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Realizing the Potential of Maternal Influenza Vaccination

Eduardo Azziz-Baumgartner, MD, MPH,

Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Public Health Service Commissioned Corps, Rockville, Maryland.

Lisa Grohskopf, MD, MPH,

Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Public Health Service Commissioned Corps, Rockville, Maryland.

Manish Patel, MD

Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Public Health Service Commissioned Corps, Rockville, Maryland.

Influenza viruses cause substantial morbidity and mortality in pregnant women and neonates worldwide annually, with higher incidence during pandemics.^{1,2} To reduce disease incidence in these vulnerable populations, the World Health Organization recommended in 2012 that countries prioritize pregnant women for influenza vaccination.² Over 2 decades, compelling evidence has accumulated about the complex interplay among risks of influenza virus infection to the mother, the fetus, and the offspring, vs the benefits and safety of vaccination.^{1–4}

Physiologic changes during pregnancy increase the risk for influenza complications in pregnant women. Severe complications after infection can occur throughout gestation, but risk is greatest during the third trimester. In an individual participant data meta-analysis including 27 699 participants from 9 studies, risk of hospitalization in pregnant women with influenza was substantially higher than in nonpregnant women (adjusted odds ratio, 6.8 [95% CI, 6.0–7.7]).⁵ Pregnant women with comorbidities, including underlying cardiac conditions, chronic respiratory diseases, and obesity, are at even greater risk of hospitalization from influenza.

Maternal infection and complications can also affect the pregnancy, possibly resulting in fetal demise or preterm birth.^{1,6} Fetal development might be adversely affected by maternal infection, with effects varying by gestation period. In a retrospective cohort study of more

Corresponding Author: Manish Patel, MD, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop H24-7, Atlanta, GA 30333 (aul3@cdc.gov).

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than 27 000 women, self-reported symptoms of cold or flu with fever during pregnancy was associated with increased risk of several congenital abnormalities when compared with no symptoms of cold or flu, whereas no association was found among women with cold or flu without fever.⁷ The concern is that these adverse effects might be related to maternal fever (a common occurrence with influenza virus infection) during early gestation or maternal immune activation after infection resulting in systemic inflammation and imbalances in cytokines.^{8,9} During the first few months of life, neonates are at increased risk of severe influenza because of factors such as waning levels of maternally derived antibodies, underdeveloped immune systems, lack of antibodies from prior infections, and ongoing alveolarization and changing lung physiology.¹⁰ In turn, adverse effects of infection on mother and offspring might have commensurate psychological, social, and economic implications for the family and society.

Maternal influenza vaccination can provide dual benefits, helping to prevent various complications in pregnant women and their fetuses. Maternal vaccination offers benefits to the infant through transplacental antibody transfer, which can protect infants during the high-risk first 6 months of life when they are not age-eligible for vaccination.^{2,4} These benefits of vaccination have been well documented, with studies showing immunogenicity in pregnant women, transplacental antibody transfer to the infant, and clinical efficacy and effectiveness against influenza-associated illness in mothers and infants. In a pooled analysis of 3 randomized trials involving 10 002 women, maternal influenza vaccination (with follow-up of infants up to 6 months) with an inactivated vaccine was associated with an efficacy of 50% in mothers (absolute rates of 18.0 vs 36.0 per 1000 person-years) and 35% in infants (absolute rates of 62.3 vs 95.4 per 1000 infant-years) against laboratory-confirmed influenza in Mali, Nepal, and South Africa.⁴ The clinical trials from Bangladesh and Nepal found that infants born to mothers vaccinated vs unvaccinated against influenza had higher mean birth weight and a reduced risk of low birth weight, but similar findings were not observed in South Africa and Mali.⁴

Against these documented benefits of vaccination, the potential risks of maternal vaccination require consideration. From the safety perspective, a systematic review and meta-analysis including 48 cohort studies, case-control studies, and randomized clinical trials did not identify any association between maternal influenza vaccination and adverse fetal outcomes including preterm birth, small for gestational age, congenital malformation, or fetal death.³ Concerns also exist that in utero exposures to infection might have long-term health consequences, possibly attributable to maternal immune activation during critical periods of development.⁸ These concerns might also cause hesitancy about maternal vaccination. While the evidence that maternal vaccination is not associated with adverse perinatal/neonatal outcomes is strong, data on longer-term potential adverse health outcomes are limited.

