”Safety and Immunogenicity of Tetanus Diphtheria and Acellular Pertussis (Tdap) Immunization During Pregnancy in Mothers and Infants: A Randomized Clinical Trial” (2014), by Flor M. Munoz, Nanette H. Bond, Maurizio Maccato, Phillip Pinell, Hunter A. Hammill, Geeta K. Swamy, Emmanuel B. Walter, Lisa A. Jackson, Janet A. Englund, Morven S. Edwards, C. Mary Healy, Carey R. Petrie, Jennifer Ferreira, Johannes B. Goll, Carol J. Baker

In 2014, Flor M. Munoz and colleagues published ”Safety and Immunogenicity of Tetanus Diphtheria and Acellular Pertussis (Tdap) Immunization During Pregnancy in Mothers and Infants: A Randomized Clinical Trial,” hereafter ”Tdap Immunization During Pregnancy,” in the Journal of the American Medical Association. The authors conducted a study to determine how Tdap immunization affected the mother and infant’s immune response to the common childhood diseases tetanus, diphtheria, and pertussis. They found that Tdap immunization did not lead to an increased risk of adverse health events. Furthermore, maternal Tdap immunization provided the infant with protective levels of pertussis antibodies after delivery and did not affect the infant differently from the DTaP vaccination series, which is the version of Tdap for young children. The authors’ findings in ”Tdap Immunization During Pregnancy” supported the United States Centers for Disease Control and Prevention’s, or CDC’s, recommendation for pregnant women to receive the Tdap vaccine to prevent disease in mother and infant.

The Tdap and DTaP vaccines both protect against tetanus, diphtheria, and pertussis, commonly called whooping cough. However, adults receive Tdap, while children receive DTaP. The two vaccines contain the same antigens, or proteins from a specific disease that induce immunity, which is when antibody production protects the person against that disease. DTaP has higher concentrations of the antigens than Tdap because children need the vaccine to build immunity, while adults only need it to boost immunity. In pregnant people, antibodies can transfer to the fetus through the placenta and provide protection upon birth. The DTaP immunization schedule in children consists of five doses at two months, four months, six months, fifteen through eighteen months, and four through six years. According to the CDC, adolescents and adults should receive one dose of Tdap every ten years. Scientists evaluate vaccine efficacy by measuring immunogenicity, which is a person’s ability to activate an immune response and produce antibodies when exposed to a disease.

Munoz, Bond, Maccato, Pinell, and Baker worked at Baylor College of Medicine in Houston, Texas, at the time of publication. Other authors were affiliated with Duke University School of Medicine in Durham, North Carolina, and research institutes in Seattle, Washington, and Rockville, Maryland. Munoz was an Associate Professor of Pediatrics and Infectious Diseases at Baylor College of Medicine and was primarily responsible for study design and supervision. Other authors contributed to data acquisition, statistical analysis, manuscript writing, and manuscript revision. Most of the authors reported potential conflicts of interest where they have acted as spokespeople, consultants, or grant recipients for companies that produce the vaccines used in the study.

”Tdap Immunization During Pregnancy” is a research article about a clinical trial conducted from 2008 to 2012 to assess the safety and immunogenicity of administering the Tdap vaccine during pregnancy. In the mid-1900s, Pearl Kendrick, a pertussis researcher, developed one of the first combination vaccines for tetanus, diphtheria, and pertussis. However, she found that the placental transfer of the mother’s antibodies to the fetus during pregnancy led to a weaker immune response in the infant when they later received the vaccine. When the authors of ”Tdap Immunization During Pregnancy” initiated their study in 2008, the effect of placental maternal antibody transfer on infant immunogenicity to the DTaP vaccine remained unclear. Researchers had also not extensively studied the safety of Tdap immunization during pregnancy. Thus, the article addresses the gap in knowledge about Tdap immunization during pregnancy and whether it should be recommended for pregnant people. Shortly after the conclusion of the study in early 2012, the CDC released its recommendation for all pregnant people to receive the Tdap vaccine for every pregnancy.

