Safety of influenza immunizations and treatment during pregnancy: the Vaccines and Medications in Pregnancy Surveillance System

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The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) has been designed to assess systematically the safety of vaccines and medications during pregnancy and is suited ideally to evaluate the gestational safety of seasonal and pandemic influenza vaccine and influenza antivirals. VAMPSS is coordinated by the American Academy of Allergy Asthma and Immunology and includes 2 complimentary data collection arms (prospective cohort and case-control surveillance) and a standing independent advisory committee. Both data collection arms obtain information directly from the mother, which facilitates accurate capture of exposures and potential confounders. The full range of perinatal outcomes, which includes specific birth defects, is assessed. Information that is obtained from VAMPSS should allow enhanced prevention and improved treatment of influenza during pregnancy by the identification of any exposures that might be associated with important risks and the provision of reassurance for exposures that are found to be relatively safe.

Key words: influenza, oseltamivir, perinatal outcomes, pregnancy, zanamivir

There are more than 4,000,000 births in the United States each year.[1] Of these, birth defects are identified in 3-4%,[2] and additional complications (eg, preeclampsia, preterm birth, intrauterine growth restriction) are each identified in 10-15% of pregnancies.[1] Birth defects are the leading cause of infant death[2] and account for 12% of pediatric hospitalizations[3]; prematurity increases the risk of neonatal death[4] and accounts for one-half of the hospital expenditures for all infants who are born in the United States each year.[5] Although the causes of most birth defects and other pregnancy complications are unknown, those complications that might be due to maternal vaccine or medication use are among the most preventable.[6] The unfortunate reality, however, is that we know little about vaccine or medication-induced birth and pregnancy complications because such adverse effects in humans are not predictable, based on pharmacologic knowledge, preclinical animal studies, or premarketing human studies.[6] Such information can come only from postmarketing studies, yet there is no systematic postmarketing surveillance system in place in this country to identify the risks and safety of vaccines or medications that are taken by pregnant women. The absence of having such a system in place becomes extremely critical at the time of a public health emergency that involves exposures during pregnancy, such as the 2009 H1N1 pandemic.

Some pharmaceutical company-sponsored exposure registries attempt to provide such risk or safety data, but they often are limited substantially by having no comparison groups, inadequate control for confounders, high lost-to-follow-up rates, and insufficient power to evaluate specific birth defects. Further, these registries may identify a "signal," but such signals typically are based on a very small number of exposed/malformed infants and require that more detailed investigations be mounted in other data sources.
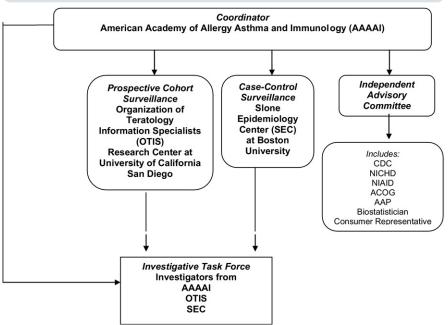
With respect to influenza vaccines, whether seasonal or pandemic, monitoring for safety has additional complications. First, pregnant women are at increased risk for influenza-related morbidity and death; unlike most agents, influenza vaccine is *specifically recommended for use in pregnant women.* Although the few studies that have focused on seasonal vaccine in pregnant women have not found evidence of harm,[7] they are limited in both design and statistical power and cannot rule out large or even moderate risks for a number of pregnancy complications, which include birth defects. Clearly, such information is critically important to the public, clinicians, public health authorities, and manufacturers. However, the process by which influenza vaccines are administered and recorded offers unique challenges to mounting an epide-

miologically valid study. These challenges include the fact that vaccines are often administered in nontraditional settings (such as occupational health clinics, pharmacies, supermarkets) where the exposure would not be recorded in the patient's medical record. As a result, exposure information from medical records (eg, based on automated health databases) would appreciably underestimate exposure prevalence; it would also misclassify as "unexposed" the large proportion of women who received influenza vaccine but whose exposures occurred in nontraditional settings.

Monitoring the use and safety of the antiinfluenza antivirals (eg, oseltamivir and zanamivir) is in some ways even more complicated. Physicians may prescribe these drugs for patients to have "on hand" in the event of exposure to confirmed influenza,[8] and this phenomenon may have expanded dramatically with anticipation of the H1N1 epidemic. Although electronic medical records would note that such prescriptions were written and perhaps filled, they do not have systematic information on whether the patient used the antiviral, nor do they provide information on critical variables that are related to such use. These include when in relation to exposure or influenza onset the antiviral was used, whether antivirals were used in response to advice of the patient's healthcare provider or public health authorities, whether it was used in response to exposure to a patient with known influenza or influenza-like symptoms, whether it was used for other reasons (eg, influenza reported in the community), or whether it was given to the patient by a friend, neighbor, or relative or vice versa.

