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-

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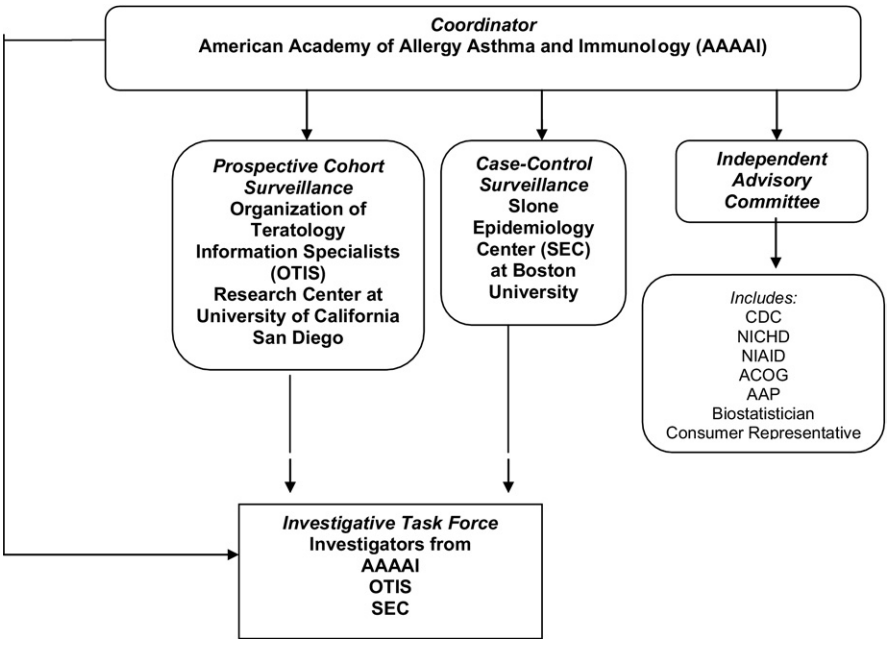
miologically valid study. These challenges include the fact that vaccines are often administered in nontraditional settings (such as occupational health clinics, pharmacies, supermarkets) where the exposure would not be recorded in the patient's medical record. As a result, exposure information from 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 oseltamivir 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.

FIGURE
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.

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