The article consists of five sections, including an unnamed introduction, ”Methods,” ”Results,” ”Discussion,” and ”Conclusions.” In the introduction, Munoz and colleagues describe the landscape of pertussis infections in infants in the US at the time, stating that antibodies they receive from their mother’s placenta can protect them. They also explain how the objective of the study was to determine whether Tdap immunization during pregnancy was safe and whether it affected infant immune responses to DTaP immunization. In ”Methods,” the authors detail the experimental design and define how they plan to assess safety and immunogenicity. They also explain the antibody tests and statistical techniques used to compare the groups of pregnant women who did or did not receive the Tdap vaccine. In ”Results,” the authors describe their findings regarding the safety and immunogenicity of Tdap. They state that Tdap administration did not lead to any safety concerns. Additionally, the authors state that when they administered Tdap during pregnancy, the women and their infants had higher levels of antibodies at birth compared to postpartum administration of Tdap. After receiving four doses of DTaP, infants born to women with Tdap immunization during pregnancy had comparable antibody responses to infants born to women with postpartum administration. In ”Discussion,” the authors contextualize the study with the recent CDC recommendation of Tdap immunization during pregnancy. In ”Conclusions,” the authors restate their findings on the safety and immunogenicity of Tdap and elaborate on the need for further studies to assess the efficacy of Tdap immunization.

In the introduction, the authors describe the reemergence of pertussis infections in young children and recent changes in CDC recommendations for Tdap administration. They state that despite ongoing childhood immunization, pertussis had recently become more prevalent in the US, especially for infants under the age of six months. In the first two months of life, infants are too young to receive the DTaP vaccine and therefore must rely on maternal antibodies. The authors explain that in 2008, the Advisory Committee on Immunization Practices, or ACIP, which is a part of the CDC, recommended Tdap immunization in postpartum women to protect infants during the vulnerable first few months after delivery. In 2011, the recommendation extended to unimmunized pregnant women, and then in 2012, to all pregnant women even if they had previously received the vaccine. The authors describe the necessity of a study to evaluate whether Tdap immunization during pregnancy is safe, as well as measure the effect of placental antibody transfer on infant immune responses.

Munoz and colleagues divided ”Methods” into six subsections, ”Study Design,” ”Study Vaccines,” ”Safety Assessments,” ”Immunogenicity Assessments,” ”Antibody Assays,” and ”Statistical Analysis.” In ”Study Design,” the authors state that they conducted the study from October 2008 to May 2012 with the enrollment of forty-eight pregnant women between the ages of eighteen and forty-five. They recruited pregnant women in the third trimester of pregnancy with low risk of birth complications from various obstetric office practices. The authors excluded women who had received Tdap in the past two years from the study. The authors then randomly divided the forty-eight women into two groups. In the first group, thirty-three women received Tdap during pregnancy and then a saline placebo injection postpartum. In the second group, fifteen women received a saline placebo injection during pregnancy and then Tdap postpartum. The study was double-blind, meaning that neither the participants nor the authors knew which treatment each woman received. For the women, the authors conducted study visits on the day of vaccination, four weeks after vaccination, at delivery, two months postpartum, with the final visit being four months postpartum. For the infants, the authors performed the study visits at birth and ages two months, seven months, and

thirteen months.

In ”Study Vaccines,” the authors outline which Tdap and DTaP vaccines they used in the study. They obtained Adacel, which is the licensed Tdap vaccine, from the manufacturer Sanofi Pasteur to administer to the adults in the study. The infants received Pentacel, which is the DTaP vaccine also from Sanofi Pasteur.

In ”Safety Assessments,” the authors explain how they assessed the safety of Tdap. The primary outcomes they monitored were injection site reactions, any adverse health events, infant development, and pertussis illness. The authors determined whether an adverse event was related to Tdap immunization by considering the time between vaccination and adverse event, as well as biologic plausibility, which is the likelihood of the relationship between a cause and effect. They monitored infant development by noting weight, length, and head circumference. The authors defined pertussis illness in mothers and infants as any report of cough that lasted for greater than two weeks. In the next two subsections, ”Immunogenicity Assessments” and ”Antibody Assays,” the authors describe how they evaluated immune responses in mother and infant. At each study visit timepoint, the authors collected blood samples from the women and infants, from which they quantified the concentrations of tetanus, diphtheria, and pertussis antibodies. In ”Statistical Analysis,” the authors outline the statistical methods they used to compare different groups in the study. They also note that they did not include one mother and four infants in the immunogenicity tests due to errors in vaccine administration, sample delivery, and timing of vaccinations.