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) has been designed to assess the safety of vaccines and medications systematically during pregnancy and is suited ideally to overcome many of these methodologic limitations. The purpose of this article is to describe the methods of the ongoing VAMPSS project to assess risks and safety during pregnancy of seasonal influenza vaccine, H1N1 influenza vaccine, and the antiviral medications osel-

The structure of the Vaccines and Medications in Pregnancy Surveillance System

The Vaccines and Medications in Pregnancy Surveillance System is coordinated by the American Academy of Allergy Asthma and Immunology (*AAAAI*) and includes prospective cohort surveillance that is provided by the Organization of Teratology Information Specialists (*OTIS*) Research Center at the University of California San Diego; case control surveillance that is provided by the Slone Epidemiology Center (*SEC*) at Boston University; and an Independent Advisory Committee. Representatives of these organizations make up the Investigative Task Force.

AAP, American Academy of Pediatrics; *ACOG*, American College of Obstetricians and Gynecologists; *CDC*, Centers for Disease Control and Prevention; *NIAID*, National Institute for Allergy and Infectious Diseases; *NICHD*, National Institute of Child Health and Human Development.

Wright. Vaccines and medications in pregnancy surveillance system. Am J Obstet Gynecol 2011.

tamivir and zanamivir that may be used in prophylaxis and early treatment of influenza in pregnant women. This project began in the fall of 2009 and is funded by the Biomedical and Advanced Research and Development Authority of the United Stated Department of Health and Human Services.

The structure and function of VAMPSS

VAMPSS is coordinated by the American Academy of Allergy Asthma and Immunology (AAAAI) and includes 2 data collection arms and a standing Independent Advisory Committee (IAC). The Investigative Task Force is comprised of the investigators from the data collection arms and a scientific representative from the AAAAI (Figure). Prospective registry surveillance is provided by the Organization of Teratology Information

Specialists (OTIS) Research Center at the University of California San Diego, and case-control surveillance is provided by the Slone Epidemiology Center (SEC) at Boston University. These programs, which use complementary designs, have each been focused actively to studying medication safety in pregnancy for >25 years, and they share a common approach that involves identification of exposures directly from study subjects.

The IAC includes a biostatistician, a consumer representative, and representatives from the Centers for Disease Control and Prevention (vaccine safety and birth defects branches), The Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Allergy and Infectious Diseases, American College of

Obstetricians and Gynecologists, and American Academy of Pediatrics (members are listed in Acknowledgments).

Prospective surveillance

OTIS is a North American–wide network of university or hospital-based teratology information services that has been in existence since 1979.[9] Pregnant callers to the OTIS network who have been exposed to ≥1 of the targeted vaccines or medications are enrolled prospectively, typically in the first 6-8 weeks of gestation for early first-trimester exposures. Maternal interviews are conducted up to 3 times during pregnancy and once after delivery, and outcomes are confirmed by chart review. Outcomes among subjects who have been exposed to the vaccine or medication under evaluation are compared with outcomes among participants who have not been exposed. These participants are recruited through the same OTIS network and are enrolled prospectively and observed in an identical manner.

Case-control surveillance

The SEC initiated its case-control surveillance Birth Defects Study in 1976.[10] Infants with the broad range of specific major malformations and infants without malformations are identified at birth hospitals and tertiary hospitals and through state-based birth defects surveillance programs; medical records are reviewed to confirm diagnoses. Mothers are interviewed by telephone within 6 months of delivery about all vaccines and medications that were used immediately before and during pregnancy. The prevalence of exposure to the targeted vaccine or medication among mothers of infants with a given specific malformation is compared with the corresponding prevalence in 2 control groups: mothers of nonmalformed infants and mothers of infants with other malformations.

Exposures

The exposures of interest for this project are the seasonal and H1N1 influenza vaccine and the antiviral medications that are used to prevent or treat influenza (eg, oseltamivir and zanamivir). As noted, both study designs obtain exposure information directly from study subjects and include whether they received an influenza or H1N1 ("swine flu") vaccination during pregnancy. Women are asked when and where they received their vaccinations, which includes not only their health care provider but also occupational health clinics, public health/community clinics, and commercial facilities such as pharmacies or supermarkets. Women also are asked to provide a medical record release that allows investigators to confirm information from the appropriate source[11]; information that is sought includes brand, manufacturer, lot number, and single vs multidose vial (the latter to identify thimerosal-containing vaccines). For the antivirals, subjects are asked whether the medication was prescribed by a physician or was obtained from another source (eg, workplace, friend, neighbor, relative) and, if prescribed, whether it was intended for use at the time of prescription or meant to be available if needed.

