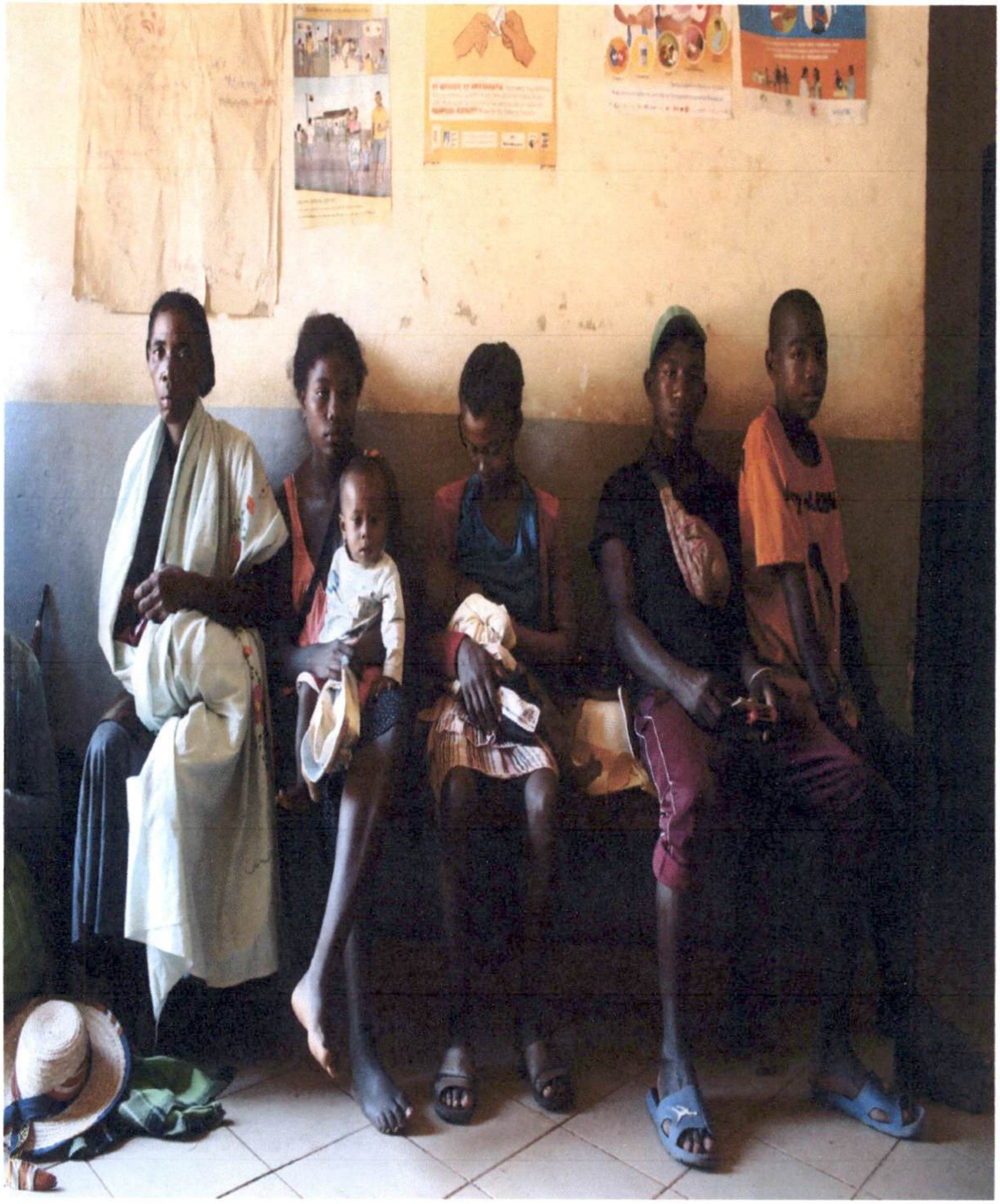
NBC NEWS

WORLD

Measles outbreak kills 1,200 in Madagascar, where parents want to vaccinate but lack means

In Madagascar, many parents would like to protect their vulnerable children but face immense challenges to receiving vaccines.



Mothers wait to have their babies vaccinated against the measles at a healthcare center in Larintsena, Madagascar, on March 21, 2019. Laetitia Bezain / AP file

April 14, 2019, 7:41 AM MDT

By Associated Press

AMBALAVAO, Madagascar – Babies wail as a nurse tries to reassure mothers who have come to vaccinate their children. They fear a measles epidemic that has killed more than 1,200 people in this island nation where many are desperately poor.

As Madagascar faces its largest measles outbreak in history and cases soar well beyond 115,000, resistance to vaccinating children is not the driving force.

Measles cases are rising in the United States and other parts of the world, in part the result of misinformation that makes some parents balk at a crucial vaccine. New York City is now trying to halt a measles outbreak by ordering mandatory vaccinations in one Brooklyn neighborhood.

In Madagascar, many parents would like to protect their children but face immense challenges including the lack of resources.

Just 58 percent percent of people on Madagascar's main island have been vaccinated against measles, a major factor in the outbreak's spread. With measles one of the most infectious diseases, immunization rates need to be 90 to 95 percent or higher to prevent outbreaks.

On a recent day the Iarintsena health center's waiting room was full, with mothers sitting on the floor and others waiting outside in the overwhelming heat. Two volunteer nurses and a midwife tried to respond to the demand.

Nifaliana Razaijafisoa had walked 15 kilometers (9 miles) with her 6-month-old baby in her arms.

"He has a fever," she said. "I think it's measles because there are these little pimples that have appeared on his face." The nurse quickly confirmed it. "I'm so scared for him because in the village everyone says it kills babies," Razaijafisoa said.

The measles outbreak has killed mostly children under age 15 since it began in September, according to the World Health Organization.

"The epidemic unfortunately continues to expand in size" though at a slower pace than a month ago, said Dr. Dossou Vincent Sodjinou, a WHO epidemiologist in Madagascar. By mid-March, 117,075 cases had been reported by the health ministry, affecting all regions of the country.

Some cases of resistance to vaccinations exist because of the influence of religion or of traditional health practitioners but they are isolated ones, he said.

This epidemic is complicated by the fact that nearly 50 percent of children in Madagascar are malnourished.

"Malnutrition is the bed of measles," Sodjinou said.

Razaijafisoa's baby weighs just 11 pounds.

"This is the case for almost all children with measles who have come here," said Lantonirina Rasolofoniaina, a volunteer at the health center.

Simply reaching a clinic for help can be a challenge. Many people in Madagascar cannot afford to see a doctor or buy medicine, and health centers often are understaffed or have poorly qualified workers.

As a result, information about health issues can be unreliable. Some parents are not aware that vaccines are free, at least in public health centers.

Four of Erika Hantriniaina's five children have had measles. She had wrongly believed that people could not be vaccinated after nine months of age.

"It's my 6-year-old daughter who had measles first. She had a lot of fever," she said. "I called the doctor but it was Friday. He had already gone to town. I went to see another doctor who told me that my daughter had an allergy. ... This misdiagnosis was almost fatal."

The girl had diarrhea and vomiting and couldn't eat, Hantriniaina said, adding that she narrowly survived.

Measles, a highly infectious disease spread by coughing, sneezing, close contact or infected surfaces, has no specific treatment. The symptoms are treated instead.

"Vitamin A is given to children to increase their immunity. We try to reduce the fever. If there is a cough, we give antibiotics," said Dr. Boniface Maronko, sent by WHO to Madagascar to supervise efforts to contain the outbreak. If the disease is not treated early enough, complications appear including diarrhea, bronchitis, pneumonia and convulsions.

Madagascar's health ministry has sent free medications to regions most affected by the epidemic. Maronko reminded heads of health centers in the Ambalavao region not to make parents pay, saying he had seen some doctors asking for money. He told the AP he feared the medicines wouldn't be enough.

The country's capital, Antananarivo, a city of some 1.3 million, has not been spared by the epidemic.

Lalatiana Ravonjisoa, a vegetable vendor in a poor district, grieves for her 5-month-old baby.

"I had 5 children. They all had measles. For the last, I did not go to see the doctor because I did not have money," she said. "I gave my baby the leftover medications from his big brother to bring down the fever."

For a few days she did not worry: "I felt like he was healed." But one morning she noticed he had trouble breathing. Later she found his feet were cold.

"Look at my baby," she told her mother.

"She hugged him for a long time and she did not say anything. Then she asked me to be strong. He was gone."

Ravonjisoa said she blames herself, "but I did not imagine for one moment that he was going to die." At the hospital, a doctor confirmed that her baby died of measles-related respiratory complications.

Late last month WHO started a third mass measles vaccination campaign in Madagascar with the overall goal of reaching 7.2 million children aged 6 months to 9 years.

"But immunization is not the only strategy for the response to this epidemic. We still need resources for care, monitoring and social mobilization," said Sodjinou, the WHO epidemiologist.

April 10, 2019
Testimony AGAINST HB19-1312
Crystal Barrett
Frederick, Colorado

My name is Crystal Barrett and I'd like to give you an example of how vaccines are not adequately tested for safety.

In 2010 and 2013 the ACIP added the flu and TDaP vaccines to the recommended schedule for all pregnant women. The safety and effectiveness of either vaccine was not tested in pregnancy ***before*** the vaccines were licensed and there is almost no data on adverse events that could affect pregnancy and birth outcomes. The FDA lists both vaccines as either Pregnancy Category B or C biologicals which means that adequate testing has **not** been done in humans to show safety for pregnancy and it is not known whether the vaccines can cause fetal harm or affect reproduction capacity. Safety and effectiveness evaluations that *have* been conducted are either small, retrospective, compare the vaccinated to the vaccinated or have been performed by drug company or government health officials using unpublished data. The FDA has licensed TDaP vaccines to be given once as a single dose booster shot to individuals over 10 or 11 years old therefore, the CDC's recommendation that doctors give ***every*** pregnant woman a TDaP vaccination during ***every*** pregnancy - regardless of whether she's already received one dose of TDaP - is an **off-label use** of the vaccine.

In February of 2019, the Informed Consent Action Network submitted a FOIA request to the FDA, requesting copies of the clinical trials it relied upon when licensing any flu vaccine for use in pregnancy. The FDA was unable to meet this request yet these vaccines are being forced on all pregnant women while the FDA admits that there was no pre licensure safety testing. What are the risks? We don't know for sure, but injuries and deaths from pertussis-containing vaccines are the most compensated claims in the Vaccine Injury Compensation Program (VICP) and flu vaccine injuries and deaths are the second most compensated claim. **AND** as we've already established, when a pregnant woman is harmed by either vaccine, drug companies are shielded from vaccine injury lawsuits.

Personally, I've experienced the change in urgency to vaccinate pregnant women first-hand since these vaccines were added to the schedule by the ACIP. I have two sets of children about a decade apart with my first two born in 2005/2008. During my first two pregnancies, I was never recommended a TDaP or Flu vaccine, it wasn't even mentioned. Flash forward to 2016 when I was pregnant with my now 2-year old, not only were the TDaP and flu shot recommended BUT after declining the vaccines with the nurse several appointments in a row, the OB said they were required and when I declined he became extremely aggressive. The longest amount of time he had ever spent with me prior to that appointment was about 10-15 min. During that appointment, he spent about 20 minutes alone on "educating" me by assuming that I was just another crazy mother concerned about autism (something I never even mentioned). Finally, he sighed and said "OK, let's just get this over with" referring to listening to my baby's heart and taking measurements. That was the day that I left his office in tears and I never went back. The bullying and aggressive push to take a vaccine that has NEVER been adequately studied for safety and is being used off-label is truly disturbing.

Therefore, I ask that you vote NO on HB19-1312 considering the proposal that we adopt the immunizations recommended by ACIP which ***could*** be vaccines recommended for off-label use **OR** vaccines not adequately studied for safety.

References:

1) **Safety of Tdap in Pregnant Women from CDC**

In prelicensure evaluations, the safety of administering a booster dose of Tdap to pregnant women was not studied. Because information on use of Tdap in pregnant women was lacking, both manufacturers of Tdap established pregnancy registries to collect information and pregnancy outcomes from pregnant women vaccinated with Tdap. Data on the safety of administering Tdap to pregnant women are now available. ACIP reviewed published and unpublished data from VAERS, Sanofi Pasteur (Adacel) and GlaxoSmithKline (Boostrix) pregnancy registries, and small studies (*7,8*). **The first study cited here (7) only looks at efficacy NOT safety and the second study (8) does not look at pregnant women specifically but a group of healthcare workers and this only looks at the interval between vaccination. ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine. Both tetanus and diphtheria toxoids (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria-toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic (*9,10*). **The first study cited here compares vaccinated to vaccinated, no real control group with inert placebo. The second study cited (10) appears to have data thrown out such as stillbirths due to no matching controls. From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks' gestation is preferred to minimize the risk for any low-frequency adverse event and the possibility that any spurious association might appear causative.

Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women

2) FOIA request to FDA on vaccine safety trials for pregnant women

WHEREAS, plaintiff Informed Consent Action Network ("ICAN") requested the following records from defendant United States Food & Drug Administration ("FDA") pursuant to the Freedom of Information Act ("FOIA"): "**A copy of the report for each clinical trial relied upon by the FDA when approving for use by pregnant women any influenza vaccine currently approved by the FDA.**"

WHEREAS, after ICAN appealed, the FDA responded, in relevant part, as follows: **These requests sought the clinical trials relied upon by the FDA prior to approving any currently licensed influenza or Tdap vaccine for use in pregnant women as an indicated use. ... We have no records responsive to your requests.**

https://icandecide.org/government/ICAvFDA-Resolved-Court-Filed-Copy.pdf

3) Package Inserts Flu

Afluria - "There are insufficient data for AFLURIA in pregnant women to inform vaccine-associated risks in pregnancy.

Fluzone, Quadrivalent - "There are, however, no adequate and well-controlled studies in pregnant women."

Fluarix - "There are, however, no adequate and well-controlled studies in pregnant women."

Fluvirin - "There are, however, no adequate and well-controlled studies in pregnant women."

Fluad - "There are, however, no adequate and well-controlled studies in pregnant women."

Flublok Quadrivalent - "Pregnancy outcomes in women who have been exposed to Flublok Quadrivalent during pregnancy are being monitored. Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Flublok Quadrivalent during pregnancy. Healthcare providers are encouraged to enroll women who receive Flublok Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463. Available data on Flublok Quadrivalent and Flublok (trivalent formulation) administered to pregnant women are insufficient to inform vaccine-associated risks in pregnant women."

Flucelvax - "There are, however, no adequate and well-controlled studies in pregnant women."

Flulaval - "There are insufficient data on FLULAVAL QUADRIVALENT in pregnant women to inform vaccine-associated risks."

4) Package Inserts TDap/DTaP

Adacel - "There are no adequate and well-controlled studies of Adacel administration in pregnant women in the U.S."

Infanrix - "Pregnancy Category C. Animal reproduction studies have not been conducted with INFANRIX. It is also not known whether INFANRIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity."

Boostrix - "There are no adequate and well-controlled studies in pregnant women."

* All package inserts can be found on FDA's website

5) Maternal immunization: US FDA regulatory considerations

"Currently, unless the vaccine is specifically indicated four maternal immunization, no data are collected regarding the vaccine's safety in pregnant women prior to licensure....Since pregnant women are usually excluded from participation in clinical trials, conclusions regarding developmental risk at the time of licensure are frequently based solely on data derived from developmental toxicity studies in animal models"

6) Inadequate post licensure safety studies

a. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. This study was retrospective but actually showed a 17% spontaneous abortion rate.

b. Influenza vaccination in pregnancy: current evidence and selected national policies This study only reviews the "few published studies" and it states "National policies differ widely, mainly because of the limited data available, particularly on vaccination in the first trimester."

c. Safety of influenza vaccination during pregnancy Retrospective ~~study~~ studies and ~~does~~ do not define what "unvaccinated" means, both "randomized controlled trials" used another vaccine, not an inert placebo.

d. Effectiveness of Maternal Influenza Immunization in Mothers and Infants There were 340 pregnant women in the study. Half of the mothers, in their third trimester received an inactivated influenza vaccine and the other half received a 23-valent pneumococcal polysaccharide vaccine as the "control." So, comparing vaccinated against vaccinated.

The authors conclude: *"The pneumococcal vaccine that was used as a control may have had an independent positive effect on the outcomes among infants. If that were the case, the observed difference between the two vaccine groups would be an* *underestimate of the true effect of influenza vaccine compared with placebo."* That's an assumption. Did the influenza vaccine *increase* that baby's weight or did the pneumococcal vaccine decrease the 'placebo' baby's weight? If the pneumococcal vaccine had negative effects, then that would minimize the observed effects seen in the influenza-vaccinated group.

7) ACIP recommends Tdap vaccine during each pregnancy Article discussing off-label use of the vaccine.

8) Inflammatory responses to trivalent influenza virus vaccine among pregnant women Study showing possible risks

> "In the U.S., seasonal trivalent influenza vaccination (TIV) is currently universally recommended for all pregnant women. However, data on the maternal inflammatory response to vaccination is lacking and would better delineate the safety and clinical utility of immunization.....Trivalent influenza virus vaccination elicits a measurable inflammatory response among pregnant women. There is sufficient variability in response for testing associations with clinical outcomes. As adverse perinatal health outcomes including preeclampsia and preterm birth have an inflammatory component, a tendency toward greater inflammatory responding to immune triggers may predict risk of adverse outcomes, providing insight into biological mechanisms underlying risk."

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™
Morbidity and Mortality Weekly Report (*MMWR*)

(1)

Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months --- Advisory Committee on Immunization Practices (ACIP), 2011

Weekly

October 21, 2011 / 60(41);1424-1426

Compared with older children and adults, infants aged <12 months have substantially higher rates of pertussis and the largest burden of pertussis-related deaths. Since 2004, a mean of 3,055 infant pertussis cases with more than 19 deaths has been reported each year through the National Notifiable Diseases Surveillance System (CDC, unpublished data, 2011). The majority of pertussis cases, hospitalizations, and deaths occur in infants aged ≤2 months, who are too young to be vaccinated; therefore, other strategies are required for prevention of pertussis in this age group. Since 2005, the Advisory Committee on Immunization Practices (ACIP) has recommended tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) booster vaccines to unvaccinated postpartum mothers and other family members of newborn infants to protect infants from pertussis, a strategy referred to as cocooning (*1*). Over the past 5 years, cocooning programs have proven difficult to implement widely (*2,3*). Cocooning programs might achieve moderate vaccination coverage among postpartum mothers but have had limited success in vaccinating fathers or other family members. On June 22, 2011, ACIP made recommendations for use of Tdap in unvaccinated pregnant women and updated recommendations on cocooning and special situations. This report summarizes data considered and conclusions made by ACIP and provides guidance for implementing its recommendations.

ACIP recommends a single Tdap dose for persons aged 11 through 18 years who have completed the recommended childhood diphtheria and tetanus toxoids and pertussis/diphtheria and tetanus toxoids and acellular pertussis (DTP/DTaP) vaccination series and for adults aged 19 through 64 years who have not previously received Tdap (*1,4*). ACIP also recommends that adults aged 65 years and older receive a single dose of Tdap if they have or anticipate having close contact with an infant aged <12 months and previously have not received Tdap (*5*). Two Tdap vaccines are available in the United States. Adacel (Sanofi Pasteur) is licensed for use in persons aged 11 through 64 years. Boostrix (GlaxoSmithKline Biologicals) is licensed for use in persons aged ≥10 years (*6*).