The authors divided ”Results” into two subsections, ”Safety” and ”Immunogenicity.” In ”Safety,” they report that between women immunized during pregnancy versus postpartum, there was no difference in injection site reactions. The most reported symptom after immunization was pain, which the participants described as mild and short-lived. In addition, frequencies of headache, muscle aches, and general feelings of discomfort were similar between both groups of women. Twenty-two women reported serious adverse events, such as high blood pressure, inflammation of the gastrointestinal tract, and seizures, but the authors declared none to be related to the Tdap vaccine. All infants in the study were born via vaginal delivery with no significant differences in birth weights and neonatal examinations. Furthermore, throughout the first thirteen months, there were no differences in development. The authors did not observe any cases of pertussis illness in either mothers or infants.

In ”Immunogenicity,” the authors describe their findings when analyzing antibody production in mothers and infants. Tdap administration in pregnant women and postpartum women did not lead to any significant differences in antibody responses. However, at the time of delivery, women who received Tdap during pregnancy produced higher concentrations of antibodies for all three diseases compared to women immunized postpartum. The authors state that for the first two months after delivery, infants born to mothers who received Tdap during pregnancy produced higher concentrations of pertussis antibodies compared to infants born to mothers who received Tdap postpartum. For the first three DTaP shots, the authors found that infants who received maternal antibodies from mothers immunized during pregnancy had lower immune responses to filamentous hemagglutinin, which is a specific component of the pertussis bacteria, when compared to infants without maternal antibodies. They note, however, that the difference between the two groups of infants subsided after the fourth shot of DTaP at the age of thirteen months. Regarding the immunogenicity of tetanus and diphtheria, the authors only measured antibody responses after the third and fourth DTaP vaccine administration. They found that between the two infant groups, there was no significant difference in immune response.

In ”Discussion,” the authors highlight the importance of their findings in the context of disease incidence in the US and current CDC recommendation for Tdap immunization. They state that in 2012, there were nearly 42,000 cases of pertussis, which is the largest outbreak in the last half century. Munoz and colleagues note that most of those cases arose from infants who were too young to receive immunizations or received incomplete immunizations, which led to the CDC recommendation for all pregnant women to be immunized with Tdap. They state that their study was one of the first controlled trials to show the safety and immunogenicity of Tdap. The authors highlight their finding that maternal pertussis antibodies from immunization could be passed to the fetus during pregnancy and protect them for the first few months after delivery, which is the period

of time with the highest risk for pertussis-related illness and death. The authors then describe a few limitations of their study. First, they state that the sample size of the study was relatively small, which limited the detection of rare events. Second, they explain that they did not measure antibody concentrations in infants at the first DTaP dose timepoint. Lastly, the authors state that they did not look at the efficacy of Tdap for preventing illness, which may be a target for future studies.

In ”Conclusions,” the authors restate their findings on how Tdap immunization during pregnancy did not increase the risk of adverse health events, and that it resulted in greater levels of antibodies in infants that conferred protection until they could receive the DTaP vaccine.

As of 2022, over 450 publications have cited ”Tdap Immunization During Pregnancy” in various academic journals. The authors’ findings on the safety and immunogenicity of the Tdap vaccine during pregnancy created a foundation for more in-depth studies on maternal immunization. In 2016, a research group in Switzerland published ”Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis” in the journal Clinical Infectious Diseases, which further expands on the topic by analyzing the optimal timing of maternal immunization for maximum transfer of antibodies to infants. They found that immunization during the early second trimester of pregnancy resulted in the greatest transfer of antibodies. Also in 2016, Munoz, the primary author of ”Tdap Immunization During Pregnancy” published ”Infant Protection Against Influenza Through Maternal Immunization,” where she explores the effect of maternal immunization against influenza, which is a respiratory infection commonly called the flu, on infants. Like her findings regarding Tdap, Munoz described how infants born to mothers who received the influenza vaccine had significantly higher antibody concentrations and protection against disease.

”Tdap Immunization During Pregnancy” was one of the first controlled clinical trials that assessed the safety and immunogenicity of Tdap during pregnancy. The article’s findings coincided with the CDC guidelines in 2012 for all pregnant woman to receive Tdap for every pregnancy, reaffirming the recommendation with scientific evidence. Since the publication of ”Tdap Immunization During Pregnancy,” other studies have continued looking into the efficacy of maternal immunization in protecting infants, especially during the first few months when they are most vulnerable to disease.

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