

The Safety of Maternal Influenza Vaccination and Infant Health Outcomes

Flor M. Munoz, MD,^a Sarah S. Long, MD^b

Influenza vaccination during pregnancy has been recommended for more than 70 years in the United States because of the high risk of complications resulting in hospitalization and mortality in pregnant women who acquire seasonal or pandemic influenza infection, particularly in the third trimester of pregnancy and during the postpartum period.^{1,2} Concerns regarding the safety of maternal immunization continue to be an important barrier to wide implementation and high rates of coverage for vaccines currently recommended for pregnant women, including influenza and pertussis vaccines.³

In this issue of *Pediatrics*, Foo et al⁴ report on their evaluation of potential adverse effects on long-term health outcomes for infants who were exposed to maternal influenza vaccination while in utero. Many studies conducted before, during, and after the 2009 influenza A (H1N1) pandemic consistently have shown that the administration of inactivated influenza vaccines during pregnancy is safe for the mother and is not associated with an increased risk of fetal or neonatal adverse outcomes such as stillbirth, preterm birth, low birth weight, or congenital anomalies.^{5,6}

The potential long-term effects of fetal exposure to maternal vaccines are not often evaluated, as evidenced by the small number of publications that met criteria for review in the current systematic review and which precluded a formal meta-analysis. The paucity of

studies does not indicate a lack of concern. In a prospective study conducted >60 years ago, Heinonen et al^{7,8} evaluated 50 000 women with various exposures during pregnancy, including to live and inactivated polio vaccines, inactivated influenza vaccines, and tetanus and diphtheria toxoid vaccines, closely following their children for 7 years for malformations, hearing impairment, and the development of learning disabilities and malignancies. Immunization of women during pregnancy was not associated with an increased risk of any adverse long-term health outcome in the children studied.

The study design and methods in Foo et al's systematic review⁴ are solid. A systematic review of the literature was conducted to include all studies evaluating health outcomes of infants 6 months of age and older after maternal influenza vaccination. Studies were identified through various search engines and scientific databases by using a comprehensive list of keywords. Exposure to both seasonal and pandemic influenza vaccines at different trimesters of gestation was considered, data were carefully extracted from selected comparative observational or randomized controlled studies, and risk of bias was assessed. Pooled effect estimates for each of the numerous outcomes reported in the studies were generated by conducting an a priori random effects meta-analysis, and potential confounders, particularly those related to maternal

^aSection of Infectious Diseases, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas; and ^bDepartment of Pediatrics, College of Medicine, Drexel University, Philadelphia, Pennsylvania

Opinions expressed in these commentaries are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

DOI: <https://doi.org/10.1542/peds.2020-006916>

Accepted for publication May 27, 2020

Address correspondence to Flor M. Munoz, MD, Baylor College of Medicine and Texas Children's Hospital, 1102 Bates Ave, Suite 1150, Houston, TX 77030. E-mail: florm@bcm.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2020 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships to disclose that are relevant to this article.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2020-0375.

To cite: Munoz FM and Long SS. The Safety of Maternal Influenza Vaccination and Infant Health Outcomes. *Pediatrics*. 2020;146(2):e2020006916

health and pregnancy characteristics, were addressed.

Unfortunately, all the studies that met inclusion criteria originated from North America or Europe, with no data from low- and middle-income countries. This finding highlights the need for a more representative evaluation of both the implementation and the safety of maternal influenza vaccination globally, particularly in low- and middle-income countries.⁹ In most studies, authors evaluated exposure to the 2009 influenza A (H1N1) pandemic vaccine, including adjuvanted and nonadjuvanted vaccines, demonstrating missed opportunities for the assessment of safety of seasonal vaccines. However, in the largest study in Foo et al's systematic review,⁴ the authors prospectively evaluated >45 000 pregnant women who received a seasonal influenza vaccine and followed their children through 15 years of age.¹⁰ Otherwise, the period of follow-up of exposed children was 1 to 5 years in most studies. Similar to Heinonen et al's^{7,8} assessment, the outcomes evaluated in this systematic review were varied, ranging from common infections and atopy to more complex outcomes categorized as autoimmune or neurodevelopmental conditions, malignancy, and all-cause morbidity and mortality. Several of these chronic conditions, including autism spectrum disorder, are important outcomes to address in the context of maternal immunization given potential concerns among providers and parents.¹¹

The robust results of Foo et al's study,⁴ indicating that influenza vaccination during pregnancy is not associated with various long-term adverse health outcomes in infants and young children, including no effects on all-cause morbidity and mortality, support current global recommendations to immunize women against influenza during

pregnancy.^{1-3,12} Although the evidence provided on the potential long-term effects on infant health outcomes after maternal influenza vaccination is limited by the small number of studies and lacks geographic generalizability, the known benefits of maternal influenza vaccination for the mother and for the infant are unequivocal.^{13,14} Taken together, these findings should lead providers to offer influenza vaccines to pregnant women confidently, factually, and in a manner that presumes rather than queries their acceptance of the recommendation. This can also be reassuring to expectant mothers interested in influenza vaccination.

