Ensuring the Safety of Maternal Immunization

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Over the past decade, the acceptance and implementation of maternal vaccination strategies has bourgeoned.[1] There are several reasons that immunizing pregnant women is an attractive vaccination strategy. First, by immunizing the pregnant woman, there is the potential to prevent the targeted infection in the woman and her infant. Second, there is a window of susceptibility in infants before the initiation of the primary infant immunization series. Maternal immunization can help bridge this window of susceptibility. Finally, pregnant women are often more adherent to medical care during their pregnancies than at other times in their lives, thus making vaccine administration more efficient.

However, although we have made significant progress in the implementation of maternal-immunization programs, the uptake of maternal immunization in the United States for influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) vaccine hovers between 50% and 70%.[2,3] When pregnant women are asked why they do not receive a vaccine, one of the more commonly reported reasons is concern about safety for the fetus and the long-term adverse risks to the infant.[2] Studies in which researchers provide data to reassure mothers about vaccine safety and the dissemination of that information to the public are important to dispel concerns and increase maternal vaccine uptake.

In this issue of *Pediatrics*, Laverty et al,[4] who are well-respected Canadian investigators, report on the long-term safety of the administration of Tdap to pregnant women. As outlined in this report, in several previous studies, researchers have assessed the immediate safety of Tdap in pregnant women and their infants, and some have followed the infant outcomes for the first 12 to 18 months of life. However, few have assessed the impact of the vaccine on long-term adverse events. In this report, the researchers seek to address those long-term adverse events using multiple linked province-wide health administrative databases in Ontario. All live births between April 2012 and March 2017 were followed for a maximum period of 6 years to determine the health outcomes. Children exposed to prenatal Tdap were propensity score matched to unexposed children in a ratio of 1:5. Numbers of infections, asthma episodes, neoplasms, sensory disorders, and medical care encounters were compared between the 2 groups. More than one-half of 1 million children were included in the database, but only 12 045 had been exposed to prenatal Tdap. There was no increase in any of the outcomes in the Tdap-exposed group, and, in fact, the Tdap-exposed group had fewer upper respiratory and gastrointestinal infections and reduced patient-care encounters. Thus, in the study, the researchers provided reassurance that exposure to Tdap vaccination was not associated with an increased risk of any of these adverse events in early childhood.

The study has many strengths, including the use of a comprehensive

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population-based health administrative database, ability to capture maternal immunizations often omitted from immunization registries, and use of propensity score methods to reduce bias.

The study also has several limitations. First, because Tdap implementation was not universally recommended in Canada until 2018, the number of infants exposed to Tdap vaccination comprised only ~2% of the birth cohort, making the sample size smaller than would be anticipated had the maternal vaccination strategy been implemented earlier. This limits the ability to assess for more uncommon adverse events. Propensity score matching was used to reduce bias, but biases may still exist, particularly if those mothers accepting vaccination in pregnancy may have been more receptive to disease prevention in general through the adaption of healthier lifestyles and routine vaccination for their infants. Additionally, it would have been helpful if neurologic events had also been captured in this database to assess long-term vaccination consequences. Such events had been evaluated in previous studies.[5,6]

Encouragingly, with greater numbers of pregnant women receiving Tdap in Canada since its universal recommendation, this database can and should be used in the future to assess long-term adverse events in the children whose mothers were immunized. It will be important that the definitions of the adverse events are standardized and are inclusive of the adverse events that are clinically important so that this and other large linked databases can be more extensively used to assess maternal-immunization safety. The Brighton Collaboration has been instrumental in standardizing the immediate adverse events associated with maternal immunization, but standardization of the long-term events would enhance the ability to assess maternal-immunization safety.[7]

As additional maternal immunizations are being tested for the prevention of important infections in young infants, such as respiratory syncytial virus and group B streptococcal infections, and we continue to strive for increased immunization rates for those maternal vaccines already recommended, it is imperative that we continue to meticulously assess the safety of maternal-immunization programs. This report marks an important step in that process.

ABBREVIATION

Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed

REFERENCES

1. Marchant A, Sadarangani M, Garand M, et al. Maternal immunisation: collaborating with mother nature. *Lancet Infect Dis*. 2017;17(7):e197–e208
2. Lindley MC, Kahn KE, Bardenheier BH, et al. Vital signs: burden and prevention of influenza and pertussis among pregnant women and infants — United States. *MMWR Morb Mortal Wkly Rep*. 2019;68(40):885–892
3. Razzaghi H, Kahn KE, Black CL, et al. Influenza and Tdap vaccination coverage among pregnant women - United States, April 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(39):1391–1397
4. Laverty M, Crowcroft N, Bolotin S, et al. Health outcomes in young children following pertussis vaccination during pregnancy. *Pediatrics*. 2021;147(5): e2020042507
5. Becerra-Culqui TA, Getahun D, Chiu V, Sy LS, Tseng HF. Prenatal tetanus, diphtheria, acellular pertussis vaccination and autism spectrum disorder. *Pediatrics*. 2018;142(3): e20180120
6. Becerra-Culqui TA, Getahun D, Chiu V, Sy LS, Tseng HF. The association of prenatal tetanus, diphtheria, and acellular pertussis (Tdap) vaccination with attention-deficit/hyperactivity disorder. *Am J Epidemiol*. 2020;189(10): 1163–1172
7. Munoz FM, Eckert LO, Katz MA, et al. Key terms for the assessment of the safety of vaccines in pregnancy: results of a global consultative process to initiate harmonization of adverse event definitions. *Vaccine*. 2015;33(47): 6441–6452

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