difference between groups is below the prespecified noninferiority margin (4). Studies that elicit noninferiority margins from pregnant women and their care providers on the degree of acceptable risks associated with influenza immunization, as well as determination of the associated sample sizes required to demonstrate "noninferiority" (i.e., no unacceptable increase in risk), would be valuable to inform the evidence base of maternal influenza immunization safety.

Nevertheless, Drs. De Serres and Skowronski's point that it is challenging to conclusively demonstrate the safety of immunization is well taken. In our article, we carefully qualified the statement that maternal influenza immunization "causes no apparent harm to the developing fetus" (2, p. 227). Adverse events in the South African randomized clinical trial of maternal influenza immunization were balanced between the vaccine and placebo groups (5), and the World Health Organization Global Advisory Committee on Vaccine Safety has reviewed maternal influenza immunization and concluded that the "evidence currently available for the vaccines reviewed are reassuring about the absence or very low risk related to their administration during pregnancy" (6, p. 7062). We cannot conclude the absence of any risk given the limitations of epidemiologic study design, as is nicely discussed in the letter by De Serres and Skowronski.

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References

1. De Serres G, Skowronski DM. RE: "Detectable risks in studies of the fetal benefits of maternal influenza vaccination" letter. *Am J Epidemiol*. 2017;185(9):860–861.
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. Savitz DA, Fell DB, Ortiz JR, et al. Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs. *Vaccine*. 2015;33(47): 6430–6435.
4. Julious SA, Owen RJ. A comparison of methods for sample size estimation for non-inferiority studies with binary outcomes. *Stat Methods Med Res*. 2011;20(6) 595–612.
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. Keller-Stanislawski B, Englund JA, Kang G, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. *Vaccine*. 2014;32(52):7057–7064.

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