The ACIP Pertussis Vaccines Work Group reviewed unpublished Tdap safety data from pregnancy registries and the Vaccine Adverse Event Reporting System (VAERS) and published studies on use of Tdap in pregnant women. The Work Group also considered the epidemiology of pertussis in infants and provider and program feedback, and then presented policy options for consideration to ACIP. These updated recommendations on use of Tdap in pregnant women are consistent with the goal of reducing the burden of pertussis in infants.

Safety of Tdap in Pregnant Women

In prelicensure evaluations, the safety of administering a booster dose of Tdap to pregnant women was not studied. Because information on use of Tdap in pregnant women was lacking, both manufacturers of Tdap established pregnancy registries to collect information and pregnancy outcomes from pregnant women vaccinated with Tdap. Data on the safety of administering Tdap to pregnant women are now available. ACIP reviewed published and unpublished data from VAERS, Sanofi Pasteur (Adacel) and GlaxoSmithKline (Boostrix) pregnancy registries, and small studies (*7,8*). ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine. Both tetanus and diphtheria toxoids (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria-toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic (*9,10*). From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks' gestation is preferred to minimize the risk for any low-frequency adverse event and the possibility that any spurious association might appear causative.

Transplacental Maternal Antibodies

For infants, transplacentally transferred maternal antibodies might provide protection against pertussis in early life and before beginning the primary DTaP series. Several studies provide evidence supporting the existence of efficient transplacental transfer of pertussis antibodies (*7,11,12*). Cord blood from newborn infants whose mothers received Tdap during pregnancy or before pregnancy had higher concentrations of pertussis antibodies when compared with cord blood from newborn infants of unvaccinated mothers (*7,11*). The half-life of transferred maternal pertussis antibodies is approximately 6 weeks (*12*). The effectiveness of maternal antipertussis antibodies in preventing infant pertussis is not yet known, but pertussis-specific antibodies likely confer protection and modify the severity of pertussis illness (*13,14*). In addition, a woman vaccinated with Tdap during pregnancy likely will be protected at time of delivery, and therefore less likely to transmit pertussis to her infant. After receipt of Tdap, boosted pertussis-specific antibody levels peak after several weeks, followed by a decline over several months (*15,16*). To optimize the concentration of maternal antibodies transferred to the fetus, ACIP concluded that unvaccinated pregnant women should receive Tdap, preferably in the third or late second (after 20 weeks gestation) trimester.

Interference with Infant Immune Response to Primary DTaP Vaccination

Several studies have suggested that maternal pertussis antibodies can inhibit active pertussis-specific antibody production after administration of DTaP vaccine to infants of mothers vaccinated with Tdap during pregnancy, referred to as blunting (*12,17*). Because correlates of protection are not fully understood, the clinical importance of blunting of an infant's immune response is not clear. Evidence suggests that any blunting would be short-lived because circulating maternal antibodies decline rapidly (*12,18*). Circulating maternal pertussis antibodies might reduce an infant's risk for pertussis in the first few months of life but slightly increase risk for disease because of a blunted immune response after receipt of primary DTaP doses. The benefit would be to reduce the risk for disease and death in infants aged <3 months, but the trade-off might be to increase the occurrence of pertussis in older infants; however, this group experiences a substantially lower burden of hospitalizations and mortality (National Notifiable Diseases Surveillance System, CDC, unpublished data, 2011).

Currently, two clinical trials are being conducted to measure the immune response of infants receiving DTaP immunization at ages 2, 4, and 6 months whose mothers received Tdap during the third trimester of pregnancy (*19,20*). These trials also are designed to evaluate safety and immunogenicity of Tdap during pregnancy, but are not sufficiently powered to assess disease endpoints. Analysis of interim data from one trial (*19*, unpublished data) measured infant antibody to pertussis antigens in a blinded fashion for two groups: infants whose mothers received Tdap and infants whose mothers received Td. The first group had elevated antipertussis antibody levels compared with the second at birth and before dose 1, which might be the result of passive antibody transfer, but had lower antipertussis antibody levels after dose 3. In both groups, antipertussis antibody levels were comparable before doses 2 and 3. Although the first group had lower antipertussis antibody levels after dose 3, the evidence of sufficient immune response to DTaP doses compared with the second group was reassuring. ACIP concluded that the interim data are consistent with previously published literature suggesting a short duration of blunting of the infant response, and that the potential benefit of protection from maternal antibodies in newborn infants outweighs the potential risk for shifting disease burden to later in infancy.

Cocooning

Cocooning is defined as the strategy of vaccinating pregnant women immediately postpartum and all other close contacts of infants aged <12 months with Tdap to reduce the risk for transmission of pertussis to infants. Cocooning has been recommended by ACIP since 2005. Cocooning programs have achieved moderate postpartum coverage among mothers but have had limited success in vaccinating fathers or other family members (*3*) (CDC, unpublished data, 2011). Programmatic challenges make implementation of cocooning programs complex and also impede program expansion and sustainability (*2*). The effectiveness of vaccinating postpartum mothers and close contacts to protect infants from pertussis is not yet known, but the delay in antibody response among those vaccinated with Tdap after an infant's birth might result in insufficient protection to infants during the first weeks of life (*21*). ACIP concluded that cocooning alone is an insufficient strategy to prevent pertussis morbidity and mortality in newborn infants. Regardless, ACIP concluded that cocooning likely provides indirect protection to infants and firmly supports vaccination with Tdap for unvaccinated persons who anticipate close contact with an infant.

Decision and Cost Effectiveness Analysis

A decision analysis and cost effectiveness model was developed to assess the impact and cost effectiveness of maternal Tdap vaccination during pregnancy compared with immediately postpartum. The model showed that Tdap vaccination during pregnancy would prevent more infant cases, hospitalizations, and deaths compared with the postpartum dose for two reasons: 1) vaccination during pregnancy benefits the mother and infant by providing earlier protection to the mother, thereby protecting the infant at birth; and 2) vaccination during late pregnancy maximizes transfer of maternal antibodies to the infant, likely providing direct protection to the infant for a period after birth. Model results were most sensitive to efficacy of maternal antibodies and risk for disease as a result of blunting; however, a sensitivity analysis in which infants were assumed to have as little as 20% efficacy of maternal antibodies and a 60% increase in risk for disease as a result of blunting found that maternal vaccination during pregnancy was more cost effective and prevented a greater proportion of infant cases and deaths than postpartum maternal vaccination (*22*).

Guidance for Use

Maternal vaccination. ACIP recommends that women's health-care personnel implement a Tdap vaccination program for pregnant women who previously have not received Tdap. Health-care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (after 20 weeks' gestation). If not administered during pregnancy, Tdap should be administered immediately postpartum.

Cocooning. ACIP recommends that adolescents and adults (e.g., parents, siblings, grandparents, child-care providers, and health-care personnel) who have or anticipate having close contact with an infant aged <12 months should receive a single dose of Tdap to protect against pertussis if they have not previously received Tdap. Ideally, these adolescents and adults should receive Tdap at least 2 weeks before beginning close contact with the infant.

Special Situations

Pregnant women due for tetanus booster. If a tetanus and diphtheria booster vaccination is indicated during pregnancy for a woman who has previously not received Tdap (i.e., more than 10 years since previous Td), then Tdap should be administered during pregnancy, preferably during the third or late second trimester (after 20 weeks' gestation).

Wound management for pregnant women. As part of standard wound management care to prevent tetanus, a tetanus toxoid--containing vaccine might be recommended for wound management in a pregnant woman if 5 years or more have elapsed since last receiving Td. If a tetanus booster is indicated for a pregnant woman who previously has not received Tdap, Tdap should be administered.

Pregnant women with unknown or incomplete tetanus vaccination. To ensure protection against maternal and neonatal tetanus, pregnant women who have never been vaccinated against tetanus should receive three vaccinations containing tetanus and reduced diphtheria toxoids. The recommended schedule is 0, 4 weeks, and 6 to 12 months. Tdap should replace 1 dose of Td, preferably during the third or late second trimester (after 20 weeks' gestation) of pregnancy.

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2

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

INFORMED CONSENT ACTION NETWORK,

Plaintiff,

-against-

UNITED STATES FOOD AND DRUG ADMINISTRATION

Defendant.

NOTICE OF VOLUNTARY DISMISSAL PURSUANT TO F.R.C.P. 41(a)(1)(A)(i)

Case No. 18-cv-11237-VEC

WHEREAS, plaintiff Informed Consent Action Network ("ICAN") requested the following records from defendant United States Food & Drug Administration ("FDA") pursuant to the Freedom of Information Act ("FOIA"): "**A copy of the report for each clinical trial relied upon by the FDA when approving for use by pregnant women any influenza vaccine currently approved by the FDA.**"

WHEREAS, after ICAN appealed, the FDA responded, in relevant part, as follows:

> **These requests sought the clinical trials relied upon by the FDA prior to approving any currently licensed influenza or Tdap vaccine for use in pregnant women as an indicated use. ... We have no records responsive to your requests.**

THEREFORE, pursuant to F.R.C.P. 41(a)(1)(A)(i) of the Federal Rules of Civil Procedure, plaintiff ICAN by its undersigned counsel, hereby gives notice that the above captioned action is voluntarily dismissed, without prejudice against the defendant FDA.

Dated: February 10, 2019

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5

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Maternal immunization: US FDA regulatory considerations

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Abstract

Vaccination of pregnant women provides important health benefits to both, mother and infant, and has been an important disease prevention strategy in these two groups. While most vaccines currently licensed in the US are not indicated for use during pregnancy, depending on the vaccine, vaccination programs do frequently include pregnant women. In addition, recent emphasis has been placed on maternal immunization strategies to protect young infants from severe infections. Currently, unless the vaccine is specifically indicated four maternal immunization, no data are collected regarding the vaccine's safety in pregnant women prior to licensure. However, more females of childbearing age participate in clinical trials and a broad range of novel vaccine products are in development indicated for adolescents and adults. Thus, there is increasing concern for the unintentional exposure of an embryo/fetus before information is available regarding the potential risk versus benefit of the vaccine. Since pregnant women are usually excluded from participation in clinical trials, conclusions regarding developmental risk at the time of licensure are frequently based solely on data derived from developmental toxicity studies in animal models. This paper will review regulatory, preclinical and clinical issues as they pertain to development programs for vaccines intended for vaccination during pregnancy.

Keywords

Maternal immunization; Vaccine; Developmental toxicity; Pregnancy; Prenatal immunization; Regulatory consideration

OBSTETRICS

6 a.

Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women

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Retrospective, small sample, BUT still showed 17% spontaneous abortion

OBJECTIVE: We sought to characterize reports to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women who received tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap).

STUDY DESIGN: We searched VAERS for reports of pregnant women who received Tdap from Jan. 1, 2005, through June 30, 2010. We conducted a clinical review of reports and available medical records.

RESULTS: We identified 132 reports of Tdap administered to pregnant women; 55 (42%) described no adverse event (AE). No maternal or infant deaths were reported. The most frequent pregnancy-specific AE was spontaneous abortion in 22 (16.7%) reports. Injection site reactions were the most frequent non-pregnancy–specific AE found in 6 (4.5%) reports. One report with a major congenital anomaly (gastroschisis) was identified.

CONCLUSION: During a time when Tdap was not routinely recommended in pregnancy, review of reports to VAERS in pregnant women after Tdap did not identify any concerning patterns in maternal, infant, or fetal outcomes.

Key words: acellular pertussis vaccine, adverse events, epidemiology, pregnancy, reduced diphtheria toxoid, surveillance, tetanus toxoid, vaccine safety

Cite this article as: Zheteyeva YA, Moro PL, Tepper NK, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol 2012;207:59.e1-7.

★ EDITORS' CHOICE ★

Administration of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) to a pregnant woman induces formation of maternal antibodies against pertussis that are transferred to the fetus across the placenta.[1] Transplacentally transferred antibodies might provide protection against pertussis infection in young infants.[1,2] In addition, Tdap vaccination of pregnant women and other family members directly prevents pertussis in these individuals and may indirectly protect infants by reducing the risk for pertussis transmission, a strategy known as cocooning.[3] Infants <3 months of age are too young to receive the primary pertussis vaccination series and have the highest risk for death from pertussis. Therefore, strategies to prevent pertussis in these infants are essential.[4]

Tdap was licensed by the Food and Drug Administration (FDA) in 2005 for booster immunization against tetanus, diphtheria, and pertussis for individuals 10-64 years of age, and is available in the United States from 2 manufacturers: Adacel (Sanofi Pasteur, Swiftwater, PA)[5] and Boostrix (GlaxoSmithKline Biologicals, Rixensart, Belgium).[6] Since 2008 the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended using Tdap in the immediate postpartum period in women who did not previously receive Tdap to protect both mothers and infants from pertussis.[7] ACIP did not routinely recommend use of Tdap in pregnant women, but recommended that providers consider use in certain situations that included instances when a pregnant woman has insufficient tetanus or diphtheria protection until delivery, or is at

From the Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases (Drs Zheteyeva, Moro, Tokars, Vellozzi, and Broder, Ms Lewis, Ms Yue, and Ms Haber); the Epidemic Intelligence Service (Dr Zheteyeva); the Women's Health and Fertility Branch, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion (Drs Tepper and Kissin); the Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities (Dr Rasmussen), Department of Pediatrics, Emory University School of Medicine (Dr Revzina), Atlanta, GA, and the Offices of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD (Dr Barash).

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The authors report no conflict of interest.

Presented, in part, during the June 22, 2011, meeting of the Advisory Committee on Immunization Practices, Atlanta, GA.

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For Editors' Commentary, see Contents

increased risk for pertussis (eg, adolescents aged 11-18 years, health care personnel, and women employed in institutions or living in a community in which a pertussis outbreak is occurring).[7] In 2011 ACIP assessed that the strategy focusing on cocooning had not achieved the intended goal of reducing the burden of pertussis in infants. In October 2011, CDC published an updated ACIP recommendation that health care providers administer Tdap during the third or late second trimester (>20 weeks' gestation) to women who have not previously received Tdap.[8]

To provide safety evidence to help inform the ACIP deliberations for Tdap use in pregnant women, we conducted a review of reports to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women given Tdap from 2005 through 2010.

MATERIALS AND METHODS

Data sources

VAERS is a spontaneous reporting system coadministered by CDC and FDA.[9] Established in 1990, VAERS monitors vaccine safety and accepts adverse event (AE) reports following receipt of any US-licensed vaccine.[10] VAERS is not designed to assess causal associations between vaccines and AEs; its primary purpose is to detect potential vaccine safety concerns that may be further investigated in defined populations.[11] The VAERS report form collects demographic and health information, including information about the vaccination and AE experience.[12] It does not specifically collect information on pregnancy status. AE signs and symptoms recorded in each VAERS report are coded by trained staff using an internationally standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA).[13] Each report can be coded with ≥1 MedDRA term. Reports are also classified as "serious" based on the Code of Federal Regulations[14] if they contain information that the AE resulted in death, hospitalization, prolongation of hospitalization, life-threatening illness, persistent or significant disability, or congenital anomalies. For this study, the definition of "serious" was slightly modified and did not include reports on hospitalizations for delivery unless they required prolonged stay in a hospital due to delivery complications or postpartum conditions. Medical records are routinely requested for nonmanufacturer serious VAERS reports.

We searched the VAERS database for reports of pregnant women vaccinated in the United States with Tdap, with or without other vaccines, from Jan. 1, 2005, through June 30, 2010. We conducted an automated search using the following criteria: MedDRA terms in 2 System Organ Classes "Pregnancy, Puerperium, and Perinatal Conditions" and "Congenital, Familial, and Genetic Disorders"; MedDRA term "Drug Exposure During Pregnancy"; and a text string search for the term "preg" in the report. Reports that had at least one of these criteria were included in the data set for further evaluation.

Clinical reviews

CDC and FDA medical officers reviewed all US reports identified in the VAERS database using the automated search to confirm pregnancy status at time of vaccination, calculate gestational age, and characterize AEs. We included reports on infants born to women vaccinated with Tdap during pregnancy. For each report we assigned a primary diagnosis. If >1 AE was reported for the same individual, we assigned the diagnosis based on what we believed was the primary clinical event of concern and assumed the primary event was the pregnancy-specific event unless information suggested otherwise. Complex reports were reviewed by physicians on the study team with expertise in obstetrics and neonatology. If a VAERS report described AEs in >1 person, we treated each person as a separate report. Reports that indicated the reported subject was not pregnant or that Tdap was administered prior to the last menstrual period were excluded.

Gestational age at the time of vaccination and at the time of the AE was calculated based on: (1) clinical determination of health care provider, (2) earliest ultrasound assessment (if the former was not available), or (3) last menstrual period, estimated delivery date, or estimated date of conception (if the first 2 options were not available) found in VAERS report and/or medical records. We used the following definition for trimesters: first (0-13 weeks), second (14-27 weeks), and third (≥28 weeks).[15] Spontaneous abortion (SAB) was defined as fetal demise <20 weeks' gestation, stillbirth was defined as fetal demise ≥20 weeks' gestation, and preterm delivery was defined as a live birth <37 weeks' gestation. Causality between reported AEs and Tdap was not assessed.

Proportional reporting ratios

To assess for disproportionately higher reporting of AEs after Tdap administered to pregnant women, we calculated proportional reporting ratios (PRRs)[16,17] compared to inactivated influenza vaccines, which have been determined to have an acceptable safety profile in pregnancy.[18,19] We compared proportions of MedDRA terms after Tdap with proportions of the same MedDRA terms after trivalent inactivated influenza vaccines (TIV) and influenza A (H1N1) 2009 monovalent vaccine (used during the 2009 through 2010 pandemic) administered without Tdap to pregnant women. For TIV and monovalent vaccine administered in pregnancy, we used VAERS reports identified for previously conducted and published studies.[18,19] We excluded reports from analysis if no AE was reported or if live vaccines (contraindicated during pregnancy[20]) or anthrax vaccine (not recommended during pregnancy[21]) were administered concomitantly. We identified MedDRA terms with disproportionately higher reporting after Tdap by applying criteria of Evans et al[16] (PRR ≥2.0, Yates χ^2 ≥4.0, and number of reports ≥3 in the Tdap group). Clinical reviews were conducted for all MedDRA terms with a PRR ≥2.0.

Because VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research, this investigation was not subject to institutional review board review and informed consent requirements.

RESULTS

During Jan. 1, 2005, through June 30, 2010, VAERS received a total of 106,573 US reports after Tdap; 163 reports met criteria of pregnancy reports using the automated search. Of these reports, 33 were excluded: 28 reports indicated that the subject was not pregnant, 2 reports indicated that Tdap was received postpartum, 2 reports indicated vaccination in children, and 1 report was a duplicate. Two reports described AEs in infant and mother; each of these reports was treated as 2 separate reports (1 for infant and 1 for mother). After the clinical review, 132 reports were identified as true pregnancy reports and were used for further analysis. Six (4.5%) reports were classified as serious and included 2 reports of ruptured ectopic pregnancies that required laparotomy; and 1 report each of stillbirth at 37 weeks' gestation due to placental abruption, influenza, gastroschisis in a newborn, and laryngotracheomalacia in a 3-month-old infant. In all these reports, the serious classification was based on the person requiring hospitalization. No maternal or infant deaths were reported.