Outcomes

The primary outcomes are (1) total major congenital malformations (OTIS), (2) specific malformations (SEC; eg, cardiovascular malformations, oral clefts, limb reduction defects, and anotia/microtia), (3) preeclampsia (OTIS), (4) preterm delivery (<37 weeks' gestation; OTIS), and (5) small for gestational age (birthweight for gestational age ≤10th percentile; OTIS). Other outcome information that is collected by OTIS includes spontaneous abortions, perinatal deaths, birthweight, length and head circumference, and gestational age. All of these diagnoses/values are confirmed by medical record review. In addition, with information that is obtained from women whose pregnancies did not involve a complication, the SEC can estimate the prevalence of exposure to both specific vaccines and antivirals.

Confounders

Direct patient interviews not only minimize exposure misclassification but also allow for the capture of potential confounders that are not obtainable in any other way. Confounders that are captured in both arms of VAMPSS include maternal demographic variables, weight/body mass index, medical/family/reproductive history, illnesses (with specific attention to confirmed and unconfirmed influenza and influenza-like illnesses and fever of any origin), smoking, alcohol, and other exposures. The last group includes detailed questions on prescription and over-the-counter medications, herbal products, other vaccines, and vitamins/minerals (including, very importantly, periconceptional use of folate-containing vitamins).

Risk signals and safety thresholds

VAMPSS uses a number of criteria, including a priori criteria, to ensure that risks and safety are rigorously and consistently defined and identified.

Risk signals. Positive associations will be brought to the IAC when (1) an unadjusted odds ratio with a 95% lower confidence bound >1.0 is observed or (2) there is an elevated odds ratio that the investigative task force deems to be important or noteworthy, such as risk estimates that are related to previous reports of an association (eg, case reports, other epidemiologic studies) or observations that are supported by biologic plausibility that is based on animal or other studies.

The objective in defining these criteria is to ensure that any potential risk signals are reviewed by the IAC. Very broad parameters have been set purposely that recognize that many observations that fit the criteria will not be meaningful and will not be deemed subsequently by the Advisory Committee to constitute a true risk signal.

Safety thresholds. Estimates of safety cannot be absolute; rather, they reflect the degree of confidence that is consistent with an observation of no increased risk between a given exposure and outcome. As more data are collected over time, power increases; for a null observation, increasing power leads to increasingly narrower confidence intervals and increasing assurance of relative safety, as reflected in the following a priori criteria for bringing findings to the IAC for their

review: (1) When an odds ratio that approximates ≤1.0 is observed with an upper 95% confidence bound of ≤4.0, the IAC may choose, among its options, to define this observation as "no evidence of risk." (2) When an odds ratio that approximates ≤1.0 is observed with an upper 95% confidence bound of ≤2.0, the IAC may choose, among its options, to define this observation as "evidence of relative safety." These deliberations would likely include evaluation of both crude and adjusted odds ratios.

Sample size considerations

Prospective cohort (OTIS). In the cohort setting, *power* is defined by 2 variables, the number of influenza vaccine-exposed subjects and unexposed comparison women accrued and the incidence of the specific adverse outcome in the comparison group. For the 2-year period that was supported initially for the VAMPSS influenza vaccine and antivirals study, projected sample size estimates for the influenza vaccine–exposed group and the comparison group for 3 key and representative endpoints indicate sufficient power to detect an increased risk of 3-fold for all major birth defects combined, 2.2-fold for preterm delivery, and 2-fold for birthweight small-for-gestational age. In addition, an *"evidence of relative safety" threshold* as defined earlier could be achieved for the latter 2 outcomes.

Case-control surveillance (SEC). In the case-control setting, *power* is defined by 2 variables. The first variable is the number of cases that are accrued of specific birth defects and control subjects. The prevalence of cases with specific birth defects varies according to the relative prevalence of the various defects in the population (eg, cardiac defects occur more commonly than oral clefts, which in turn occur more commonly than limb-reduction defects). The second variable is the prevalence of use of the specific vaccine or drug in the population. Because power varies according to the size of each case group and the prevalence of exposure, power is greatest where public health concerns are greatest (ie, common exposure/common outcome). For example, over a 2-year period, assuming a 10% exposure rate and a common defect (eg, cardiovascular defects), we will be able to identify an increased risk as small as 1.5-fold, and in the absence of risk, we will be able to rule out increases of >1.4-fold, which translates to a safety threshold of evidence of relative safety. Even for less common defects, such as oral clefts, there will be sufficient power for commonly used drugs to identify a risk as low as 1.8-fold and a safety threshold that is consistent with "evidence of relative safety."

Data analysis

For both data collection arms, the same analytic approaches will be followed both for the influenza vaccines (seasonal and H1N1) and for the antivirals.

