

May 7, 2018

Written submission to the Research Specific to Pregnant Women and Lactating Women Task Force
From VAMPSS, the Vaccines and Medications in Pregnancy Surveillance System

Introduction

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a unique nationwide post-marketing surveillance system established to comprehensively monitor the use and safety of vaccines and medications during pregnancy. Spearheaded by the American Academy of Allergy, Asthma & Immunology (AAAAI), VAMPSS provides a coordinated effort involving *prospective registry surveillance*, *case-control surveillance* and *database surveillance* to study the safety of exposures in pregnancy.

The *prospective surveillance arm* is coordinated by the Organization of Teratology Information Specialists (OTIS) at the University of California-San Diego and involves prospective enrollment and follow-up of pregnant women exposed to selected vaccines or medications during pregnancy. Outcomes among participants exposed to a vaccine or medication under evaluation are compared to outcomes among participants not exposed.

The *case-control surveillance arm* is coordinated by Slone Epidemiology Center at Boston University (SEC) and involves enrollment of mothers of infants with congenital malformations and infants without malformations. Among mothers of infants with each specific malformation, the prevalence of antenatal exposure to the vaccines and medications of interest is compared to the corresponding exposure prevalences in comparison groups: mothers of non-malformed infants and mothers of infants with other malformations. SEC ceased data collection activities on November 30, 2015 but continues to provide historical analysis for drugs and medications available prior to that date.

The *database surveillance arm* is coordinated by the Harvard Pregnancy Research Group, which utilizes the Medicaid Analytic eXtract (MAX) database as its primary data source. The MAX database includes Medicaid enrollment and healthcare utilization data from more than 1.6 million pregnancies ending in live birth from 2000-2010. A secondary data source of commercially insured women is Truven MarketScan, which includes data from more than 604,000 pregnancies ending in live birth between 2011 and 2015.

The prospective and case control arms of VAMPSS collect information directly from participating mothers, thus obtaining comprehensive data on actual exposures and important confounders such as alcohol and tobacco use. Because the system obtains exposure information directly from the subject, this coordinated effort will provide the ability to address questions regarding the safety of over-the-counter medications, dietary supplements and products not acquired by the pregnant woman in traditional medical settings.

Under the guidance of an Investigative Team that includes representatives from AAAAI, all three research arms, and an independent Advisory Committee, VAMPSS brings together three complementary methods of surveillance, taking advantage of the benefits of all. The Investigative Task Force coordinates all aspects of protocol development, data collection, data analyses, data interpretation, and generation of reports, and meets weekly by teleconference to discuss methodological issues and review progress.

The Advisory Committee includes members from the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP), American Thoracic Society (ATS), as well as a biostatistician and a consumer representative. Including these organizations creates significant opportunities to reach out to practitioners and, in turn, their pregnant and lactating patients. This independent Advisory Committee provides advice regarding overall VAMPSS goals, methods, results and reports. It provides independent, scientifically rigorous and confidential peer review of accumulating data and the related analyses.

The major goal of VAMPSS is to provide national systematic post-marketing surveillance system for pharmacologic therapy during pregnancy. With this system, we hope to identify as early as possible the circumstances in which a drug or immunization causes harm. We hope to provide reassuring data in a timely manner to all concerned for those drugs and immunizations (likely the majority) that are safe during pregnancy. To date, VAMPSS has published articles on the safety of the 2009-10 pandemic H1N1 influenza vaccine and 2011-12, 2012-13 and 2013-14 seasonal influenza vaccines in pregnancy.

Feedback regarding specific needs of the scientific community in order to conduct more research on therapies used by pregnant and/or lactating women

Randomized clinical trials are typically powered to be large enough to identify maternal and fetal benefits of a given therapeutic intervention, and they may be large enough to identify relatively common maternal risks and pregnancy complications, but they are yet too small to identify risks of specific birth defects (teratogenesis). Such defects (e.g., neural tube defects, oral clefts) affect approximately 1 in 1000 live births, and many defects are even less common. Typical RCTs may include a few hundred to as many as 1000 or so exposed subjects, and even if all subjects in a given RCT were pregnant women who were exposed in the first trimester (when organogenesis is most vulnerable to teratogenesis), RCTs would have insufficient statistical power to identify important (e.g., up to 20-fold) increases in risks for specific birth defects. Providing meaningful data on a medication's relative safety in pregnancy will require, as it always has, observational (epidemiologic, or "opportunistic") studies that, because of their sample size or design, have sufficient statistical power to identify or rule out large and moderate increases in risk. It is critical that those who propose RCTs involving pregnant women recognize that such trials may advance knowledge in many areas of benefit and risk, but they cannot be relied upon to provide information on teratogenic risks.

VAMPSS believes the inclusion of pregnant women and lactating women in both pre- and post-market studies should be dependent on risk benefit considerations. The likely benefit of the exposure must be considered to outweigh the likely risks, to both the pregnant woman and the fetus, based on available animal or human data. In many cases, the available data are insufficient to define those risks, such that only unique benefit would warrant inclusion of pregnant women in the trial. Some medications should only be studied in pregnant and lactating women in the post-market environment when efficacy in non-pregnant patients has been confirmed and the benefit-risk considerations can be individualized.

For further information, contact Sheila Heitzig, JD MNM CAE, at sheitzig@aaaai.org, or call 414-272-6071.