Characteristics of VAERS reports are presented in Table 1. A majority of the reports (69, 52.3%) were received from manufacturers. In 48 (36.4%) reports Tdap was the only vaccine received. The median maternal age was 22 years. Information to determine the trimester of Tdap exposure was available for 110 (83.3%) reports. In most of the reports where trimester at time of vaccination was known, 85 (77.3%), indicated that Tdap was administered during the first trimester of pregnancy. A total of 95 (72.0%) reports indicated administration of Adacel.

In all, 55 (41.7%) reports did not describe any AE; these reports were submitted because vaccine had been administered during pregnancy at a time period when Tdap in pregnancy was not routinely recommended (Table 2). The most frequent pregnancy-specific outcome was SAB in 22 (16.7%) reports. The median gestational age at the time of SAB was 9 weeks (range, 5–16 weeks). The median onset interval between vaccination and SAB was 33 days (range, 9–61 days). We did not observe any temporal clustering of SAB reports. Two stillbirth cases were reported. One case occurred in a 20-year-old woman at 37 weeks of gestation and was reported to be due to placental abruption; Tdap was administered several hours before the outcome. The other case was in a 27-year-old woman at 22 weeks of gestation (46 days after exposure to Tdap) with no other pregnancy complications reported before fetal demise.

There were 3 infants born preterm: (1) the first to a 22-year-old woman with a cesarean section at 36 weeks of gestation, described as being indicated because of a history of having a cesarean section delivery; the woman delivered a normal infant; (2) the second case was in a 40-year-old woman with multiple previous pregnancies who also had preeclampsia; she delivered a normal infant at 35 weeks of gestation; and (3) the third case was in an 18-year-old woman who delivered a normal infant at 35 weeks of gestation.

The most frequent non-pregnancy-specific outcomes were injection site reactions, in 6 (4.5%) reports (Table 2).

Six (4.5%) reports indicated adverse infant outcomes, including 1 report each of gastroschisis, patent foramen ovale and peripheral pulmonic stenosis, physiologic neonatal jaundice, transient tachypnea and infiltrates in the lower lobes, bilateral hydrocele, and laryngotracheomalacia (Table 2). Only 1 of these infants had a major birth defect (gastroschisis). This infant was born to a 15-year-old mother who received Tdap and quadrivalent human papillomavirus vaccines concomitantly at approximately 8 weeks' gestation; additional information regarding the maternal history was not available.

In all, 24 (18.2%) pregnancies resulted in vaginal deliveries (including 2 preterm). Eight (6.1%) pregnancies resulted in cesarean deliveries, which included 1 preterm delivery in a 22-year-old woman (described above). Reasons for cesarean deliveries were described in 5 of 8 reports and included 2 reports of severe fetal bradycardia and placental abruption; and 1 report each of macrosomia, arrest of descent, and prolonged labor. Four elective abortions were reported. These reports did not describe any AEs and reasons for elective termination of pregnancy were not indicated.

TABLE 1
US VAERS reports following Tdap in pregnant women (n = 132)

Characteristic	Value
Serious reports, n (%)	6 (4.5)
Tdap administered alone,[a] n (%)	48 (36.4)
Median maternal age, y (range)[b]	22 (13–42)
Median interval from vaccination to adverse event, d (range)[c]	7 (0–268)
Median gestational age at time of vaccination, wk (range)[d]	6 (1–37)
Trimester of pregnancy at time of vaccination (n = 110),[e] n (%)	
First (0–13 wk)	85 (77.3)
Second (14–27 wk)	21 (19.1)
Third (≥28 wk)	4 (3.6)
Brand name of Tdap, n (%)	
Adacel[f]	95 (72.0)
Boostrix[g]	20 (15.2)
Unknown	17 (12.9)
Type of reporter, n (%)	
Manufacturer	69 (52.3)
Provider	42 (31.8)
Other	20 (15.2)
Patient/parent	1 (0.8)

Characteristics of Vaccine Adverse Event Reporting System (VAERS) reports received following Tdap vaccine in pregnant women, United States, Jan. 1, 2005, through June 30, 2010 (n = 132).
Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] Other vaccines given with Tdap included meningococcal conjugate (7; 5.4%); human papillomavirus (7; 5.4%); measles, mumps, and rubella (4; 3.1%); and influenza (3; 2.3%); [b] Missing for 1 pregnant woman; [c] Unknown for 61 reports; [d] Unknown for 43 reports; [e] Unknown for 22 reports; [f] Sanofi Pasteur, Swiftwater, PA; [g] GlaxoSmithKline Biologicals, Rixensart, Belgium.

Zheteyeva. Safety of Tdap in pregnancy. Am J Obstet Gynecol 2012.

Proportional reporting ratios

The PRR screening criteria were met for higher proportional reporting after Tdap in pregnancy for the following MedDRA terms: anemia, antepartum hemorrhage, gestational diabetes, oligohydramnios, and upper respiratory tract infection

TABLE 2
Adverse events[a] in pregnant women following Tdap vaccine, VAERS

Adverse events	n	%
Pregnancy-specific adverse events		
Spontaneous abortion[b]	22	16.7
Gestational diabetes	7	5.3
Oligohydramnios[c]	3	2.3
Induction of labor[d]	2	1.5
Stillbirth	2	1.5
Ruptured ectopic pregnancy	2	1.5
Preterm delivery	2	1.5
Subchorionic hemorrhage by ultrasound	1	0.8
Cesarean delivery	1	0.8
Low-lying placenta on ultrasound	1	0.8
Placental abruption and fetal intolerance	1	0.8
Preeclampsia[e]	1	0.8
Prolonged labor	1	0.8
Toxemia[f]	1	0.8
Total	47	35.6
Non-pregnancy–specific outcomes		
Injection site reactions	6	4.5
Anemia	5	3.8
Headache or fever with abdominal pain	3	2.3
Urinary tract infection	2	1.5
Syncope	2	1.5
Upper respiratory infection	2	1.5
Influenza	1	0.8
Nausea and vomiting	1	0.8
Rash on arms/thigh	1	0.8
Superficial thrombophlebitis	1	0.8
Total	24	18.2
Infant outcomes		
Gastroschisis	1	0.8
Laryngotracheomalacia (diagnosed at age 3 mo)[e]	1	0.8
Patent foramen ovale and peripheral pulmonic stenosis	1	0.8
Mild physiologic jaundice	1	0.8
Transient tachypnea and infiltrates in lower lobes	1	0.8
Bilateral hydrocele	1	0.8
Total	6	4.5
No adverse events	55	41.7

Reported adverse events[a] in pregnant women following receipt of Tdap vaccine, Vaccine Adverse Event Reporting System (VAERS), Jan. 1, 2005, through June 30, 2010 (n = 132).
Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] Based on primary reported diagnosis identified during clinical review–1 diagnosis assigned to 1 report; [b] Pregnancy outcomes were not reported in 65 (42%) reports–other pregnancy outcomes included 4 (3.0%) elective termination of pregnancy, 24 (18.2%) vaginal deliveries, and 8 (6.1%) cesarean deliveries; [c] 2 cases with oligohydramnios had induction of labor as secondary diagnosis and 1 case had threatened abortion in early pregnancy as secondary diagnosis; [d] Chorioamnionitis was reported as secondary to labor induction; [e] Preterm delivery reported as secondary diagnosis for this case; [f] Threatened abortion in early pregnancy is reported for this case as secondary diagnosis.

Zheteyeva. Safety of Tdap in pregnancy. Am J Obstet Gynecol 2012.

(Table 3). No disproportionality was found in reporting SAB, stillbirth, or preterm deliveries.

The 3 reports with the MedDRA code for anemia were nonserious reports. The lowest hemoglobin values listed in 3 reports ranged from 9.3–10 g/dL. All anemia cases were treated with iron supplements and prenatal vitamins.

The 3 antepartum hemorrhage reports were nonserious: 1 case of vaginal bleeding/threatened abortion in early pregnancy that subsequently resolved (pregnancy resulted in full-term delivery without complications), 1 subchorionic hemorrhage detected by ultrasound at 12 weeks' gestation that occurred before Tdap, and 1 subchorionic hemorrhage detected by ultrasound at 6 weeks' gestation that was described as "small."

Seven reports were coded as gestational diabetes, all of which were nonserious. Among these cases, the median age of the women was 31 years (range, 25–38 years). Four of the 7 reports described at least 1 risk factor for gestational diabetes that included a body mass index reported as "high" in 3 reports, and history of gestational diabetes in a previous pregnancy in 1 report. One report coded as gestational diabetes described history of type 2 diabetes mellitus and did not refer to the current pregnancy.

Three mothers had oligohydramnios occurring at 33, 40, and 36 weeks of gestation. However, 2 reports did not appear to meet clinical criteria for oligohydramnios (amniotic fluid index <5 cm)[22] as these patients had an amniotic fluid index >5 cm. All 3 women delivered term normal infants with normal birth weight. In one case, a nuchal cord had to be reduced and brief intubation of the newborn was performed.

+Three women developed upper respiratory infection at 3, 23, and 20 weeks of gestation. The first 2 pregnancies resulted in SAB at 9 weeks and term vaginal delivery, respectively, and the outcome of the third pregnancy was not reported.

Comment

During 2005 through 2010 when Tdap was not routinely recommended for use in pregnant women, we found 132 reports submitted to VAERS after receipt of Tdap in pregnant women, accounting for approximately 0.1% of all US reports after Tdap during this period. Our review did not find any unusual or unexpected pattern of maternal, infant, or fetal AEs. A sizable minority of reports (42%) did not describe an AE other than the exposure to Tdap during pregnancy. About 5% of reports met the definition of serious, which is lower than observed in the pregnancy registry of one of the Tdap manufacturers.[23]

SAB was the most frequent pregnancy-specific outcome, reported in 16.7% of reports. SAB is a relatively common event that occurs in about 15-20% of all pregnancies.[24] SAB was also the most frequent pregnancy-specific AE reported in studies of influenza vaccine safety.[18,19] Our analysis did not reveal disproportionate reporting for SAB in VAERS for Tdap compared with influenza vaccines. We identified only 1 infant with a major birth defect in our review: an infant with gastroschisis born to a 15-year-old mother who concomitantly received Tdap with human papillomavirus vaccine. The prevalence of gastroschisis in the United States is 3.73 cases per 10,000 live births[25] and the risk factor most consistently identified for gastroschisis is younger maternal age.[26] Because the total number of pregnant women vaccinated with Tdap is not known, it is difficult to interpret the VAERS findings. No other infants with major birth defects were reported.

As expected, the most frequent non-pregnancy-specific outcome was injection site reaction found in 4.5% of reports; injection site reactions have been identified as a common AE in prelicensure trials in non-pregnant persons.[5,6]

Disproportionality analysis for reports in pregnant women revealed that gestational diabetes, anemia, antepartum hemorrhage, oligohydramnios, and upper respiratory infection were reported to VAERS more frequently after Tdap than after inactivated influenza vaccines. However, further clinical review found that most of these conditions were minor, and there were no concerning patterns for these outcomes that required additional investigation. Because most VAERS reports were from women vaccinated during the first trimester, we were not able to separately evaluate VAERS reports of vaccinations in second and third trimesters of pregnancy. As a national surveillance system, VAERS may be used to detect signals of potential vaccine safety concerns, which can be further explored in carefully designed epidemiological studies. For example, during the 2010-2011 influenza season, a vaccine safety signal for febrile seizures after TIV in young children was identified in VAERS[27] and subsequently confirmed in the Vaccine Safety Datalink,[28] an active surveillance system used to monitor the safety of vaccines in the United States. VAERS has inherent limitations of all passive surveillance systems including underreporting, reporting biases, and inconsistency in quality of reports. Events occurring temporally closer to the time of vaccination are more likely to be reported to VAERS[9]; birth defects diagnosed months after the vaccination may be underreported. Therefore, VAERS data must be interpreted with caution and cannot generally be used to assess causality.[9] The regulatory definition of a serious report in VAERS can have limitations as it may not reflect the true severity of an outcome. For example, in our review 1 stillbirth report at 37 weeks was coded as serious because the patient was hospitalized, whereas a second stillbirth report at 22 weeks was coded as nonserious because the report did not indicate the patient had been hospitalized.

TABLE 3
MedDRA terms among pregnant women after Tdap vaccines compared to inactivated influenza vaccines

MedDRA term	Tdap reports, no. (%) (n = 71)	MIV + TIV, no. (%) (n = 467)	PRR (95% CI)
Anemia	3 (4.2)	1 (0.2)	19.73 (2.1–187.1)
Antepartum hemorrhage	3 (4.2)	1 (0.2)	19.73 (2.1–187.1)
Gestational diabetes	7 (9.9)	3 (0.6)	15.35 (4.1–58.0)
Oligohydramnios	3 (4.2)	3 (0.6)	6.58 (1.4–32.0)
Upper respiratory tract infection	3 (4.2)	3 (0.6)	6.58 (1.4–32.0)

CI, confidence interval; *MedDRA*, Medical Dictionary for Regulatory Activities; *MIV*, monovalent inactivated vaccine (H1N1); *PRR*, proportional reporting ratio; *Tdap*, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; *TIV*, trivalent inactivated influenza vaccine.

Zheteyeva. Safety of Tdap in pregnancy. Am J Obstet Gynecol 2012.

Since Tdap was not routinely recommended for use in pregnancy during the period of this review, no national survey was conducted to assessed Tdap coverage in pregnant women. Therefore, because there were no data on the number of Tdap doses administered to pregnant women, reporting rates cannot be calculated and findings are difficult to interpret.

Prelicensure trials of Tdap did not include pregnant women, and the package inserts for Tdap state that the products should only be used in pregnancy if they are clearly needed.[5,6] ACIP may sometimes make recommendations for off-label use of vaccines after thorough review of risks and benefits.[29]

Our findings are consistent with those of previous observations. Case-control studies of tetanus toxoid have found no association between vaccination with tetanus toxoid during pregnancy and congenital anomalies.[30,31] Few studies have been conducted on the safety of Tdap in pregnant women. A recent review from 2005 through 2011 of the Adacel Vaccine Pregnancy Registry reported 539 pregnant women who received Tdap during pregnancy. Among the 480 spontaneous prospective reports in this series, 27 (5.6%) were classified as serious AEs using a similar definition as our review and there were 16 (3.3%) SAB and 8 (1.7%) preterm deliveries.[23] In another study of 4524 health care workers who were vaccinated with Tdap during a mass vaccination campaign, 16 women received Tdap during pregnancy, all of whom gave birth to full-term infants who had normal newborn evaluations.[32]

In June 2011, ACIP recommended that health care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (>20 weeks' gestation).[8] Although we anticipate that Tdap will continue to have a good safety profile, it is important to continue safety monitoring as more pregnant women are vaccinated.

CONCLUSION

In this comprehensive review encompassing >5 years of reports to VAERS in pregnant women who received Tdap during a time when Tdap was not routinely recommended for pregnant women, we identified no safety concerns. Although our review was subject to limitations of a spontaneous reporting system, our data provide useful baseline information as the new ACIP recommendation for routine use of Tdap in pregnant women is implemented.[8] ■

ACKNOWLEDGMENTS

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Influenza vaccination in pregnancy: current evidence and selected national policies

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Summary

In several countries, pregnant women are recommended seasonal influenza vaccination and identified as a priority group for vaccination in the event of a pandemic. We review the evidence for the risks of influenza and the risks and benefits of seasonal influenza vaccination in pregnancy. Data on influenza vaccine safety in pregnancy are inadequate, but the few published studies report no serious side-effects in women or their infants, including no indication of harm from vaccination in the first trimester. National policies differ widely, mainly because of the limited data available, particularly on vaccination in the first trimester. The evidence of excess morbidity during seasonal influenza supports vaccinating healthy pregnant women in the second or third trimester and those with comorbidities in any trimester. The evidence of excess mortality in two previous influenza pandemics supports vaccinating in any trimester during a pandemic.

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Safety of influenza vaccination during pregnancy

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The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommends routine influenza vaccination for all women who are or will be pregnant during the influenza season. During seasonal influenza epidemics, during previous pandemics, and with the current influenza A (H1N1) pandemic, pregnancy places otherwise healthy women at increased risk for serious complications from influenza, including death. Inactivated influenza vaccine can be safely and effectively administered during any trimester of pregnancy. No study to date has demonstrated an increased risk of either maternal complications or adverse fetal outcomes associated with inactivated influenza vaccination. Moreover, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received influenza vaccine during pregnancy. In this article, we review the evidentiary basis for the recommendation of vaccination of all women who will be pregnant during the influenza season and safety data of influenza vaccination during pregnancy.

Key words: H1N1, influenza vaccine, pregnancy, safety

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine influenza vaccination for all women who are or will be pregnant during the influenza season.[1] The basis for this unambiguous recommendation is clear. During seasonal influenza epidemics, during previous pandemics, and with the ongoing influenza A (H1N1) pandemic, pregnancy places otherwise healthy women at increased risk for serious complications from influenza.[1-4] Vaccination continues to be the most effective method for preventing severe influenza illness and its sequelae.[5-9] Despite robust epidemiologic evidence for increased influenza-related fatality in pregnancy, pregnant women have historically had the lowest vaccine coverage rates of all adults recommended to receive seasonal influenza vaccination.[10] The current pandemic of influenza has once again reminded us that pregnant women are at particularly high risk for morbidity and mortality from influenza and that they are a population that should be vaccinated.

★ EDITORS' CHOICE ★

From April 15 through May 18, 2009, 34 confirmed or probable cases of novel influenza A (H1N1) in pregnant women were reported to the CDC; 32% of these women required hospitalization.[4] Pregnant women were >4 times more likely to be hospitalized for novel influenza A (H1N1)-related complications than those infected in the general population, and accounted for 13% of all deaths from pandemic influenza A (H1N1) during this time period. Most of the pregnant women who died as a consequence of pandemic influenza A (H1N1) were healthy prior to their influenza illness.[4] As a result of this and earlier evidence, CDC has placed pregnant women in the highest-priority group to receive vaccination once the novel influenza A (H1N1) vaccine becomes available.[11]

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For Editors' Commentary, see Table of Contents

Serious influenza-related illnesses in pregnant women will undoubtedly continue to escalate as the influenza A (H1N1) pandemic proceeds. Physicians and other health care providers play a crucial role in the decision-making process with regard to influenza vaccination. They can explore the determinants of vaccine refusal and alleviate fears by addressing real and perceived concerns regarding immunizations during pregnancy. In this article, we review the evidentiary basis for the recommendation of vaccination of all women who will be pregnant during the influenza season and safety data of influenza vaccination during pregnancy.