Prospective cohort analysis (OTIS). For each vaccine or medication in relation to each primary outcome, outcomes in exposed patients will be compared with outcomes in nonexposed control subjects. These comparisons will be expressed as relative risks and 95% CIs and are considered the primary cohort data analyses. When either a safety or risk threshold is reached for any exposure/outcome combination, an adjusted analysis will be performed that will compare the outcome in vaccine-exposed women with the outcome in unexposed women and be adjusted for confounders by means of logistic regression or other appropriate multivariate analyses.

Case-control surveillance (SEC). For each specific malformation (eg, cardiovascular, oral clefts, limb-reductions, anotia/microtia), exposures to influenza vaccine or medication will be compared in mothers of infants with the specific malformation vs mothers of infants without malformations. These comparisons will be expressed as odds ratios and 95% CIs and are considered the primary case-control data analyses. When either a safety or risk threshold is reached for any outcome/exposure combination, the following additional analyses will be conducted: (1) comparison of exposure to influenza vaccine or medication in mothers of infants with the specific malformation group vs exposure in mothers of infants without malformations, which is adjusted for confounders by means of logistic regression; and (2) comparison of exposure to influenza vaccine or medication in mothers of infants with the specific malformation group vs exposure in mothers of infants with selected other malformations, again adjusted for the confounders by means of logistic regression.

Comment

VAMPSS is a unique and comprehensive approach to studying the risks and safety of vaccines and medications that are taken by pregnant women. The AAAAI provides independent, efficient, and cost-effective coordination and management of VAMPSS.

The subject recruitment process for the prospective cohort arm (which includes outreach through professional provider organizations, lay organizations, and the media) should provide more data more quickly than traditional company registries could and, at the same time, provide a comparison group and low losses to follow-up evaluation. The case-control surveillance arm provides risk and safety estimates for specific birth defects and estimates of use of the vaccines and antivirals in the pregnant population. VAMPSS meets industry and regulatory needs to provide, on the product label, the most rigorous available information on the risks and safety of specific vaccines or medications that are used by pregnant women. This information is necessary to allow practitioners and their patients to balance benefits and risks properly when choosing pharmaceutical interventions during pregnancy.

VAMPSS includes the capacity to evaluate risks and safety that are related to overall birth defects and to specific birth defects and to other reproductive outcomes. Data collection is based on 2 universally recognized study designs (prospective pregnancy cohorts and case-control surveillance for specific defects) that are conducted by investigator groups with decades of experience and established scientific credibility and perspective. By interviewing study subjects directly, both the OTIS and SEC arms permit capture of information that is not

routinely or systematically available in paper or electronic medical records, which includes nontraditional sources of exposure to influenza vaccines and related antiviral medications and information on potential confounders (such as exposures to the wide range of prescription, over-the-counter, and herbal products, the use of folic acid supplements, alcohol consumption, and smoking). In addition to interviews, outcomes in both arms are confirmed by review of medical records. Because data will accumulate over the years of activity, confidence intervals will become narrower and will provide increasingly stable estimates of risk or safety over time.

Independent scientific expertise is provided by an advisory committee, which is comprised of experts with recognized skills and experience in evaluating the risks and safety of exposures in pregnancy. The stable and independent IAC membership and structure ensure both consistency in assessments and coherence in recommendations.

The focus of the current projects is influenza vaccines and antivirals. However, this model system could be expanded easily, with substantial economy of scale, to include surveillance for other vaccines and prescription medications and the unique opportunity to provide surveillance for over-the-counter and herbal products.

The VAMPSS approach does have some potential limitations. Risks and safety in pregnancy can be assessed only in the postmarketing setting, so information on pregnancy risk and safety cannot become available until sometime after a vaccine or medication is approved for marketing. However, the design of VAMPSS reduces that time interval to the minimum.

Information from observational studies can be subject to potential biases (eg, selection bias and recall bias) and confounding. However, data collection and analytic approaches that are used by the investigative team are well-established and designed to minimize the likelihood and impact of biases and adjust for as many confounders as possible. Further, conclusions that are drawn from the data will have the benefit of the wisdom and guidance that are provided by the standing IAC.

Even in the setting where influenza vaccines and related antiviral medications are used widely, it must be recognized that this (and any other study approach) will be unlikely to provide stable estimates of risk and safety for extremely rare outcomes; increased risks in such settings can escape detection in any surveillance system. However, the continued active surveillance provided by VAMPSS offers the best chance of the identification of such risks over time. Moreover, an ongoing VAMPSS system, with its infrastructure well-established, offers the best chance of providing critical safety information when it is needed for a public health emergency that involves pregnant women. A major goal of VAMPSS in the surveillance of influenza-related products during pregnancy is to provide much needed information that will allow enhanced prevention and improved treatment of influenza during pregnancy by identifying any exposures that might be associated with important risks and providing reassurance for exposures that are found to be relatively safe. ∎

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