In this issue of *JAMA*, Mehrabadi and colleagues¹¹ report findings from a population-based retrospective cohort study from Nova Scotia, Canada, that evaluated the risks of a broad range of adverse health outcomes among offspring of mothers vaccinated with inactivated influenza vaccines vs those who were unvaccinated. This study included all live births (28 255 children) during 4 influenza seasons (October 2010-March 2014), with a mean duration of follow-up of 3.6 years. Investigators leveraged a large database from a publicly

funded universal health care system that linked nearly all live births with a broad range of prenatal risk factors, maternal vaccination, and outcomes. To address potential biases of observational studies from inherent imbalances in characteristics between vaccinated and unvaccinated pregnant mothers, the authors used inverse probability of treatment weighting to generate propensity scores using many covariates to achieve balance between vaccinated and unvaccinated pregnant women. This method helps to reduce bias related to confounding by indication. Among 28 255 children, 36% were born to mothers who received influenza vaccination during pregnancy. No statistically significant associations with any outcome (eg, childhood asthma, neoplasms, sensory impairment, all-cause infections, or increased health care utilization) were identified, including in a post hoc analysis stratifying by gestational period of vaccine receipt. The rates of adverse outcomes were similar between vaccinated and unvaccinated mothers.

The data supporting benefits and safety of maternal influenza vaccination during any gestational stage are now abundant.⁴ Global policies that recommend maternal influenza vaccination have been in place for a decade. Nevertheless, influenza vaccination coverage in high-income countries remains suboptimal. For example, vaccination coverage among pregnant women was only 61% in the US during the 2019–2020 influenza season¹² and 36% in Nova Scotia during the 2010–2014 study period.¹¹ Most countries in North, Central, and South America recommend maternal influenza vaccination, but usage falls short of global goals in part because of health care clinician perceptions about the safety, efficacy, and utility of influenza vaccine.¹³

More research is needed to understand barriers to adoption of maternal influenza vaccination.¹³ Among low- and middle-income countries that have yet to adopt maternal influenza vaccination programs or that struggle to sustain influenza vaccine supplies, vaccine cost can be substantial, and information about the cost-effectiveness of vaccination is limited.¹⁴ Influenza vaccines do have operational challenges of annual delivery because of the need for updates of the vaccine strains in response to evolving influenza viruses. However, this is less of a challenge for maternal influenza vaccination programs in which healthy women would only be vaccinated during each pregnancy and vaccination could be coupled with routine antenatal care. Furthermore, unlike other influenza vaccination risk groups such as children and older adults, pregnant women represent a small fraction of the target population and their vaccination protects both the mother and the unborn infant. Creative strategies are needed to implement sustainable influenza vaccination programs in low- and low–middle-income countries such as the Partnership for Influenza Vaccine Introduction, which uses donated influenza vaccines to initiate or expand national seasonal vaccination programs.¹⁵ Assessing the benefits of vaccination and widely sharing the lessons from regions with maternal influenza vaccination experience or demonstration projects could have far-reaching benefits for improving the health of mothers and infants worldwide.²

Pregnancy is a unique period for women who face potential complications of influenza infections that can have immediate effects during pregnancy and possibly long-term negative health consequences for the offspring. Acknowledging the safety concerns of mothers considering a parenteral injection during pregnancy with empathy is essential. Data on the benefits and safety, now including longer-term outcomes in offspring, are

compelling.^{3,4,11} In countries with vaccination programs, these data provide clinicians with evidence to address safety concerns, communicate benefit-risk balance, and provide a strong recommendation for pregnant women to get vaccinated against influenza. In countries without programs, donors and decision-makers can act to fund and implement vaccination programs that allow these crucial discussions to occur, providing access to safe and effective influenza vaccines to pregnant women worldwide.

The notable absence of the annual influenza epidemic during the 2020–2021 northern and southern hemisphere influenza seasons, the first such occurrence in a century, might have specific implications for infants in the 2021–2022 influenza seasons. Infants younger than 6 months rely on maternal antibodies for protection. A potential implication of markedly reduced influenza circulation and low incidence of infections is that pregnant women might not have antibodies that could protect their infants from increased risk of infection and severe illness during the next influenza epidemic.¹⁶ Efforts are needed now to encourage maternal influenza vaccination worldwide and to act on the compelling efficacy and safety data.

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