Evolution of US immunization recommendations

The serious consequences of influenza infection during pregnancy have been recognized for almost a century. In a series of 1350 pregnant women reported during the 1918 pandemic, about 50% developed pneumonia, and of these women, more than half died, with a case fatality rate of 27%.[2,12] The highest mortality was seen in the third trimester. During the pandemic of 1957, nearly half of all women of childbearing age who died were pregnant.[3,13-15]

Over the years, as data regarding the deleterious effects of influenza on the pregnant female have mounted, and in the absence of evidence linking influenza vaccination during pregnancy to any serious negative consequences for the mother or fetus, the recommendations for influenza vaccination during pregnancy have expanded. Since 2004, ACIP has encouraged pregnant women, regardless of gestational age, to receive routine inactivated influenza vaccination.[1,16] The American College of Obstetricians and Gynecologists considers the influenza vaccine an "essential element of prenatal care."[17,18]

Risks of influenza infection in pregnancy

Pregnancy is associated with biochemical, mechanical, hemodynamic, as well as immunologic changes in the mother that become most pronounced by the third trimester. These changes include decreased lung capacity and tidal volume, along with increased cardiac output and oxygen consumption.[19-21] Adaptive humoral immunity remains generally intact with augmentation of the T-helper-type 2 antibody-mediated response.[22] This is in contrast to the selective suppression of T-helper-type 1 cell–mediated immunity that likely protects the developing fetus from maternal cytotoxic-T-lymphocyte activity, but as a consequence, impairs maternal response to infection.[22-24] Although pregnant women do not have a higher incidence of seasonal influenza than the general population, the combination of impaired cell-mediated immunity as well as physiologic changes that accompany pregnancy leave women increasingly vulnerable to serious influenza-related complications.

Influenza-related hospitalization of healthy pregnant women occurs at a rate of 1-2 per 1000.[25] Schanzer et al[26] determined this risk is 18-fold above that of healthy nonpregnant women. Pregnant women with coexisting medical conditions are at even greater risk of severe influenza-related morbidity. When pregnancy is superimposed on high-risk conditions such as asthma or diabetes mellitus, influenza infection contributes to morbidity that is 3-4 times greater than nonpregnant control subjects with similar high-risk conditions.[27-29]

Safety of inactivated influenza vaccine for the pregnant woman

The lack of harmful effects of inactivated influenza vaccination on maternal health during pregnancy has been demonstrated in several studies (Table[30-41]). Munoz et al[32] performed a retrospective analysis of data from 5 influenza seasons using an electronic database of a large multispecialty clinic in the United States. Outcomes of pregnancy were compared between a cohort of 225 healthy women who received influenza vaccine during the second and third trimesters of pregnancy and a control group of 826 healthy unvaccinated women who were matched by age, month of delivery, and type of medical insurance. No serious adverse events occurred within 42 days of vaccination, and there was no difference between the groups in the rates of cesarean section, premature birth, and infant medical conditions from birth to 6 months of age.[32]

During the 1976-1977 influenza season, 56 women who received the inactivated influenza vaccine during the second and third trimesters of pregnancy were evaluated. No notable immediate reactions were observed, nor were there any differences between the course or outcome of pregnancies between the vaccinated women and control group of 40 nonvaccinated pregnant women.[37] No significant adverse reactions, including fever, moderate or severe pain, or need to visit a physician, were observed in another study in which 26 women were randomized to receive the inactivated influenza vaccine or tetanus toxoid vaccine in the third trimester of pregnancy.[35] Deinard and Ogburn[36] evaluated 189 women immunized with the trivalent inactivated influenza vaccine during the 3 trimesters of pregnancy and noted no differences in maternal health or pregnancy outcome compared to the control group of 517 pregnant women who did not receive the vaccine. The few serological studies on pregnant women suggest that antibody response to influenza vaccine is comparable to age-matched, nonpregnant control subjects.[35-37]

The Vaccine Adverse Event Reporting System contains a database for reports regarding influenza vaccination during pregnancy. It is a postmarketing surveillance system with strengths and weaknesses inherent to passive surveillance systems.[42] Of 26 reports related to influenza vaccine in pregnant women from 2000 through 2003, 6 concerned misadministration of the influenza vaccine without negative consequences, 9 described self-limited injection site reactions, 8 were related to systemic symptoms that regressed with time, and 3 reported miscarriages.[43] During this time period, an estimated 2 million pregnant women received influenza vaccination.[44] These data suggest a low rate of adverse events associated with administration of the inactivated influenza vaccine during pregnancy.[43] Licensed 2009 H1N1 monovalent vaccines will be produced using the same manufacturing

TABLE

Summary of data on safety outcomes of studies of influenza immunization during pregnancy

Study	Design	Study group	Control group	Follow-up period	Maternal outcomes	Infant outcomes
Zaman et al,[30] 2008	Prospective, randomized, double-blind controlled trial	172 pregnant women in third trimester	168 pregnant women who received 23-valent pneumococcal polysaccharide vaccine No inert placebo	7 d postvaccination; mother-infant pairs followed up to 24 wk of life	No serious adverse events or differences in pregnancy outcomes	No differences in gestational age, proportion with cesarean delivery, birthweight, or APGAR score
France et al,[31] 2006	Retrospective, matched cohort	3160 infants born to vaccinated mothers	37,969 infants born to nonvaccinated mothers	End of influenza season	Not assessed	No difference with regard to birthweight, gestational age, or length of stay for birth hospitalization
Munoz et al,[32] 2005	Retrospective, matched cohort	225 pregnant women in second and third trimesters	826 nonimmunized pregnant women	42 d after immunization; birth to 6 mo of age	No serious adverse events or differences in pregnancy outcomes	No differences in outcomes of pregnancy (cesarean delivery and premature delivery) and infant medical conditions
Black et al,[33] 2004	Retrospective cohort	3719 pregnant women immunized	45,866 women	Until delivery	No difference in cesarean section	No difference in cesarean section or preterm delivery
Yeager et al,[34] 1999	Prospective cohort	319 pregnant women immunized in second and third trimesters	None	Next prenatal visit	No preterm labor or other serious events	Not assessed
Englund et al,[35] 1993	Randomized, controlled trial	13 pregnant women in third trimester	13 pregnant women who received tetanus toxoid vaccine No inert placebo	Not specified	No significant adverse reactions, including fever, moderate or severe pain, or need to visit a physician noted in either group	Similar gestational ages in both groups; no health concerns in infants examined between 1-3 mo of age
Deinard and Ogburn,[36] 1981	Prospective cohort	189 pregnant women (13 prior to conception; 41, 58, and 77 in first, second, and third trimesters, respectively)	517 nonvaccinated pregnant women	48 h after immunization; pregnancy outcome to 8 wk of life	No differences in maternal health, pregnancy outcome, or postpartum course	No significant differences in adverse pregnancy outcomes (congenital anomalies, neonatal mortality)
Sumaya and Gibbs,[37] 1979	Retrospective, matched cohort	56 women in second and third trimesters	40 nonvaccinated pregnant women	24 h after immunization	No significant immediate reactions or differences in pregnancy course	No increased fetal complications associated with vaccine
Murray et al,[38] 1979	Prospective, matched cohort	59 pregnant immunized women (5, 22, and 32 in first, second, and third trimesters, respectively)	27 nonpregnant vaccinated women	Not specified	No significant side effects after immunization in any women	Not assessed
Heinonen et al, 1973,[39] and 1977[40]	Prospective cohort	2291 pregnant immunized women; up to 650 in first trimester	None	Up to 7 y of age		No suggestive associations for congenital malformations, malignancies, or neurocognitive disabilities
Hulka,[41] 1964	Retrospective and prospective cohort	225 pregnant immunized women (19 in first trimester)	44 nonpregnant influenza immunized; 104 pregnant and 25 nonpregnant immunized with placebo	Up to 3 d after vaccination and at delivery	Local pain at injection site and some systemic symptoms greater in women immunized with influenza vaccine	No association with fetal anomalies or miscarriage

Tamma. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2009.

process as seasonal influenza vaccines, thus it is anticipated that they will have a similar safety profile with serious adverse events after vaccination uncommon.[1,11]

Benefits of influenza vaccination for the neonate

Studies from the United States and Hong Kong demonstrate high rates of hospitalization among infants with influenza, especially in the age group <6 months.[45-47] A review of the US influenza mortality during the 2003-2004 influenza season revealed that childhood deaths associated with influenza were most frequent in infants aged <6 months.[48] Because of limited immunogenicity in this age group, inactivated influenza vaccine is not currently licensed for infants <6 months of age.[1]

Transplacental influenza antibody has been postulated to provide indirect protection in newborns, a period of increased vulnerability to influenza and its complications. Zaman et al[30] conducted a prospective, controlled, blinded trial that assessed the clinical effectiveness of maternal influenza vaccine in their infants. Among infants of the 172 mothers who received influenza vaccination, there were fewer cases of laboratory-confirmed influenza than among infants in the control group, with a vaccine effectiveness of 63% until at least 6 months of age. There was a 29% and 36% reduction in the rates of febrile respiratory illnesses in infants and mothers, respectively.

The advantage of endowing the fetus with maternal antibody prior to birth was also demonstrated during the influenza H1N1 epidemic of 1979. Infants born to mothers with natural serum antibody to influenza A had higher H1-specific passive antibody titers than control subjects. They also had influenza symptoms that were delayed in onset and of shorter mean duration as compared with infants of nonimmune mothers.[49,50] Immunization of pregnant women with influenza virus antigens evokes an antibody response that could result in the passive transfer of sufficient antibody to protect the very young infant for the duration of the influenza season.[37,38]

Safety of maternal influenza vaccination for the fetus

Many pregnant women struggle with the concept of vaccination during pregnancy because of theoretical concerns regarding harm to the fetus. In the longitudinal, population-based Collaborative Perinatal Project that was conducted between 1959-1965, >2000 pregnant women received influenza vaccination, almost a third during the first trimester. The children of these women were followed up for the first 7 years of life, and maternal influenza immunization did not increase the number of stillbirths, congenital malformations, malignancies, or neurocognitive disabilities.[39,40]

In another longitudinal, prospective study, Deinard and Ogburn[36] detected no association between maternal influenza immunization and maternal, perinatal, or infant complications. No teratogenicity was documented, and the infants of vaccinated mothers did not differ from nonvaccinated offspring in physical or neurological assessments at birth and 8 weeks of life.

Similarly, a large retrospective, matched cohort study, which included 3160 infants born to influenza-vaccinated mothers and 37,969 infants born to nonvaccinated mothers, revealed no differences with regard to birthweight, gestational age, or length of stay for birth hospitalization.[31] The safety of the inactivated influenza vaccine was assessed in 7 other trials in which >4500 pregnant women were vaccinated and no significant adverse effects to the fetus were identified[30,32,33,35,37,41] (Table).

It is always beneficial to have an active surveillance system in place to provide feedback of the adequacy, strengths, and weaknesses of the vaccine in question. This will be no different for the novel influenza A (H1N1) vaccine. The CDC and the Food and Drug Administration will be closely monitoring any adverse effects of the influenza A (H1N1) 2009 monovalent vaccine through the Vaccine Adverse Event Reporting System and Vaccine Safety Datalink.[51] The Vaccine Safety Datalink uses rapid cycle analysis to monitor specified adverse events in near real time, with appropriate comparison groups. Moreover, large-scale safety monitoring studies, led by academic researchers, are being established. Ongoing proactive safety monitoring will maintain confidence in the immunization efforts related to maternal influenza vaccination and encourage continued improvements to the vaccine.

Influenza vaccination and thimerosal

Thimerosal, a mercury-containing compound, is a preservative that has been used in some vaccines, including multivial inactivated influenza vaccines, to reduce the likelihood of microbial growth. Concerns came to public attention in 1999 because of uncertainty regarding the applicability of guidelines for long-term exposure to methylmercury, primarily from fish consumption, to intermittent exposure to ethylmercury, a breakdown product of thimerosal. Subsequent studies have shown that ethylmercury does not accumulate and cause harm to the fetal brain like methylmercury, and mounting evidence suggests no increased risk for neurodevelopmental disorders from exposure to thimerosal-containing vaccines.[52-61] In 2004, the US Institute of Medicine reviewed cumulative pediatric exposure to thimerosal-containing vaccines, which led them to reject the hypothesis of a causal link between infants exposed to thimerosal-containing vaccines and autism.[62] The US Public Health Service and other organizations have recommended that efforts be made to eliminate or reduce the thimerosal content in vaccines as part of a strategy to reduce mercury exposures from all sources.[63]

Thimerosal-free versions of the trivalent-inactivated vaccine are increasingly available and a thimerosal-free version of the novel influenza A (H1N1) vaccine will be available in the fall. Limitations in the availability of thimerosal-free influenza vaccines should not preclude administration of inactivated influenza vaccines in pregnant women.[1]

After reviewing the existing body of evidence with regard to thimerosal and the concerns for the developing fetus, the ACIP concludes: "The benefits of influenza vaccination for all recommended groups, including pregnant women and young children, outweigh concerns on the basis of a theoretical risk from thimerosal exposure through vaccination. The risks for severe illness from influenza virus infection are elevated among both young children and pregnant women, and vaccination has been demonstrated to reduce the risk for severe influenza illness and subsequent medical complications. In contrast, no scientifically conclusive evidence has demonstrated harm from exposure to vaccine containing thimerosal preservative. For these reasons, persons recommended to receive TIV [trivalent inactivated influenza vaccine] may receive any age- and risk factor-appropriate vaccine preparation, depending on availability."[1]

Conclusion

Inactivated influenza vaccine can be safely and effectively administered during any trimester of pregnancy. No study to date has demonstrated an increased risk of either maternal complications or untoward fetal outcomes associated with inactivated influenza vaccination. In addition, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received influenza vaccine during pregnancy. Immunization of the mother reduces 1 potential source of viral exposure to the infant, and immunization of other family members will decrease other potential sources. Health care workers caring for pregnant females can play a pivotal role in helping to protect women and newborns from this vaccine-preventable disease and should anticipate questions that expecting mothers may have regarding vaccine safety.

Over the next several months, we will likely witness a surge of infections caused by the novel influenza A (H1N1) virus. As health care workers it is essential that we encourage the vaccination of pregnant women against both the pandemic influenza A (H1N1) virus, as well as seasonal influenza. If pregnancy-related mortality data from prior influenza pandemics are a predictor of what we are to expect in the upcoming months, a significant number of deaths can be averted with influenza vaccination. ■

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6d.

ORIGINAL ARTICLE

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

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ABSTRACT

BACKGROUND

Young infants and pregnant women are at increased risk for serious consequences of influenza infection. Inactivated influenza vaccine is recommended for pregnant women but is not licensed for infants younger than 6 months of age. We assessed the clinical effectiveness of inactivated influenza vaccine administered during pregnancy in Bangladesh.

METHODS

In this randomized study, we assigned 340 mothers to receive either inactivated influenza vaccine (influenza-vaccine group) or the 23-valent pneumococcal polysaccharide vaccine (control group). Mothers were interviewed weekly to assess illnesses until 24 weeks after birth. Subjects with febrile respiratory illness were assessed clinically, and ill infants were tested for influenza antigens. We estimated the incidence of illness, incidence rate ratios, and vaccine effectiveness.

No inert placebo

RESULTS

Mothers and infants were observed from August 2004 through December 2005. Among infants of mothers who received influenza vaccine, there were fewer cases of laboratory-confirmed influenza than among infants in the control group (6 cases and 16 cases, respectively), with a vaccine effectiveness of 63% (95% confidence interval [CI], 5 to 85). Respiratory illness with fever occurred in 110 infants in the influenza-vaccine group and 153 infants in the control group, with a vaccine effectiveness of 29% (95% CI, 7 to 46). Among the mothers, there was a reduction in the rate of respiratory illness with fever of 36% (95% CI, 4 to 57).

CONCLUSIONS

Inactivated influenza vaccine reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants. Maternal influenza immunization is a strategy with substantial benefits for both mothers and infants. (ClinicalTrials.gov number, NCT00142389.)

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Infection with influenza virus is associated with serious illness and hospitalization among pregnant women[1-3] and young infants, including neonates.[4-6] Maternal influenza infection has been associated with an increased risk of maternal hospitalization, fetal malformation, and other illnesses.[7,8] Influenza infection in young infants often prompts hospitalization and can predispose the infants to bacterial pneumonia or otitis media.[9,10] Studies from North America[11] and Hong Kong[12] have shown high rates of hospitalization among infants with influenza, especially those under 6 months of age.[13] The rate of hospitalization for such infants is higher than that for other high-risk groups. A national survey in the United States showed that childhood deaths associated with influenza are most frequent in infants under the age of 6 months.[14]

Natural maternal influenza antibodies protect infants during the first few months of life.[15,16] A study of influenza immunization of pregnant women showed that active transport of immunoglobulin G produced umbilical-cord antibody levels that were higher than those in maternal serum.[17] Epidemiologic data suggest that breast-feeding is also protective against influenza in young infants.[18]

Immunization of pregnant women with inactivated trivalent influenza vaccine has been recommended in the United States for more than a decade[19] and by the World Health Organization (WHO) since 2005.[20] However, few mothers receive the vaccine.[7] The general safety of this strategy has been shown,[21,22] but there has been no randomized, prospective evaluation of its clinical effectiveness.[19,23] Antiviral drugs are not recommended for use in early pregnancy.[19]

Since 2003 in the United States, influenza immunization has been recommended for infants between the ages of 6 months and 23 months,[19] although vaccine immunogenicity may be reduced in children under the age of 2 years.[24,25] Influenza vaccines are not licensed in the United States for use in infants under the age of 6 months, and antiviral drugs for influenza therapy are not licensed for infants under the age of 1 year.[19,26]

The Mother's Gift project is a randomized trial of the strategy of maternal immunization, with the primary goal of assessing the safety and immunogenicity of sequential maternal and infant immunization with pneumococcal vaccines in Bangladesh. In our study of influenza vaccine, mothers in the control group received pneumococcal vaccine only. No infants received the influenza vaccine. We made use of the opportunity afforded by the randomized, blinded design to assess the influenza-related illnesses of the mothers who had received the influenza vaccine and their infants, as compared with those who received only pneumococcal vaccine. We report here estimates of the clinical effectiveness of maternal immunization with inactivated influenza vaccine on influenza illness in infants and mothers.

METHODS

STUDY DESIGN

We conducted a prospective, controlled, blinded, randomized trial to assess the safety and immunogenicity of pneumococcal vaccines, as well as the clinical effectiveness of influenza vaccine (Fig. 1). The primary outcome in infants was the first episode of laboratory-confirmed influenza before 24 weeks of age. Other outcomes in the infants were the confirmation of influenza-like illness by a clinician and confirmation by obtaining a throat swab for influenza antigen testing. Study outcomes for both mothers and infants were the numbers of episodes of respiratory illness with fever or of documented fever of more than 38°C, clinic visits with respiratory illness, and episodes of diarrhea (nonrespiratory end point for both groups).

Exclusion criteria for mothers were a history of systemic disease, previous complicated pregnancy or preterm delivery, spontaneous or medical abortion, congenital anomaly, and hypersensitivity to or receipt of a study vaccine in the previous 3 years. After providing written informed consent, pregnant women were randomly assigned to one of four groups for the primary study, with women in groups 1 and 2 receiving pneumococcal vaccine and those in groups 3 and 4 receiving influenza vaccine. For our analysis of the effect of maternal influenza immunization, the mothers and their infants were analyzed in two groups: those who received influenza vaccine and the control group (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

The randomization sequence was computer-generated, stratified according to clinic, and blocked in groups of four; sequentially numbered opaque envelopes with data regarding assignments to study groups were provided to each clinic.