Meanwhile, the assessment of the safety of maternal vaccination must continue through well-conducted prospective studies and the use of efficient surveillance systems. Safety surveillance must be strengthened given the need to evaluate health outcomes in mothers and their infants in a time of active vaccine development targeting pregnant women, as well as of health uncertainties and disparities potentiated by the severe acute respiratory syndrome coronavirus 2 pandemic in 2020.^{9,15-17} Foo et al⁴ have astutely delineated the knowledge gaps that need to be addressed in future studies. They have also provided important methodologic suggestions to help design the epidemiological studies needed to evaluate the safety of maternal influenza vaccination during pregnancy in relation to relevant short- and long-term childhood health outcomes.

REFERENCES

1. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices -

- United States, 2019-20 influenza season. *MMWR Recomm Rep*. 2019;68(3):1-21
2. Committee on Obstetric Practice. ACOG Committee Opinion No. 732: influenza vaccination during pregnancy. *Obstet Gynecol*. 2018;131:e109-e114
3. Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group. ACOG Committee Opinion No. 741: maternal immunization. *Obstet Gynecol*. 2018;131:e214-e217
4. Foo DYP, Sarna M, Pereira G, Moore HC, Fell DB, Reġan AK. Early childhood health outcomes following in utero exposure to influenza vaccines: a systematic review. *Pediatrics*. 2019; 146(2):e20200375
5. 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
6. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. *Hum Vaccin Immunother*. 2019;15(3):687-699
7. Heinonen OP, Slone D, Shapiro S. Immunizing Agents. In: Kaufman DW, ed. *Birth Defects and Drugs in Pregnancy*. Littleton, MA: Publishing Sciences Group; 1977:314-321
8. Heinonen OP, Shapiro S, Monson RR, Hartz SC, Rosenberg L, Slone D. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol*. 1973;2(3):229-235
9. Sobanjo-Ter Meulen A, Liljestrand J, Lawn JE, et al. Preparing to introduce new maternal immunizations in low- and lower-middle-income countries: a report from the Bill & Melinda Gates Foundation convening "Allies in Maternal and Newborn Care; May 3-4, 2018. *Vaccine* 2020;38(28):4355-4361
10. Zerbo O, Qian Y, Yoshida C, Fireman BH, Klein NP, Croen LA. Association between influenza infection and vaccination during pregnancy and risk of autism spectrum disorder. *JAMA Pediatr*. 2017; 171(1):e163609
11. Wilcox CR, Calvert A, Metz J, et al. Determinants of influenza and pertussis vaccination uptake in pregnancy: a multicenter questionnaire

- study of pregnant women and healthcare professionals. *Pediatr Infect Dis J*. 2019;38(6):625–630
12. World Health Organization. Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec*. 2012;87(47):461–476
13. Fell DB, Azziz-Baumgartner E, Baker MG, et al; WHO Taskforce to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling. Influenza epidemiology and immunization during pregnancy: final report of a World Health Organization working group. *Vaccine*. 2017;35(43):5738–5750
14. Jarvis JR, Dorey RB, Warricker FDM, Alwan NA, Jones CE. The effectiveness of influenza vaccination in pregnancy in relation to child health outcomes: systematic review and meta-analysis. *Vaccine*. 2020;38(7):1601–1613
15. Berrueta M, Bardach A, Ciaponni A, et al. Maternal and neonatal data collection systems in low- and middle-income countries: scoping review protocol. *Gates Open Res*. 2020;4:18
16. Buekens P, Alger J, Breart G, Cafferata ML, Harville E, Tomasso G. A call for action for COVID-19 surveillance and research during pregnancy [published online ahead of print April 22, 2020]. *Lancet Glob Health*. doi:10.1016/S2214-109X(20)30206-0
17. Engmann C, Fleming JA, Khan S, et al. Closer and closer? Maternal immunization: current promise, future horizons. *J Perinatol*. 2020;40(6):844–857