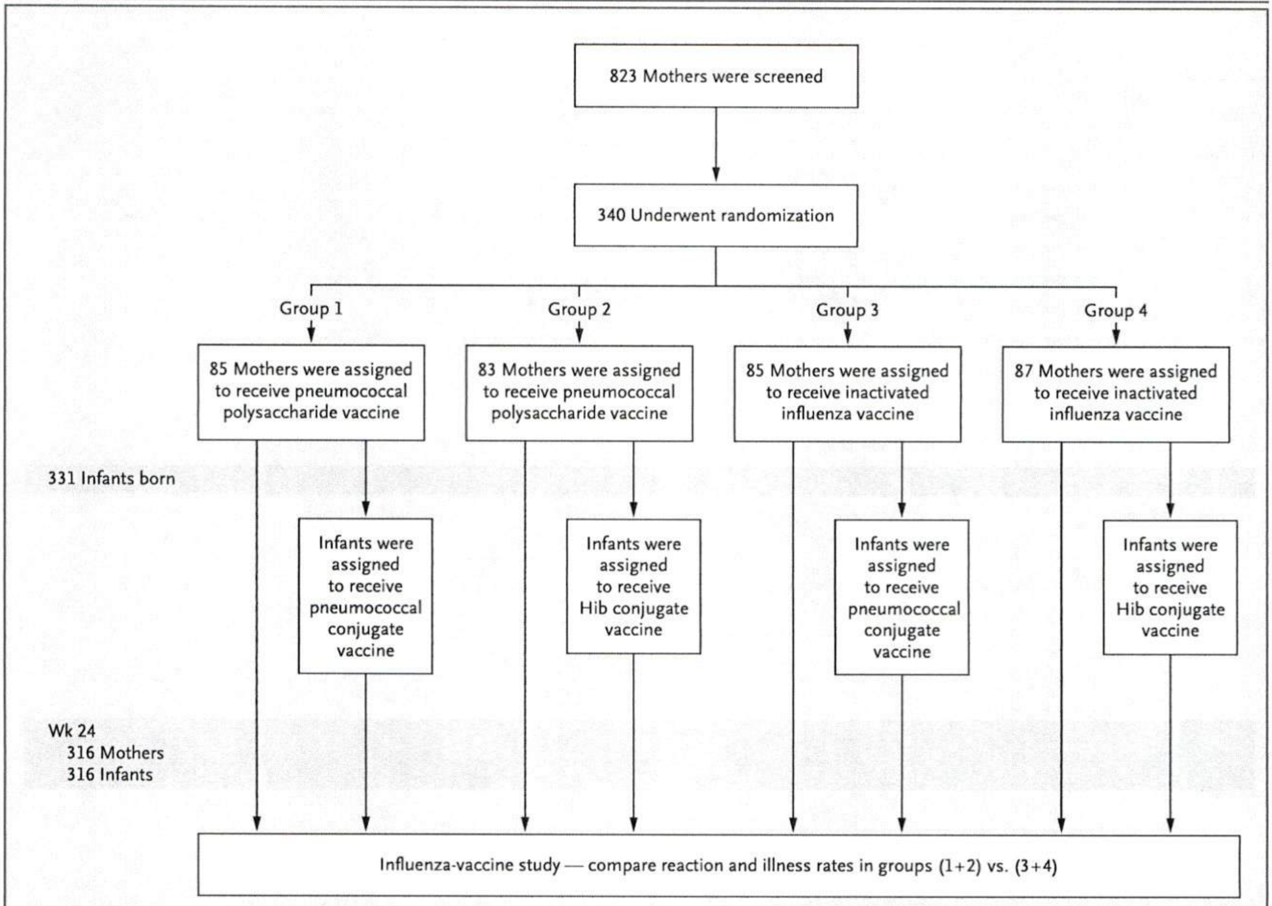

Figure 1. Original Study Design, Showing Subgroups of Mothers and Infants Included in the Current Analysis.
After undergoing screening, 340 pregnant women were randomly assigned to one of four groups for the primary study of the safety and immunogenicity of sequential maternal and infant immunization with pneumococcal vaccines, with mothers in groups 1 and 2 receiving pneumococcal vaccine and those in groups 3 and 4 receiving influenza vaccine. For our current analysis of the effect of maternal influenza immunization, the mothers and their infants were analyzed in two larger groups: mothers who received inactivated influenza vaccine and those who received pneumococcal vaccine only (control group). None of the infants received the vaccine against influenza virus. Hib denotes *Haemophilus influenzae* type b, a bacterium that causes a range of severe infections, including meningitis.

Mothers, families, and study staff who collected data regarding illnesses and adverse events were unaware of the study-group assignments. Blood was collected from mothers before and after immunization; for infants, cord blood was collected at birth, and samples were taken at 6, 10, 14, and 18 weeks and between 22 and 24 weeks for serologic assessment. All infants received the local routine childhood immunizations at 6, 10, and 14 weeks. Infants in the primary immunogenicity study received either three doses of pneumococcal conjugate vaccine (Prevnar, Wyeth) or *Haemophilus influenzae* type b conjugate vaccine (Hiberix, GlaxoSmithKline) at 6, 10, and 14 weeks.

The project protocol was reviewed and approved by the institutional review boards at the International Centre for Diarrheal Disease Research, Bangladesh, and the Bloomberg School of Public Health at Johns Hopkins University, Baltimore. Use of study vaccines was approved by the Directorate of Drug Administration, the Government of the People's Republic of Bangladesh. All the authors vouch for the completeness of the data and the analyses presented.

STUDY VACCINES

Mothers were randomly assigned to receive an inactivated influenza virus vaccine, Fluarix (lot number, AFLUA004BC), containing strains for 2004 (including A/New Caledonia/20/99 [H1N1], A/Fujian/411/2002 [H3N2], and B/Hong Kong/330/2001), as recommended by the WHO for the southern hemisphere, or the 23-valent polysaccharide pneumococcal vaccine, Pneumovax (lot number, 0987N). All study vaccines were purchased from the manufacturer. Clinic staff members who were not involved with study-outcome assessments administered all doses of vaccine by intramuscular injection.

SURVEILLANCE

All mothers were interviewed 8, 24, 48, and 72 hours after immunization and then 1 week later by telephone or home interview to record local and systemic side effects. Most mothers were followed from 2 weeks after immunization through pregnancy and delivery, and all mothers were interviewed once a week from the birth of the infant through 24 weeks of age to assess the occurrence of illnesses in themselves and their infants. Of the 340 mothers who underwent randomization, 331 mothers and their infants (97.4%) began surveillance after delivery, and 316 mother–infant pairs (92.9%) completed the 24 weeks of study surveillance.

Mothers were given digital thermometers and were taught to record axillary temperatures of their infants. Families were asked to bring infants who were ill to the study clinic for evaluation, influenza-antigen testing, and treatment. For clinician-confirmed acute febrile respiratory illness in infants, throat swabs were collected and tested within 24 hours after collection by laboratory technicians at the International Centre for Diarrheal Disease Research in Dhaka, using a rapid test for both influenza A and B (Zstat, ZymeTx). Test results were provided to the clinicians to guide treatment of the patients. Because of a shortage of rapid tests, episodes of respiratory illness with fever in infants from August 2004 through October 2004 could not be tested, and maternal illnesses were not tested. An independent data and safety monitoring board and both institutional review boards reviewed all severe adverse events (for details, see the Supplementary Appendix).

STATISTICAL ANALYSIS

The numbers of subjects that were needed for the primary study were calculated to detect a specified difference in the mean pneumococcal antibody titer in the two groups[27] (see the Supplementary Appendix for details). The sample size had a power of 80% to detect a difference in illness rate of 30% or more. For a comparison of study groups, we assessed group means with Student's t-test and proportions with the chi-square test and Fisher's exact test; all tests were two-sided. Intention-to-treat analysis was performed on the outcome data. Incidence rate ratios (IRRs) were calculated for the study outcomes with the use of Poisson regression models (see the Supplementary Appendix for details). Estimates of clinical effectiveness were calculated with the formula $(1-\text{IRR})\times 100$. We used a post hoc analysis with an interaction term to assess the effect of all infant vaccines that did not contain the inactivated influenza virus. There were no interim analyses of the data. All P values are two-sided and not adjusted for multiple testing. Associations with a P value of less than 0.05 or effectiveness confidence intervals that did not include 0 were considered to have statistical significance.

RESULTS

POPULATION AND ADVERSE EVENTS

A total of 340 women in the third trimester of pregnancy who met the inclusion criteria agreed to participate in the study. The mothers and infants in the two study groups were similar in both demographic and other characteristics (Table 1). Minor local and systemic side effects that occurred during the first 7 days after immunization were similar in the two groups of mothers except for local pain, which was more frequent among the mothers who received pneumococcal vaccine. The difference in the rate of severe adverse events between the two groups was not significant (for details, see the Supplementary Appendix).

EFFECTIVENESS

Mothers were recruited and immunized from August 2004 through May 2005, and cohorts of mother–infant pairs were observed through November 2005, for a total of 1651 person-months in the group of infants and 2165 person-months in the group of mothers. Of the mother–infant pairs, 316 were observed for the full 24-week period. During this time, 22 infants had at least one laboratory-confirmed influenza infection (Fig. 2).

Maternal influenza immunization significantly reduced the rate of laboratory-confirmed influenza in the infants (Table 2). Among the 159 infants whose mothers received influenza vac-

Table 1. Characteristics of the Patients.

Characteristic	Control (N=168)	Influenza Vaccine (N=172)	P Value*
Maternal age (yr)			0.63
Mean	24.9	25.1	
Range	18.0–36.0	18.0–36.0	
Maternal education (yr)			0.42
Mean	10.9	11.2	
Range	0–16.0	0–16.0	
Gravidity			0.93
Mean	2	2	
Range	1–7	1–6	
Parity			0.80
Mean	1.2	1.1	
Range	0–4.0	0–4.0	
Rooms in house (no.)			0.97
Mean	4	4	
Range	1–10	1–10	
Smoker in family (%)	45	40	0.32
Maternal height (cm)			0.64
Mean	153	153	
Range	126–168	140–168	
Interval between vaccination and birth (days)			0.41
Mean	56	54†	
Range	13–94	0–89	
Gestational age at birth (wk)			0.55
Mean	39.3	39.4	
Range	32.2–43.2	32.3–43.9	
Gestational age <37 wk (%)	8.4	6.5	0.54
Delivery in hospital or clinic (%)	92.2	92.3	1.0
Cesarean delivery (%)‡	47.3	45.6	0.83
Birth weight (kg)			0.08
Mean	3.0	3.1	
Range	1.9–4.6	1.8–5.0	
Birth weight <2.5 kg (%)	7.8	4.1	0.17
Mean Apgar score at 1 min and 5 min§	7.5 and 8.5	7.3 and 8.5	0.50 and 0.77
Sex of infant female (%)	43.1	46.1	0.58
Duration of exclusive breast-feeding (wk)			0.18
Mean	15	14	
Range	1–25	1–25	

* Means were compared with the use of Student's t-test, and proportions were compared with the use of Fisher's exact test. None of the differences between the two study groups were significant.

† One mother in the influenza-vaccine group began labor about 8 hours after receiving a dose of the vaccine. The delivery was uneventful, and the infant weighed 2400 g at an estimated gestational age of 34 weeks. This mother–infant pair was included in the intention-to-treat analyses.

‡ The rate of cesarean delivery was typical for the population of patients at the study centers.

§ The Apgar score ranges from 0 to 10, with scores above 7 indicating that the baby's condition is good to excellent.

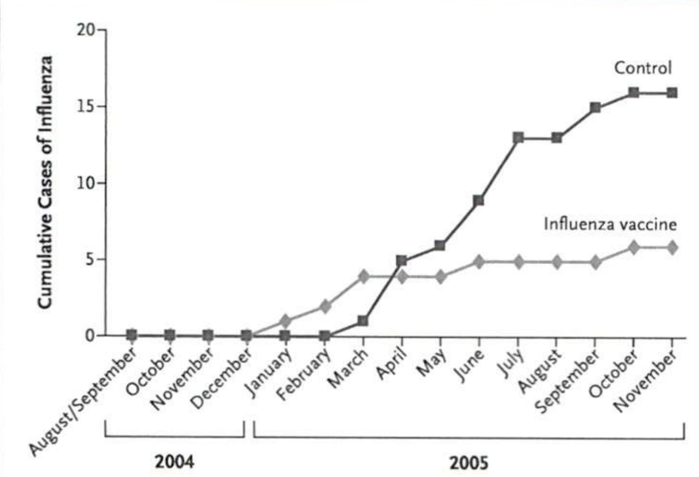

Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.
Testing for influenza antigen was performed from December 2004 to November 2005.

cine, 6 had laboratory-confirmed influenza, as compared with 16 among the 157 infants whose mothers were in the control group, an effectiveness of 63% (95% confidence interval, 5 to 85). Influenza immunization also had substantial effectiveness against the other clinical outcomes in the infants, including a reduction of 29% in the rate of respiratory illness with fever, a reduction of 42% in the rate of infant clinic visits for respiratory illness with fever, and a reduction of 49% in the rate of clinician testing for influenza. Antigen-test–positive influenza was detected from January through October 2005, and vaccine effectiveness appeared to vary somewhat during the 15 months of observation, with apparent increased effectiveness from March through November 2005 (Fig. 2).

Mothers who received influenza vaccine were significantly less likely to have respiratory illness with fever, as compared with the control group, and had fewer respiratory illnesses with a temperature of more than 38°C and fewer clinic visits (Table 2). We observed clinical effectiveness in the reduction of febrile respiratory illness in infants up to 5 and 6 months of age (Fig. 3 and 4). Reported diarrheal illness in mothers and infants was similar in both study groups. The post hoc analysis that was performed with the use of Poisson regression including an interaction term accounting for the noninfluenza childhood vaccines did not show a significant interaction for the infant end-point data (P=0.80), suggesting the effectiveness of maternal influenza immunization did not vary according to infant immunization with *H. influenzae* type b vaccine or pneumococcal vaccine.

INFLUENZA DISEASE AND IMMUNIZATION IN SOUTH ASIA

The frequent, close observation of our Bangladeshi subjects provided unique, serendipitous descriptive data on the natural history of influenza in this South Asian environment, although these observations were not a primary objective of our study. In tropical and subtropical regions, influenza viruses may be perennial with some seasonal variation, causing disease for much of the year.[12,28,29] Limited data regarding influenza are available for Dhaka, which is located at 23.5°N, virtually on the Tropic of Cancer.[30,31] Our surveillance in Dhaka showed evidence of the circulation of influenza virus for 10 of 11 months of observation. Our preliminary data for infants showed that in the control group, the incidence of laboratory-proven influenza illness was at least 10% in the first 6 months of life. In addition, we observed that one infant in each study group had two episodes of laboratory-confirmed influenza (at 1 and 12 weeks in the influenza-vaccine group and at 9 and 28 weeks in the control group). In the mothers, the observed effect of influenza vaccine on febrile illnesses suggested that at least 36% of all maternal febrile respiratory illnesses are attributable to influenza up to 6 months post partum.[32,33]

DISCUSSION

Our study showed that maternal immunization with influenza vaccine had significant clinical effectiveness, with a reduction of 63% in laboratory-proven influenza illness in infants up to 6 months of age and reductions of 29% and 36% in rates of respiratory illness with fever in infants and mothers, respectively. Although the confidence limits for the effectiveness of passive immunization were wide, the point estimates of effectiveness against both laboratory-proven influenza and multiple clinical end points in the infants were similar to those reported in trials of active influenza vaccine in infants older than 6 months of age.[25] However, our findings differ from those of some non-

Table 2. Clinical Effectiveness of Influenza Vaccine in Infants and Mothers.*

Variable	Episodes		Clinical Effectiveness (95% CI)†	Risk Difference (95% CI)‡
	Control	Influenza Vaccine		
	no.		%	
Infants				
Person-months	870	881		
Respiratory illness with fever				
Any fever	153	110	28.9 (6.9 to 45.7)	−28.1 (−48.2 to −8.0)§
Temperature >38°C	77	56	28.1 (−4.6 to 50.6)	−13.7 (−28.0 to 0.5)
Diarrheal disease	138	137	1.9 (−30.0 to 26.0)	−1.6 (−22.1 to 18.9)
Clinic visit	92	54	42.0 (18.2 to 58.8)	−24.5 (−39.5 to −9.5)§
Influenza test ordered	79	41	48.7 (25.4 to 64.7)	−24.4 (−38.0 to −10.8)§
Influenza test positive	16	6	62.8 (5.0 to 85.4)	−6.4 (−12.2 to −0.5)§
Mothers				
Person-months	1076	1089		
Respiratory illness with fever				
Any fever	77	50	35.8 (3.7 to 57.2)	−14.2 (−25.5 to −2.9)§
Temperature >38°C	33	19	43.1 (−9.0 to 70.3)	−7.3 (−14.5 to −0.1)§
Diarrheal disease	60	49	19.3 (−24.6 to 47.8)	−5.9 (−16.4 to 4.5)
Clinic visit	25	19	24.9 (−43.9 to 60.8)	−3.2 (−9.8 to 3.4)

* A total of 300 mothers were followed from 2 weeks after antenatal immunization to delivery, and 316 were followed from delivery until their infants were 24 weeks of age. For case definitions, see the Supplementary Appendix.
† Clinical effectiveness was calculated according to the formula (1 − incidence rate ratio) × 100. The incidence rate ratio was calculated with the use of Poisson regression.
‡ The risk difference was calculated as the difference in the incidence of influenza per 100 subjects at 6 months among infants and mothers in the influenza-vaccine group, as compared with those in the control group, according to the formula ([episodes in influenza group/person/day] × 168 × 100) − ([episodes in control group/person/day] × 168 × 100).
§ P<0.05.

randomized, retrospective studies involving a review of patient records.[34,35]

The randomized and masked nature of the intervention, with the prospective weekly surveillance, allowed us to measure the clinical effects of influenza immunization in both mothers and infants with minimal bias, as evidenced by similar rates in study groups for reported diarrheal disease. The observed vaccine effect in the context of perennial circulation of a variety of influenza virus strains provides a generalizable estimate of the clinical effectiveness of the strategy of maternal immunization in this setting. These data also suggest that infants were protected from clinical illness up to the age of 5 to 6 months, somewhat longer than earlier estimates of passive protection.[16,17]

The rapid test that we used detects influenza neuraminidase and is reported to have a specificity of 80 to 90% and a sensitivity of 70 to 72% for both type A and type B influenza.[36,37] These sensitivity data suggest that perhaps a quarter of true influenza cases were not detected. The test probably was performed in a similar fashion in the two study groups, so that the observed relative reduction or effectiveness would be unaffected, but the absolute incidence of influenza illness in study subjects was underestimated. An independent community surveillance for influenza illness, carried out in Dhaka by the International Centre for Diarrheal Disease Research and the Centers for Disease Control and Prevention during the same period as this study, corroborated the perennial local presence of influenza viruses during the study period and documented the variety of influenza virus strains in circulation.[30]

The study was randomized and controlled, but the analytic comparison was between groups who had received maternal influenza vaccine or another active noninfluenza vaccine, not between

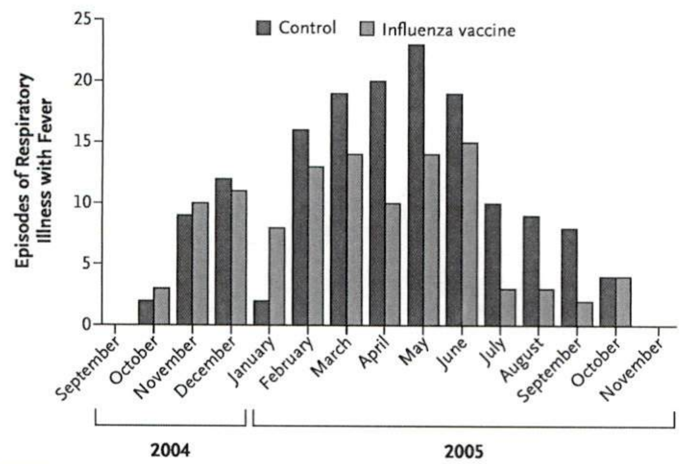

Figure 3. Episodes of Respiratory Illness with Fever in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.

Data were recorded from September 2004 to November 2005 for all ages in each vaccine group.

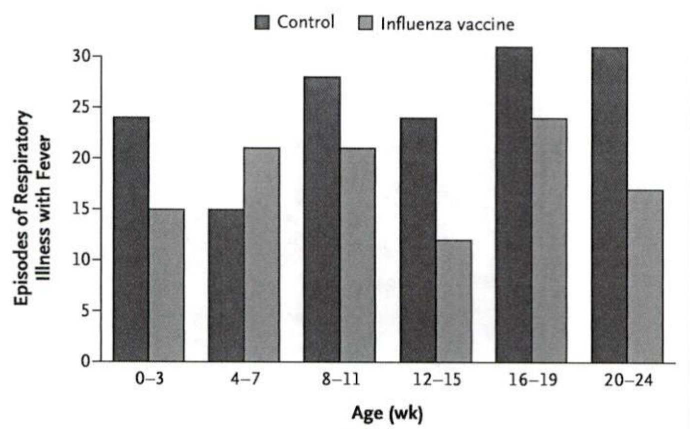

Figure 4. Episodes of Respiratory Illness with Fever in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects, According to Age.

active immunization and placebo. It is possible that in the control group, infants of mothers who received pneumococcal vaccine had a reduced incidence of pneumococcus-associated respiratory illness with fever and a reduced number of clinic visits.[38,39] Such a possibility would reduce the apparent effectiveness of maternal influenza vaccine. In addition, infants were randomly assigned to receive either haemophilus conjugate or pneumococcus conjugate vaccine (Fig. 1), which after several doses may have reduced cases of respiratory illness with fever and clinic visits during the fourth and fifth months of life.[40] However, the randomization of infants ensured that the clinical effect of the infant immunizations would have been similar in the two study groups, with minimal influence on the apparent effectiveness of maternal influenza vaccine. The post hoc interaction analysis was consistent with the lack of effect of infant noninfluenza immunization on influenza-associated illness. Overall, the assessment of these factors suggests that the effect of influenza vaccine we observed in this study underestimated the true effect of maternal influenza immunization.

Our study had several potential limitations. The project did not have resources for carrying out virologic studies, so we had no study data on the strains of influenza virus that were prevalent during the study period, though independent local data describing the variety of influenza viruses in Dhaka during the study period were reported previously.[30] Our study did not have statistical power to assess the infrequent outcomes of influenza, including hospitalization and severe illness. However, the substantial reduction of laboratory-proven influenza illness suggests that a proportion of infrequent serious outcomes of influenza infection would have been averted also. The influenza rapid diagnostic tests were received late and were in short supply, so we tested only some of the infants; this suggests that some episodes of laboratory-proven influenza were not detected in both mothers and infants. However, we did record in detail all illnesses each week throughout the entire project, providing a measure of illnesses that were prevented by the influenza vaccine.

The study surveillance continued for 15 months, representing a relatively brief assessment of the strategy of maternal immunization in this setting. Since a variety of influenza viruses circulated during at least 10 of those months, we suggest that the effectiveness data are representative for this Asian region and are probably generalizable elsewhere as a biologic effect of influenza immunization in pregnant women.

Our data show that a single dose of maternal influenza vaccine provides a considerable two-for-one benefit to both mothers and their young infants. The absolute reduction in the rate of illness showed that every 100 influenza immunizations in pregnancy prevented respiratory illness with fever of more than 38°C in 14 infants and

7 mothers. In other words, five pregnant women would need to be vaccinated to prevent a single case of respiratory illness with fever in a mother or infant.[41] These study data also indicate that influenza immunization of fewer than 16 mothers prevented one laboratory-proven influenza illness in the young infants.

In summary, the clinical effectiveness of influenza vaccine against both laboratory-proven influenza and several other respiratory illnesses shown in this randomized study is unique evidence supporting the strategy of maternal immunization to prevent influenza infection in young infants and their mothers. In a tropical setting of perennial transmission of influenza virus, maternal influenza immunization for much of the year had a substantial protective effect in both mothers and their young infants. In regions with limited financial resources, the strategy of maternal immunization is widely used for tetanus prevention, and antenatal-immunization systems are in place. Our study suggests that the antenatal-immunization strategy should be evaluated further for the prevention of influenza. Additional, larger studies will need to be carried out for several years with annual new formulations of influenza vaccine to show the full effect of the strategy of maternal influenza immunization in tropical and subtropical regions.

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(7)

BREAKING NEWS **PERSPECTIVE**

ACIP recommends Tdap vaccine during each pregnancy

Infectious Diseases in Children, November 2012

ADD TOPIC TO EMAIL ALERTS

The Advisory Committee on Immunization Practices voted Wednesday, 14-0 with one abstention, to recommend that a tetanus-diphtheria-acellular pertussis booster vaccine be given to pregnant women during each pregnancy, despite concern over the lack of data for the safety of multiple Tdap vaccinations.

Last year, ACIP recommended that pregnant women receive the Tdap vaccine only if they have previously not received one.

In a Vaccine for Children vote, the committee voted unanimously to include a change that recommends that adolescents who are pregnant should receive a dose of Tdap, regardless of their Tdap vaccination history.

Carol Baker

"There is absolutely no question that we need more data," **Carol Baker, MD,** professor of pediatrics at Baylor College of Medicine, said while representing the IDSA at the meeting. "But we have to consider risk to the mother vs. the benefit, just like this committee always has."

According to **Jennifer Liang, MD,** epidemiologist in the CDC's National Center for Immunization and Respiratory Diseases, antibody response from the Tdap vaccine peaks at 1 month after vaccination and decreases significantly after 1 year. Because of this, women who have received the vaccine during a previous pregnancy may not have the same protection at future pregnancies.

"A single dose of Tdap at one pregnancy is insufficient to provide protection for subsequent pregnancies," Liang said.

A lack of safety data about multiple Tdap vaccinations caused some hesitancy among the committee, especially when considering women who have short intervals between pregnancies. There are no data available that address this specific issue, but available data suggest that there is no excess risk of adverse events, Liang said, adding that the CDC working group supports the need for a prospective study to determine the adverse event risk in women with multiple pregnancies.

She said data indicate that the average woman has two children, and most have an interval of at least 13 months between pregnancies, meaning that most women would not receive more than two doses of the vaccine.

After recommendations, the ACIP continues to review data about its recommendations and will continue reviewing data on the safety of giving multiple Tdap vaccinations to pregnant women.

Because the recommendation is an off-label use of the Tdap vaccine, there was concern about whether insurance programs, including Medicare and Medicaid, would cover the vaccinations for these women.

"In making an off-label use recommendation, what we need to understand is how the coverage of immunizations under Medicare and Medicaid and individual insurance plans will be affected," committee member **Sara Rosenbaum, JD,** said.

A representative from American's Health Insurance Plans (AHIP) indicated that insurance plans almost always follow ACIP recommendations, even when those recommendations are for off-label use, and there is precedent for it. A representative for the CMS indicated that, for Medicaid, the ACIP recommendations are followed, but for Medicare, ACIP recommendations are not followed under Part D.

PERSPECTIVE

Sandra A. Fryhofer

I'm relieved. Recent epidemics suggest that cocooning strategies are not enough to prevent pertussis in infants. It's time to go to plan B, which is vaccinating mom during every pregnancy. We know that the majority of transmission to the baby is not from the mother. Babies aged 2 months and younger have the most pertussis-related deaths and hospitalizations. These babies are too young to get vaccinated. They need protection and this is a way to do it. Vaccinating mom late in pregnancy means that mom's antibodies will pass to baby, protecting baby during their first 2 months of life when they are most vulnerable.

That said, this is uncharted territory. Studies need to be done to make sure that mom's antibodies don't significantly blunt baby's immune response when given vaccination. We also don't know, for sure, if there will be adverse effects for mom when multiple doses of the vaccine are administered. Is there a need for a single antigen vaccine that only provides acellular pertussis component, so that the moms won't be getting extra doses of tetanus or diphtheria vaccine? The other concern is getting the word out to providers and to women. Influenza vaccine recommendations for pregnant women have helped women get comfortable with idea of vaccination during pregnancy. The recent pertussis epidemic in Washington and the resulting infant deaths is a wake-up call. Women need to make sure they can do everything they can to protect baby from contracting this deadly disease.

Sandra A. Fryhofer, MD

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(8)

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Inflammatory Responses to Trivalent Influenza Virus Vaccine Among Pregnant Women

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Abstract

Objective—In the U.S., seasonal trivalent influenza vaccination (TIV) is currently universally recommended for all pregnant women. However, data on the maternal inflammatory response to vaccination is lacking and would better delineate the safety and clinical utility of immunization. In addition, for research purposes, vaccination has been used as a mild immune trigger to examine *in vivo* inflammatory responses in nonpregnant adults. The utility of such a model in pregnancy is unknown. Given the clinical and empirical justifications, the current study examined the magnitude, time course, and variance in inflammatory responses following seasonal influenza virus vaccination among pregnant women.

Methods—Women were assessed prior to and at one day (n=15), two days (n=10), or approximately one week (n=21) following TIV. Serum interleukin (IL)-6, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), and macrophage migration inhibitory factor (MIF) were determined by high sensitivity immunoassay.

Results—Significant increases in CRP were seen at one and two days post-vaccination (*ps* <.05). A similar effect was seen for TNF-α, for which an increase at two days post-vaccination approached statistical significance (*p* = .06). There was considerable variability in magnitude of response; coefficients of variation for change at two days post-vaccination ranged from 122% to 728%, with the greatest variability in IL-6 responses at this timepoint.

Conclusions—Trivalent influenza virus vaccination elicits a measurable inflammatory response among pregnant women. There is sufficient variability in response for testing associations with clinical outcomes. As adverse perinatal health outcomes including preeclampsia and preterm birth

* please research "maternal immune activation"

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have an inflammatory component, a tendency toward greater inflammatory responding to immune triggers may predict risk of adverse outcomes, providing insight into biological mechanisms underlying risk. The inflammatory response elicited by vaccination is substantially milder and more transient than seen in infectious illness, arguing for the clinical value of vaccination. However, further research is needed to confirm that the mild inflammatory response elicited by vaccination is benign in pregnancy.

Pregnant women are considered at greater risk than the general population for complications, hospitalization, and death due to influenza [1–3]. Based on known risks versus benefits of immunization, routine influenza vaccination is currently recommended by the Centers for Disease Control (CDC) and American College of Obstetricians and Gynecologists (ACOG) for all healthy pregnant women in any trimester [4, 5]. Several studies have shown no harmful effects resulting from influenza vaccination during pregnancy [for review see 2]. However, because vaccination could confer risks that have not been measured or would require larger sample sizes to detect, the wisdom of universal vaccination of pregnant women has been a topic of debate [6, 7].

Studies of TIV in pregnancy have shown no differences among vaccinated versus unvaccinated women and their infants in rates of miscarriage, C-section, gestational age at delivery, birth weight, APGAR scores, length of hospitalization after birth, or fetal malformations and mortality to age four among offspring [8–19]. Maternal vaccination has been associated with 63% reduction in clinical influenza in infants from birth to six months of age [12]. Among infants born during influenza season, maternal vaccination may reduce risk of preterm delivery and small for gestational age birth [20]. Further, maternal influenza infection has been linked to increased risk of schizophrenia in adult offspring [21–23], a risk that vaccination could mitigate. However, given that this link may be mediated by the maternal inflammatory response to infection, it has been postulated that the inflammatory response to vaccination may itself be detrimental to fetal brain development [7]. To our knowledge, there are no available data regarding the magnitude or duration of inflammatory responses elicited by TIV in pregnant women. Thus, better understanding of the maternal inflammatory response elicited by vaccination is highly warranted from a clinical standpoint.

In addition, assuming health benefits, vaccination may provide a useful research model. Inflammatory processes play an important role in the maintenance of successful pregnancy. Pregnancy has been associated with decreased inflammatory responses and maintained/increased antiinflammatory responses to immune challenges in human and animal models [24–29]. It has been postulated that this immune adaptation may prevent rejection of the fetus by the maternal immune system. Thus, a tendency toward inflammatory responding may increase risk of adverse outcomes, including preeclampsia and preterm birth (PTB) [30–33].

Human studies of the inflammatory response system in pregnant women to-date have relied on *in vitro* models [27, 28]. Because in vitro techniques involve isolation of specific cells, removal of cells from the complex *in vivo* environment, and exposure to higher levels of antigen than normally occurs *in vivo*, the clinical relevance of *in vitro* assessments is often unclear. By providing insight into immune function in the complex, multifaceted, naturally-occurring environment, *in vivo* models arguably provide data with clearer clinical relevance.

Vaccines have been used as a mild immune trigger to examine individual differences *in vivo* inflammatory responses in non-pregnant adults [34–40]. Differential inflammatory responses to vaccination have been reported in association with depressive symptoms [38] and carotid artery disease [39], conditions with an inflammatory component. Translating this research to pregnancy, differential inflammatory responses to immune triggers may predict risk for preeclampsia and preterm birth. The utility of such a model is dependent on 1) vaccination eliciting a measurable inflammatory response and 2) the presence of sufficient variability in response to allow for differential classification (e.g., high versus low responders). Due to substantial immune adaptation that occurs during pregnancy, with reported down-regulation of inflammatory responding, findings regarding the inflammatory response elicited by vaccination in nonpregnant adults may not extend to pregnant women.

Given both the clinical and empirical justifications for better understanding inflammatory responses elicited by immunization in pregnancy, the current study examined the magnitude, time course, and variance in inflammatory responses following seasonal trivalent influenza virus vaccination (TIV) among pregnant women.

Method

Participants

This study included 46 pregnant women who were assessed prior to and at either one day (n=15), two days (n=10), or approximately one week (6–9 days; n=21) following seasonal influenza virus vaccination. Women were recruited through the Ohio State University Medical Center General Perinatal Clinic. Women were excluded from participation if they reported recent acute illness, chronic health conditions with implications for immune function, or if fetal anomaly or preeclampsia were indicated per medical records.

At a regular prenatal visit, women were informed of the study. Women were asked if they planned to receive the seasonal flu shot. If they were undecided, they were encouraged to speak with their physician about vaccination prior to study enrollment. Women who were eligible and chose to participate completed an informed consent. Participants received compensation for their participation. The study was approved by The OSU Biomedical Institutional Review Board. Data were collected between November 2006 to April 2009.

Demographic and Psychosocial Measures

Demographic and descriptive information regarding height, current weight, pre-pregnancy weight, age, race, education level, marital status, and income was collected. The following health behaviors were assessed at the initial study visit: smoking, participation in regular physical activity (i.e., at least one hour per week of vigorous activity), and frequency of prenatal vitamin use.

Measurement of Serum Inflammatory Markers

At each study visit, whole blood was collected into vacutainer tubes while subjects were in a seated position. All samples were collected between 9:30 am – 1:30 pm. Samples were immediately centrifuged, aliquoted, and placed in −80 C degree freezer storage until analysis. Serum levels of IL-6 and TNF-α were assayed in duplicate with ultra-sensitive multiplex kits from Meso Scale Discovery (MSD) and chemilluminescence methodology using the Immulite 1000 (Siemens Healthcare Diagnostics, Inc., 1717 Deerfield Rd., Deerfield, Il.) Serum levels of MIF were assayed in duplicate using ultra-sensitive multiplex kits from R&D Systems (Minneapolis, MN) per kit instructions.

Physical Measurements

Body mass index (BMI) was calculated (kg/m^2) using height as measured by a nurse at the study visit and self-reported weight prior to pregnancy. The general accuracy of self-reported pre-pregnancy weight was confirmed by calculation of expected pre-pregnancy weight based on weight by scale at the study visit.

Influenza Virus Vaccination

Each woman received Fluarix (GlaxoSmithKline) seasonal trivalent influenza virus vaccination. During the 2006–2007 influenza season, each 0.5 mL dose contained 45 μg hemagglutinin (HA), with 15 μg HA of each of the following three virus strains: A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. During the 2008–2009 influenza season, the vaccination contained A/Brisbane/59/2007 (A/H1N1), A/Uruguay/716/2007 (A/Brisbane/10/2007-like strain) (A/H3N2), and B/Florida/04/2006. The vaccine was administered following baseline blood sampling. Data regarding inflammatory markers at one week post-vaccination were collected during the 2006–2007 influenza season. During the 2008–2009 influenza season, women were assessed at either one day or two days post-vaccination.

Statistical Analyses

Women assessed at one day, two days, and one week post-vaccination were compared in terms of demographic and behavioral characteristics using ANOVA and chi-square analyses to determine the extent to which groups were comparable.

Cytokine data were log transformed to normalize the data distribution. Log-transformed data were used for all statistical analyses. Datapoints ≥ 3 standard deviations from the mean change from baseline were considered to be outliers and were excluded from analyses except where both pre- and post-vaccination measures exceeded this limit. Paired t-tests were conducted to compare serum levels of proinflammatory proteins pre- and post-vaccination. To estimate the time course of response, analysis of covariance (ANCOVA) models were fit to responses from each time point with the baseline value included as a covariate. Estimates and standard errors were obtained for each follow-up time and plotted in comparison to the overall baseline mean. Coefficients of variation (CV = 100% × SD/mean) for change from baseline to post-vaccination at each time point and standard deviations of change scores are reported to summarize variability of responses.

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Results

Demographic and Behavioral Characteristics

Demographic and behavioral characteristics of the study sample are presented in Table 1. Reflecting the demographic characteristics of the women served at the OSU General Perinatal clinic, women in the study were predominately African-American (61.7%). The average age was = 24.43 (SD = 4.38). Women were predominately in the late first to early second trimester at the time of vaccination [average weeks gestation = 15.1 (SD = 8.1)]. Few women endorsed receiving seasonal influenza vaccination in the previous year (n=5, 10.6%).

Women assessed at one day, two days, and one week post-vaccination were not significantly different in age ($F(2,44) = 2.15$, $p = 0.13$), body mass index ($F(2,44) = 0.50$, $p = 0.61$), gravidity ($F(2,44) = 1.6$) $p = 0.21$), or race (X^2 (4) = 2.01, $p = 0.74$). In terms of health behaviors, women in these three groups did not differ significantly in rates of smoking ($X^2(2) = 0.21$, $p = 0.90$), hours of sleep in the night prior to vaccination ($F(2,44) = 1.83$), $p = 0.17$), or rates of vaccination in the previous year ($X^2(2) = 0.17$, $p = 0.92$).

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Inflammatory Responses Following Influenza Virus Vaccination

Paired t-tests indicated that compared to baseline, increases in CRP were seen at one day post-vaccination (mean increase 0.19 lg mg/dl (95% CI: 0.08, 0.30), $t(14) = 3.76$, $p = 0.002$) and two days post-vaccination; (0.24 lg mg/dl (0.03, 0.45), $t(9) = 2.58$, $p = 0.03$; Figure 1). When assessed at one week post-vaccination, CRP levels were not significantly different than baseline; (−0.07 lg mg/dl (−0.15, 0.01), $t(21) = -0.41$, $p = 0.69$). For TNF-α, a similar pattern of results was seen (Figure 2). As compared to baseline, no significant increase was seen at one day post-vaccination (−0.0004 lg pg/ml (−0.08, 0.08), $t(14) = -0.01$, $p = 0.991$). However, increases in TNF-α approached statistical significance at two days post-vaccination (0.04 lg pg/ml (−0.002, 0.08), $t(9) = 2.15$, $p = 0.06$). At one week post-vaccination, TNF-α levels were comparable to baseline (−0.01 lg pg/ml (−0.04, 0.03), $t(20) = 0.30$, $p= 0.77$). A decrease in IL-6 at one week post-vaccination also approached statistical significance (mean decrease −0.07 lg pg/ml (−0.15, 0.005), $t(19) = -1.97$, $p = 0.06$). Changes in MIF and IL-6 did not reach statistical significance at any timepoint ($ps \geq 0.46$ other than IL-6 at one week). MIF measures for two subjects were excluded as outliers (low baseline MIF).

Considerable variability in response to vaccination was evidenced (Table 2). For each marker at each timepoint, the standard deviation in change scores from baseline to post-vaccination was equivalent or greater in magnitude than the mean increase. Coefficients of variation for change at two days post-vaccination ranged from 122% to 728%, with the greatest variability in IL-6 responses at this timepoint.

Discussion

These data demonstrate that seasonal influenza virus vaccination elicits a significant inflammatory response among pregnant women. The response was most robust at two days post-vaccination for C-reactive protein, with a similar, though nonsignificant, pattern of response for TNF-α. No statistically significant changes in IL-6 or MIF were evidenced. However, the power to detect effects was limited by sample size. Thus, despite changes in immune regulation previously reported in pregnancy, vaccination resulted in a transient inflammatory response among pregnant women. As there was no nonpregnant comparison group in this study, and participants in previous studies are not demographically equivalent to the current study [39, 40], the magnitude or duration of response during pregnancy versus nonpregnancy is unknown.

The utility of vaccination as a model for examining differential risk for adverse outcomes is dependent on sufficient variability in responses, allowing for meaningful classification of individuals as high versus low responders. In the current study, substantial variability was evidenced, as indicated by large standard deviations relative to mean increases and resulting high coefficients of variation. From a research standpoint, the presence of this variability may be of greater importance than the average magnitude of response overall. For example, we have previously reported that pregnant women with greater depressive symptoms exhibited significant inflammatory responses in terms of serum MIF at one week post-vaccination although there was not a statistically significant increase in MIF among women overall [41].

The assessment of *in vivo* inflammatory responses and factors affecting such responses has important applications in the context of pregnancy. Pregnancy is a period of tight inflammatory control. Attenuation of inflammatory responses during pregnancy has been reported in both human and animal models [24, 26–28] and lack of such adaptation has been associated with adverse pregnancy outcomes. For example, peripheral blood mononuclear cells (PBMCs) stimulated *in vitro* with antigen or mitogen showed decreased proinflammatory cytokine production and increased antiinflammatory cytokine production during healthy pregnancy ending in full term delivery as compared to nonpregnancy, with the strongest effects seen in the third trimester [28]. In contrast, among pregnancies that subsequently ended in miscarriage or small for gestational age babies, PBMCs exhibited *greater* proinflammatory cytokine production and *reduced* antiinflammatory cytokine production as compared to cells from both nonpregnant women and healthy pregnancies [28].

Inflammatory processes may also contribute to gestational hypertension and preeclampsia which affect 6–8% of all pregnancies and are responsible for 40% of medically-indicated preterm deliveries [31]. These disorders are characterized by high levels of circulating inflammatory markers [31, 32, 42–45]. Many features of preeclampsia, including impaired lipid metabolism and endothelial dysfunction, can be induced by proinflammatory cytokines [46] and the clinical severity of preeclampsia correlates with the degree of dysregulation seen in cytokine function [47]. Inflammation associated with infections may disrupt lipid metabolism and cause endothelial damage, predisposing women to the development of hypertensive disorders of pregnancy [48]. Therefore, women prone to exhibit exaggerated inflammatory responses to immune triggers may show increased risk of these disorders and related increased risk of preterm birth.

Studies in pregnant women to-date have relied on *in vitro* methodology. As compared to *in vitro* models, examination of similar processes in the *in vivo* setting provides rich data regarding inflammatory processes in the complex natural environment. Thus, vaccination provides a model that may be useful in understanding differences in risk for pregnancy-related conditions with an inflammatory component, including preterm birth and preeclampsia.

These research directions are suggested in relation to conceptualizing vaccination as a mild inflammatory trigger that may serve as a model for understanding a general propensity toward inflammatory responding. However, there are important gaps in our knowledge of the effects of vaccination on fetal health. Relatedly, the wisdom of universal vaccination for healthy pregnant women is a topic of debate [6, 7]. Due to the known risks of influenza infection in pregnancy and evidence for no effects of vaccination on birth outcomes including preterm labor, rates of C-section, or fetal malformation [8–19], vaccination is considered beneficial and is currently standardly recommended to all pregnant women [1]. There is strong evidence that exposure to infectious agents during the prenatal period influences developmental outcomes including stress reactivity, disease susceptibility, and risk for disorders including schizophrenia and cerebral palsy [49–54]. Thus, by preventing infection, vaccination may mitigate long-term risks for offspring health. The inflammatory response elicited by vaccination is considerably milder and more transient than that elicited by infection [55], arguing for protective benefits of vaccination. However, as demonstrated in the current study, there is substantial variability in the magnitude of response to vaccination. Thus, continued research is needed to further delineate whether the mild inflammatory response elicited by vaccination is benign for fetal development. In particular, birth cohort studies examining maternal cytokine responses to vaccination in conjunction with long-term offspring health outcomes are warranted [7].

Despite current recommendations for routine immunization, historically, vaccination coverage among pregnant women in the U.S. has been low. According to data from the National Health Interview Survey (NHIS), only 11.3% of pregnant women were vaccinated during the 2008–2009 flu season [5]. Reflecting substantial public health efforts and greater public awareness of risk during the 2009–2010 influenza pandemic, coverage of pregnant women was markedly higher; it is estimated that 50.7% of pregnant women received seasonal vaccination and 46.6% received the 2009 H1N1 vaccine [56]. Among pregnant women who did not receive seasonal vaccine during the 2009–2010 season, 47.7% indicated safety concerns for the baby and 45.2% indicated safety concerns for themselves were a factor [56]. Similarly, among women who didn't receive the novel H1N1 vaccine, 63.6% cited safety concerns for the baby and 61.4% had safety concerns for themselves. Utilizing vaccination as research model promotes current clinical recommendations and may ultimately serve to increase vaccine acceptance by provision of greater safety data.

An important limitation of this study is that women were assessed primarily in the first trimester or early second trimester of pregnancy and that no nonpregnant comparison group was assessed. Due to the small sample size, assessment of effects of stage of gestation or statistically controlling for stage of gestation was not possible. Prior data on *in vitro* inflammatory responses indicate that, as compared to nonpregnant women, pregnant women show attenuation of inflammatory responses which is greatest during the third trimester [28]. The extent to which similar effects are seen in the context of *in vivo* immune triggers is unknown. In addition, this study did not permit examination of effects of behavioral, demographic, or psychosocial variables on the trajectory of inflammatory responses. Key potential modifiers of this response include race, smoking, sleep, body mass index, prior vaccine exposure, and prior influenza exposure which may be influenced by the number of children in one's household. A clear future direction using vaccination as an *in vivo* model is to examine the extent to which these factors predict differential inflammatory responding.

Women in this study were assessed during two different influenza seasons; however, data at one and two days post-vaccination were collected in the same influenza season and this is when an inflammatory response was noted. This time course of response is similar as that noted in nonpregnant samples [34, 40], thus we believe these effects are reliable. However, it is certainly possible that the inflammatory response to vaccination is affected by the specific viral strains in a given flu season, in part due to different rates of prior exposure to specific strains. Future research using larger samples assessed in different vaccine years would help to address this issue. In this study, a decrease in IL-6 from baseline to one-week post-vaccination approached statistical significance ($p = 0.06$). Additional studies are needed to document if this is a consistent and reliable effect. If so, this may indicate a temporary "overshooting" as the body regains homeostasis following exposure to an inflammatory trigger. Finally, each woman was assessed at only a single follow-up timepoint. Women assessed at each follow-up timepoint were recruited from the same clinic and were demographically similar in terms of age, race, BMI, and parity. However, because the kinetic across different individuals likely differs, even minimal differences between groups may affect responses at a given timepoint. Thus, future research should ideally follow the same women at multiple timepoints to most clearly describe the inflammatory response trajectory following vaccination.

In sum, this study demonstrates that trivalent influenza virus vaccine (TIV) elicits a measurable inflammatory response during pregnancy, and that considerable variability is seen between women in the magnitude of this response. Thus, vaccination may serve as a useful model for examining individual differences in propensity toward inflammatory responses to immune triggers; this model may have implications for understanding risk of adverse pregnancy outcomes. The inflammatory response elicited by TIV is substantially milder and more transient than seen in infectious illness, arguing for the clinical value of vaccination. However, given the current clinical recommendation of routine immunization of healthy pregnant women, further research is warranted to confirm that the mild inflammatory response elicited by vaccination is benign in pregnancy.

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Highlights

- Examined inflammatory responses to trivalent influenza virus vaccine (TIV) in pregnant women
- Significant increases in serum CRP were seen at one and two days after vaccination
- TIV elicits measurable and highly variable inflammatory responses
- TIV may be useful as an *in vivo* model to examine inflammatory processes in pregnancy
- Research is needed to confirm that the mild inflammatory response to TIV is benign in pregnancy

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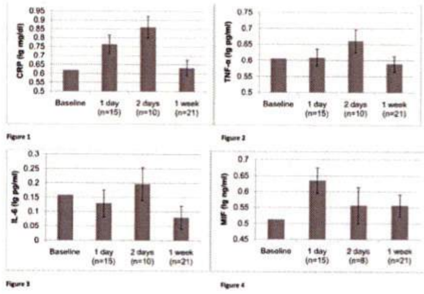

Figure 1–4. Inflammatory responses following seasonal influenza virus vaccination among pregnant women

Analyses utilized paired t-tests at baseline and follow-up for each set of data. Data are presented using a normalized baseline value for illustrative purposes.

Table 1

Demographic Characteristics

	Follow-Up Timepoint			
	One day (n=15)	**Two days (n=10)**	**One week (n=21)**	**Total (n=46)**
Age	22.71 (3.92)	24.31 (4.0)	25.66 (4.6)	24.43 (4.38)
Race				
African-American	10 (66.7%)	5 (50%)	14 (63.6%)	29 (61.7%)
Caucasian	3 (20%)	4 (40%)	7 (31.8%)	14 (29.8%)
Other	2 (13.3%)	1 (10%)	1 (4.5%)	4 (8.5%)
BMI	26.94 (6.92)	28.83 (10.6)	26.82 (6.01)	27.28 (7.34)
Weeks Gestation	13.9 (6.9)	12.9 (6.8)	16.9 (9.2)	15.1 (8.1)
Gravidity	2.4 (1.5)	3.6 (2.5)	3.2 (1.5)	3.0 (1.8)
Current Smoker	4 (26.7%)	3 (30%)	5 (22.7%)	12 (25.5%
Hours Sleep Prior to Vaccination	6.4 (1.9)	7.0 (1.2)	7.5 (1.6)	7.0 (1.7)
Vaccinated Previous Year	2 (13.3%)	1 (10%)	2 (9.1%)	5 (10.6%)

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Table 2

Mean Change from Baseline and Coefficients of Variation in Change Scores

Cytokine	Mean (SD) Change from Baseline ($\log_{10}$ scale)			CV in Change from Baseline ($\log_{10}$ scale)		
	One Day (n=15)	Two Days (n=10)	One Week (n=21)	One Day (n=15)	Two Days (n=10)	One Week (n=21)
CRP	0.19 (0.20)	0.24 (0.29)	−.02 (0.19)	103%	122%	1126%
IL-6	−0.02 (0.24)	0.02 (0.16)	−0.07 (0.17)	991%	728%	227%
TNF-α	0.00 (0.15)	0.04 (0.06)	−0.01 (0.08)	---†	147%	1521%
MIF	0.04 (0.18)	−0.08 (0.22)*	−0.02 (0.17)	512%	283%	778%

*n=8

†absolute mean change < 0.0005; CV not reported

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENGERIX-B safely and effectively. See full prescribing information for ENGERIX-B.

ENGERIX-B [Hepatitis B Vaccine (Recombinant)] injectable suspension, for intramuscular use
Initial U.S. Approval: 1989

INDICATIONS AND USAGE

ENGERIX-B is a vaccine indicated for immunization against infection caused by all known subtypes of hepatitis B virus. (1)

DOSAGE AND ADMINISTRATION

For intramuscular administration. (2, 2.2)

- Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Persons 20 years of age and older: A series of 3 doses (1 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Adults on hemodialysis: A series of 4 doses (2 mL each) as a single 2-mL dose or as two 1-mL doses on a 0-, 1-, 2-, 6-month schedule. (2.3)

DOSAGE FORMS AND STRENGTHS

ENGERIX-B is a sterile suspension available in the following presentations:

- 0.5-mL (10 mcg) single-dose vials and prefilled syringes (3)
- 1-mL (20 mcg) single-dose vials and prefilled syringes (3)

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast. (4)

WARNINGS AND PRECAUTIONS

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)
- Temporarily defer vaccination of infants with a birth weight less than 2,000 g born to hepatitis B surface antigen (HBsAg)-negative mothers. (5.3)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. (5.4)

ADVERSE REACTIONS

The most common solicited adverse reactions were injection-site soreness (22%) and fatigue (14%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

DRUG INTERACTIONS

Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial. (7.1)

USE IN SPECIFIC POPULATIONS

- Antibody responses are lower in persons older than 60 years than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENGERIX-B is indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration. See Section 2.2 for subcutaneous administration in persons at risk of hemorrhage.

2.1 Preparation for Administration

Shake well before use. With thorough agitation, ENGERIX-B is a homogeneous, turbid white suspension. Do not administer if it appears otherwise. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the vaccine dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

2.2 Administration

ENGERIX-B should be administered by intramuscular injection. The preferred administration site is the anterolateral aspect of the thigh for infants younger than 1 year and the deltoid muscle in older children (whose deltoid is large enough for an intramuscular injection) and adults. ENGERIX-B should not be administered in the gluteal region; such injections may result in suboptimal response.

ENGERIX-B may be administered subcutaneously to persons at risk of hemorrhage (e.g., hemophiliacs). However, hepatitis B vaccines administered subcutaneously are known to result in a lower antibody response. Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons who are at risk of hemorrhage with intramuscular injections.

Do not administer this product intravenously or intradermally.

2.3 Recommended Dose and Schedule

<u>Persons from Birth through 19 Years</u>

Primary immunization for infants (born of hepatitis B surface antigen [HBsAg]-negative or HBsAg-positive mothers), children (birth through 10 years), and adolescents (aged 11 through 19 years) consists of a series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule.

<u>Persons Aged 20 Years and Older</u>

Primary immunization for persons aged 20 years and older consists of a series of 3 doses (1 mL each) given on a 0-, 1-, and 6-month schedule.

Adults on Hemodialysis

Primary immunization consists of a series of 4 doses (2-mL each) given as a single 2-mL dose or two 1-mL doses on a 0-, 1-, 2-, and 6-month schedule. In hemodialysis patients, antibody response is lower than in healthy persons and protection may persist only as long as antibody levels remain above 10 mIU/mL. Therefore, the need for booster doses should be assessed by annual antibody testing. A 2-mL booster dose (as a single 2-mL dose or two 1-mL doses) should be given when antibody levels decline below 10 mIU/mL.[1] *[See Clinical Studies (14.2).]*

Table 1. Recommended Dosage and Administration Schedules

Group	Dose[a]	Schedules
Infants born of:		
HBsAg-negative mothers	0.5 mL	0, 1, 6 months
HBsAg-positive mothers[b]	0.5 mL	0, 1, 6 months
Children:		
Birth through 10 years	0.5 mL	0, 1, 6 months
Adolescents:		
Aged 11 through 19 years	0.5 mL	0, 1, 6 months
Adults:		
Aged 20 years and older	1 mL	0, 1, 6 months
Adults on hemodialysis	2 mL[c]	0, 1, 2, 6 months

HBsAg = Hepatitis B surface antigen.

[a] 0.5 mL (10 mcg); 1 mL (20 mcg).

[b] Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth *[see Dosage and Administration (2.6)]*.

[c] Given as a single 2-mL dose or as two 1-mL doses.

2.4 Alternate Dosing Schedules

There are alternate dosing and administration schedules which may be used for specific populations (e.g., neonates born of hepatitis B–infected mothers, persons who have or might have been recently exposed to the virus, and travelers to high-risk areas) (Table 2). For some of these alternate schedules, an additional dose at 12 months is recommended for prolonged maintenance of protective titers.

Table 2. Alternate Dosage and Administration Schedules

Group	Dose[a]	Schedules
Infants born of: HBsAg-positive mothers[b]	0.5 mL	0, 1, 2, 12 months
Children: Birth through 10 years Aged 5 through 10 years	 0.5 mL 0.5 mL	 0, 1, 2, 12 months 0, 12, 24 months[c]
Adolescents: Aged 11 through 16 years Aged 11 through 19 years Aged 11 through 19 years	 0.5 mL 1 mL 1 mL	 0, 12, 24 months[c] 0, 1, 6 months 0, 1, 2, 12 months
Adults: Aged 20 years and older	 1 mL	 0, 1, 2, 12 months

HBsAg = Hepatitis B surface antigen.

[a] 0.5 mL (10 mcg); 1 mL (20 mcg).

[b] Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth *[see Dosage and Administration (2.6)]*.

[c] For children and adolescents for whom an extended administration schedule is acceptable based on risk of exposure.

2.5 Booster Vaccinations

Whenever administration of a booster dose is appropriate, the dose of ENGERIX-B is 0.5 mL for children aged 10 years and younger and 1 mL for persons aged 11 years and older. Studies have demonstrated a substantial increase in antibody titers after booster vaccination with ENGERIX-B. See Section 2.3 for information on booster vaccination for adults on hemodialysis.

2.6 Known or Presumed Exposure to Hepatitis B Virus

Persons with known or presumed exposure to the hepatitis B virus (e.g., neonates born of infected mothers, persons who experienced percutaneous or permucosal exposure to the virus) should be given hepatitis B immune globulin (HBIG) in addition to ENGERIX-B in accordance with Advisory Committee on Immunization Practices recommendations and with the package insert for HBIG. ENGERIX-B can be given on either dosing schedule (0, 1, and 6 months or 0, 1, 2, and 12 months).

3 DOSAGE FORMS AND STRENGTHS

ENGERIX-B is a sterile suspension available in the following presentations:

- 0.5-mL (10 mcg) single-dose vials and prefilled TIP-LOK syringes
- 1-mL (20 mcg) single-dose vials and prefilled TIP-LOK syringes

[See Description (11), How Supplied/Storage and Handling (16).]

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast, is a contraindication to administration of ENGERIX-B *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Infants Weighing Less than 2,000 g at Birth

Hepatitis B vaccine should be deferred for infants with a birth weight <2,000 g if the mother is documented to be HBsAg negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or hospital discharge. Infants born weighing <2,000 g to HBsAg-positive mothers should receive vaccine and HBIG within 12 hours after birth. Infants born weighing <2,000 g to mothers of unknown HBsAg status should receive vaccine and HBIG within 12 hours after birth if the mother's HBsAg status cannot be determined within the first 12 hours of life. The birth dose in infants born weighing <2,000 g should not be counted as the first dose in the vaccine series and it should be followed with a full 3-dose standard regimen (total of 4 doses).[2] *[See Dosage and Administration (2).]*

5.4 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. For ENGERIX-B, this assessment should include consideration of the mother's hepatitis B antigen status and the high probability of maternal transmission of hepatitis B virus to infants born of mothers who are HBsAg positive if vaccination is delayed.

5.5 Preventing and Managing Allergic Vaccine Reactions

Prior to immunization, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur. *[See Contraindications (4).]*

5.6 Moderate or Severe Acute Illness

To avoid diagnostic confusion between manifestations of an acute illness and possible vaccine adverse effects, vaccination with ENGERIX-B should be postponed in persons with moderate or severe acute febrile illness unless they are at immediate risk of hepatitis B infection (e.g., infants born of HBsAg-positive mothers).

5.7 Altered Immunocompetence

Immunocompromised persons may have a diminished immune response to ENGERIX-B, including individuals receiving immunosuppressant therapy.

5.8 Multiple Sclerosis

Results from 2 clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis,[3] and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.[4]

5.9 Limitations of Vaccine Effectiveness

Hepatitis B has a long incubation period. ENGERIX-B may not prevent hepatitis B infection in individuals who had an unrecognized hepatitis B infection at the time of vaccine administration. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The most common solicited adverse reactions were injection site soreness (22%) and fatigue (14%).

In 36 clinical studies, a total of 13,495 doses of ENGERIX-B were administered to 5,071 healthy adults and children who were initially seronegative for hepatitis B markers, and healthy neonates. All subjects were monitored for 4 days post-administration. Frequency of adverse reactions tended to decrease with successive doses of ENGERIX-B.

Using a symptom checklist, the most frequently reported adverse reactions were injection site soreness (22%) and fatigue (14%). Other reactions are listed below. Parent or guardian completed forms for children and neonates. Neonatal checklist did not include headache, fatigue, or dizziness.

Incidence 1% to 10% of Injections

Nervous System Disorders: Dizziness, headache.

General Disorders and Administration Site Conditions: Fever (>37.5°C), injection site erythema, injection site induration, injection site swelling.

Incidence <1% of Injections

Infections and Infestations: Upper respiratory tract illnesses.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Agitation, insomnia.

Nervous System Disorders: Somnolence, tingling.

Vascular Disorders: Flushing, hypotension.

Gastrointestinal Disorders: Abdominal pain/cramps, constipation, diarrhea, nausea, vomiting.

Skin and Subcutaneous Tissue Disorders: Erythema, petechiae, pruritus, rash, sweating, urticaria.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, myalgia, pain/stiffness in arm, shoulder, or neck.

General Disorders and Administration Site Conditions: Chills, influenza-like symptoms, injection site ecchymosis, injection site pain, injection site pruritus, irritability, malaise, weakness.

In a clinical trial, 416 adults with type 2 diabetes and 258 control subjects without type 2 diabetes who were seronegative for hepatitis B markers received at least 1 dose of ENGERIX-B. Subjects were monitored for solicited adverse reactions for 4 days following each vaccination. The most frequently reported solicited adverse reactions in the entire study population were injection site pain (reported in 39% of diabetic subjects and 45% of control subjects) and fatigue (reported in 29% of diabetic subjects and 27% of control subjects). Serious adverse events were monitored through 30 days following the last vaccination. Serious adverse events (SAEs) occurred in 3.8% of diabetic subjects and 1.6% of controls. No SAEs were deemed related to ENGERIX-B.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ENGERIX-B. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Infections and Infestations

Herpes zoster, meningitis.

Blood and Lymphatic System Disorders

Thrombocytopenia.

Immune System Disorders

Allergic reaction, anaphylactoid reaction, anaphylaxis. An apparent hypersensitivity syndrome (serum sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as urticaria, erythema multiforme, ecchymoses, and erythema nodosum.

Nervous System Disorders

Encephalitis; encephalopathy; migraine; multiple sclerosis; neuritis; neuropathy including hypoesthesia, paresthesia, Guillain-Barré syndrome and Bell's palsy; optic neuritis; paralysis; paresis; seizures; syncope; transverse myelitis.

Eye Disorders

Conjunctivitis, keratitis, visual disturbances.

Ear and Labyrinth Disorders

Earache, tinnitus, vertigo.

Cardiac Disorders

Palpitations, tachycardia.

Vascular Disorders

Vasculitis.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, bronchospasm including asthma-like symptoms.

Gastrointestinal Disorders

Dyspepsia.

Skin and Subcutaneous Tissue Disorders

Alopecia, angioedema, eczema, erythema multiforme including Stevens-Johnson syndrome, erythema nodosum, lichen planus, purpura.

Musculoskeletal and Connective Tissue Disorders

Arthritis, muscular weakness.

General Disorders and Administration Site Conditions

Injection site reaction.

Investigations

Abnormal liver function tests.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Vaccines and Immune Globulin

ENGERIX-B may be administered concomitantly with immune globulin.

When concomitant administration of other vaccines or immune globulin is required, they should be given with different syringes and at different injection sites. Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial.

7.2 Interference with Laboratory Tests

HBsAg derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of a hepatitis B vaccine, including ENGERIX-B.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no adequate and well-controlled studies of ENGERIX-B in pregnant women in the U.S. Available data do not suggest an increased risk of major birth defects and miscarriage in women who received ENGERIX-B during pregnancy *(see Data)*.

There are no animal studies with ENGERIX-B to inform use during pregnancy. A developmental toxicity study was performed in female rats administered a vaccine with the same hepatitis B surface antigen component and quantity as ENGERIX-B prior to mating and during gestation (0.2 mL at each occasion). This study revealed no adverse effects on fetal or pre-weaning development (*see Data*).

Data

Human Data: In an evaluation of pre- and post-licensure clinical trials of ENGERIX-B, 58 pregnant women were inadvertently administered ENGERIX-B following their last menstrual period. After excluding elective terminations (n = 6), those with an unknown outcome (n = 3), those with exposure in the third trimester (n = 1), and those with an unknown exposure timing (n = 22), there were 26 pregnancies with known outcomes with exposure in the first or second trimester. Miscarriage was reported in 11.5% of pregnancies with exposure prior to 20 weeks of gestation (3/26) and major birth defects were reported in 0% (0/23) of live births born to women with exposure during the first or second trimester. The rates of miscarriage and major birth defects were consistent with estimated background rates.

No pregnancy registry for ENGERIX-B was conducted. TWINRIX [Hepatitis A & Hepatitis B (Recombinant) Vaccine] is a bivalent vaccine containing the same hepatitis B surface antigen component and quantity as used in ENGERIX-B. Therefore, clinical data accrued with TWINRIX are relevant to ENGERIX-B. A pregnancy exposure registry was maintained for TWINRIX from 2001 to 2015. The registry prospectively enrolled 245 women who received a dose of TWINRIX during pregnancy or within 28 days prior to conception. After excluding induced abortions (n = 6, including one of a fetus with congenital anomalies), those lost to follow-up (n = 142), those with exposure in the third trimester (n = 1), and those with an unknown exposure timing (n = 9), there were 87 pregnancies with known outcomes with exposure within 28 days prior to conception, or in the first or second trimesters. Miscarriage was reported for 9.6% of pregnancies with exposure to TWINRIX prior to 20 weeks gestation (8/83). Major birth defects were reported for 3.8% of live born infants whose mothers were exposed within 28 days prior to conception or during the first or second trimester (3/80). The rates of miscarriage and major birth defects were consistent with estimated background rates.

Animal Data: In a developmental toxicity study, female rats were administered TWINRIX, which contains the same hepatitis B surface antigen component and quantity as ENGERIX-B, by intramuscular injection on Day 30 prior to mating and on gestation Days 6, 8, 11, and 15. The total dose was 0.2 mL (divided) at each occasion (a single human dose is 1 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no fetal malformations or variations.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ENGERIX-B in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENGERIX-B and any potential adverse effects on the breastfed child from ENGERIX-B or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of ENGERIX-B have been established in all pediatric age-groups. Maternally transferred antibodies do not interfere with the active immune response to the vaccine. *[See Adverse Reactions (6), Clinical Studies (14.1, 14.3, 14.4).]*

The timing of the first dose in infants weighing less than 2,000 g at birth depends on the HBsAg status of the mother. *[See Warnings and Precautions (5.3).]*

8.5 Geriatric Use

Clinical studies of ENGERIX-B used for licensure did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. However, in later studies it has been shown that a diminished antibody response and seroprotective levels can be expected in persons older than 60 years.[5] *[See Clinical Studies (14.2).]*

11 DESCRIPTION

ENGERIX-B [Hepatitis B Vaccine (Recombinant)] is a sterile suspension of noninfectious HBsAg for intramuscular administration. It contains purified surface antigen of the virus obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus. The HBsAg expressed in the cells is purified by several physicochemical steps and formulated as a suspension of the antigen adsorbed on aluminum hydroxide. The procedures used to manufacture ENGERIX-B result in a product that contains no more than 5% yeast protein.

Each 0.5-mL pediatric/adolescent dose contains 10 mcg of HBsAg adsorbed on 0.25 mg aluminum as aluminum hydroxide.

Each 1-mL adult dose contains 20 mcg of HBsAg adsorbed on 0.5 mg aluminum as aluminum hydroxide.

ENGERIX-B contains the following excipients: Sodium chloride (9 mg/mL) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).

ENGERIX-B is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

ENGERIX-B is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.[1] Seroconversion is defined as antibody titers ≥1 mIU/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ENGERIX-B has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Vaccination of female rats with TWINRIX, which contains the same HBsAg component and quantity as ENGERIX-B, had no effect on fertility. *[See Use in Specific Populations (8.1).]*

14 CLINICAL STUDIES

14.1 Efficacy in Neonates

Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at high risk of hepatitis B infection.[6,7] Fifty-eight neonates born of mothers who were both HBsAg-positive and hepatitis B "e" antigen (HBeAg)-positive were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 2 months, without concomitant hepatitis B immune globulin (HBIG). Two infants became chronic carriers in the 12-month follow-up period after initial inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the chronic carrier state during the first 12 months of life was 95%.

14.2 Efficacy and Immunogenicity in Specific Populations

Homosexual Men

ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months was evaluated in homosexual men aged 16 to 59 years. Four of 244 subjects became infected with hepatitis B during the period prior to completion of the 3-dose immunization schedule. No additional subjects became infected during the 18-month follow-up period after completion of the immunization course.

Adults with Chronic Hepatitis C

In a clinical trial of 67 adults aged 25 to 67 years with chronic hepatitis C, ENGERIX-B (20 mcg/1 mL) was given at 0, 1, and 6 months. Of the subjects assessed at Month 7 (n = 31), 100% responded with seroprotective titers. The geometric mean antibody titer (GMT) was 1,260 mIU/mL (95% Confidence Interval [CI]: 709, 2,237).

Adults on Hemodialysis

Hemodialysis patients given hepatitis B vaccines respond with lower titers, which remain at protective levels for shorter durations than in normal subjects. In a clinical trial of 56 adults who had been on hemodialysis for a mean period of 56 months, ENGERIX-B (40 mcg/2 mL given as two 1-mL doses) was given at 0, 1, 2, and 6 months. Two months after the fourth dose, 67% (29/43) of patients had seroprotective antibody levels (≥10 mIU/mL) and the GMT among seroconverters was 93 mIU/mL.

Adults with Type 2 Diabetes Mellitus

In a descriptive study, 674 adult subjects with type 2 diabetes (diagnosed within the preceding 5 years) or without type 2 diabetes were enrolled and stratified by age and body mass index (BMI). The per-protocol immunogenicity cohort included 378 diabetic subjects and 189 matched control subjects who received ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months. Among these subjects, the mean age was 54 years (range: 20 to 82 years); mean BMI was 32 kg/m^2 (range: 17 to 64 kg/m^2); 51% were male; 88% were white, 3% were American Indian or Alaskan Native, 3% were black, 2% were Asian, 4% were other racial groups; 2% were Hispanic or Latino.

The overall seroprotection rates (1 month after the third dose) were 75% (95% CI: 71, 80) in patients with diabetes and 82% (95% CI: 76, 87) in control subjects. The seroprotection rates in those with diabetes aged 20 to 39 years, 40 to 49 years, 50 to 59 years, and at least 60 years were 89%, 81%, 83%, and 58%, respectively. The seroprotection rates in those without diabetes in these same age-groups were 100%, 86%, 82%, and 70%, respectively. Subjects with diabetes and a BMI of at least 30 kg/m^2 had a seroprotection rate of 72% compared with 80% in diabetic subjects with lower BMIs. In control subjects, seroprotection rates were 82% in those with a BMI of at least 30 kg/m^2 and 83% in those with lower BMIs.

14.3 Immunogenicity in Neonates

In clinical studies, neonates were given ENGERIX-B (10 mcg/0.5 mL) at age 0, 1, and 6 months or at age 0, 1, and 2 months. The immune response to vaccination was evaluated in sera obtained 1 month after the third dose of ENGERIX-B.

Among infants administered ENGERIX-B at age 0, 1, and 6 months, 100% of evaluable subjects (n = 52) seroconverted by Month 7. The GMT was 713 mIU/mL. Of these, 97% had seroprotective levels (≥10 mIU/mL).

Among infants enrolled (n = 381) to receive ENGERIX-B at age 0, 1, and 2 months, 96% had seroprotective levels (≥10 mIU/mL) by Month 4. The GMT among seroconverters (n = 311) (antibody titer ≥1 mIU/mL) was 210 mIU/mL. A subset of these children received a fourth dose of ENGERIX-B at age 12 months. One month following this dose, seroconverters (n = 126) had a GMT of 2,941 mIU/mL.

14.4 Immunogenicity in Children and Adults

Persons Aged 6 Months through 10 Years

In clinical trials, children (N = 242) aged 6 months through 10 years were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 6 months. One to 2 months after the third dose, the seroprotection rate was 98% and the GMT of seroconverters was 4,023 mIU/mL.

Persons Aged 5 through 16 Years

In a separate clinical trial including both children and adolescents aged 5 through 16 years, ENGERIX-B (10 mcg/0.5 mL) was administered at 0, 1, and 6 months (n = 181) or 0, 12, and

24 months (n = 161). Immediately before the third dose of vaccine, seroprotection was achieved in 92.3% of subjects vaccinated on the 0-, 1-, and 6-month schedule and 88.8% of subjects on the 0-, 12-, and 24-month schedule (GMT: 118 mIU/mL versus 162 mIU/mL, respectively, $P = 0.18$). One month following the third dose, seroprotection was achieved in 99.5% of children vaccinated on the 0-, 1-, and 6-month schedule compared with 98.1% of those on the 0-, 12-, and 24-month schedule. GMTs were higher ($P = 0.02$) for children receiving vaccine on the 0-, 1-, and 6-month schedule compared with those on the 0-, 12-, and 24-month schedule (5,687 mIU/mL versus 3,159 mIU/mL, respectively).

Persons Aged 11 through 19 Years

In clinical trials with healthy adolescent subjects aged 11 through 19 years, ENGERIX-B (10 mcg/0.5 mL) given at 0, 1, and 6 months produced a seroprotection rate of 97% at Month 8 (n = 119) with a GMT of 1,989 mIU/mL (n = 118, 95% CI: 1,318, 3,020). Immunization with ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months produced a seroprotection rate of 99% at Month 8 (n = 122) with a GMT of 7,672 mIU/mL (n = 122, 95% CI: 5,248, 10,965).

Persons Aged 16 through 65 Years

Clinical trials in healthy adult and adolescent subjects (aged 16 through 65 years) have shown that following a course of 3 doses of ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months, the seroprotection (antibody titers ≥10 mIU/mL) rate for all individuals was 79% at Month 6 (5 months after second dose) and 96% at Month 7 (1 month after third dose); the GMT for seroconverters was 2,204 mIU/mL at Month 7 (n = 110).

An alternate 3-dose schedule (20 mcg/1 mL given at 0, 1, and 2 months) designed for certain populations (e.g., individuals who have or might have been recently exposed to the virus and travelers to high-risk areas) was also evaluated. At Month 3 (1 month after third dose), 99% of all individuals were seroprotected and remained protected through Month 12. On the alternate schedule, a fourth dose of ENGERIX-B (20 mcg/1 mL) at 12 months produced a GMT of 9,163 mIU/mL at Month 13 (1 month after fourth dose) (n = 373).

Persons Aged 40 Years and Older

Among subjects aged 40 years and older given ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months, the seroprotection rate 1 month after the third dose was 88% and the GMT for seroconverters was 610 mIU/mL (n = 50). In adults aged older than 40 years, ENGERIX-B produced anti-HBsAg antibody titers that were lower than those in younger adults.

14.5 Interchangeability with Other Hepatitis B Vaccines

A controlled study (N = 48) demonstrated that completion of a course of immunization with 1 dose of ENGERIX-B (20 mcg/1 mL) at Month 6 following 2 doses of RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant)] (10 mcg) at Months 0 and 1 produced a similar GMT (4,077 mIU/mL) to immunization with 3 doses of RECOMBIVAX HB (10 mcg) at Months 0, 1, and 6 (GMT: 2,654 mIU/mL). Thus, ENGERIX-B can be used to complete a vaccination course initiated with RECOMBIVAX HB.[8]

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16 HOW SUPPLIED/STORAGE AND HANDLING

ENGERIX-B is available in single-dose vials and prefilled disposable TIP-LOK syringes (packaged without needles) (Preservative-Free Formulation):

10 mcg/0.5 mL Pediatric/Adolescent Dose

NDC 58160-820-01 Vial in Package of 10: NDC 58160-820-11

NDC 58160-820-43 Syringe in Package of 10: NDC 58160-820-52

20 mcg/mL Adult Dose

NDC 58160-821-01 Vial in Package of 10: NDC 58160-821-11

NDC 58160-821-05 Syringe in Package of 1: NDC 58160-821-34

NDC 58160-821-43 Syringe in Package of 10: NDC 58160-821-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been frozen. Do not dilute to administer.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients and parents or guardians of the potential benefits and risks of immunization with ENGERIX-B.
- Emphasize, when educating vaccine recipients and parents or guardians regarding potential side effects, that ENGERIX-B contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Instruct vaccine recipients and parents or guardians to report any adverse events to their healthcare provider.
- Give vaccine recipients and parents or guardians the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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