Methodology for Safety Surveillance of Adverse Events Following Vaccination During Pregnancy

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Fondation Merieux
Presentation Outline

- Background
- Company run pregnancy registry (spontaneous reports)
- Organization of Teratology Information Services (Pregnancy Registry)
- Case-control surveillance (Slone Epidemiology Center)
Background

Regional differences

- US FDA requires pregnancy registry for newly licensed products
- EMA and other national authorities required pregnancy registry in light of H1N1 flu pandemic
Overview of Sanofi Pasteur Pregnancy Registries

- **Company-run passive surveillance systems**
  - Health Insurance Portability and Accountability Act (HIPAA) compliant
  - Participation is voluntary
  - Mainly US licensed products

- **Objective:** To collect and analyze information on vaccine exposures and pregnancy outcomes and monitor for any potential safety signal that might arise in this population

- **Women are enrolled in the registry either prospectively or retrospectively**
  - Prospectively – after exposure to the vaccine but before the conduct of any prenatal tests that could provide knowledge related to the outcome of pregnancy
  - Retrospectively – when the registry is notified after the outcome of pregnancy is already known
SP Pregnancy Registries

- **SP currently operates the following pregnancy registries in the US:**
  - Menactra® (MCV4) – established in Jan 2005
  - Adacel® (Tdap) – established in June 2005
  - Fluzone® Intradermal – established in September 2011
- **Additional or expanded registries are under discussion**
Methods of Reporting

- Reports are encouraged from
  - Health-care providers and
  - Pregnant women who are exposed to SP products

- Reports can be made
  - By calling a toll free number (1-800-822-2463) included in Prescribing Information
    - Contact information is also found on the website [http://www.sanofipasteurpregnancyregistry.com/](http://www.sanofipasteurpregnancyregistry.com/)

- In addition to reports from HCPs and consumers, exposure to SP products during pregnancy can be reported from any source, e.g.
  - Sanofi Pasteur-sponsored studies
  - Medical literature
  - Health authorities
Data Collection and Follow-Up

- Pregnancy cases with or without adverse events are recorded in the Sanofi Pasteur Global Pharmacovigilance database and are assessed by Product Safety Officers (MD or PharmD)
- Pregnancy outcomes are followed up via questionnaire sent to the reporter
  - Several follow-ups during pregnancy and up to 3 follow-up attempts after expected delivery date to get information on the outcome of pregnancy
- Information collected includes
  - Woman’s demographic data
  - Details regarding vaccination (product, administration date, latency)
  - Details about the pregnancy (gestational age, date of last menstrual period, prenatal test results, delivery and perinatal information, previous pregnancy history/outcomes)
  - Underlying medical conditions
  - Concomitantly received medications and vaccinations
Reporting of Pregnancy Outcomes

- Outcomes prompting a 15-day alert report and submission to the Health Authorities as per regulations (21CFR600.80)
  - Spontaneous abortion
  - Stillbirth
  - Congenital anomaly
  - Any other event that meets the regulatory definition of seriousness for the mother or the baby (e.g., death, life-threatening condition, hospitalization, or medically significant event)

- Events reported to Regulatory Agencies through Periodic Safety Update Reports (PSUR) include
  - All other cases of pregnancy exposure that do not meet the definition of seriousness
  - All serious AEs
Data Presentation and Analysis (1)

- Data collected prospectively is analyzed separately from data collected retrospectively
  - Descriptive analyses

- All reports within each category are stratified by pregnancy outcomes
  - Spontaneous abortion
  - Elective termination
  - Fetal death/stillbirth
  - Live birth

- Retrospective reports are considered only for qualitative evaluation as individual case reports or as a case series

- Each case report is evaluated for
  - Timing of exposure
  - Date of conception (or last menstrual period)
  - Maternal age
  - Medical history (maternal disease, familial and genetic association)
  - Biological plausibility
  - Concomitant medication exposures (any association for birth defects, timing)
Data Presentation and Analysis (2)

- Estimates of incidence rates are calculated if potential safety concerns are identified.

- Expected numbers of cases with outcomes of interest from prospective cases are compared to the numbers of reported cases of those events following vaccination with the same product.
  - Product exposure is derived from sales data and utilization in pregnant women.

- Population-based outcome data from surveillance systems and/or exposure registries are used to determine background rates.
  - Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defect Program.
  - National Birth Defects Prevention Network.
Example: Reports Received through the Adacel (Tdap) Pregnancy Registry, Jun 2005 – Jun 2011

577 pregnancy reports

49 study reports
- 2 lost to follow-up
- 1 spontaneous abortion
- 44 live births
- 1 congenital anomaly
- 2 elective abortions

528 spontaneous reports
- 2 lost to follow-up
- 2 elective abortions
- 1 spontaneous abortion
- 1 congenital anomaly
- 109 live births
- 16 spontaneous abortions
- 345 lost to follow-up*

518 prospective reports
- 46 waiting outcome
- 44 live births
- 8 live births

10 retrospective reports
- 2 spontaneous abortions
- 1 congenital anomaly

* The loss of follow-up is high (67%), largely because the initial reporters did not provide the contact information for the patients or their Ob-Gyn physicians
Limitations

- **Loss to follow-up**
  - Initial reporter (HCP) may not have further contact with a woman (e.g. if not her primary care provider)
  - Example – during a recent pertussis outbreak, only line listings were received from the hospital

- **Lack of precise denominator of women exposed to vaccine**

- **No control group**

- **No “unexposed” group**
US: external collaboration with OTIS and Slone Epi Center
Organization of Teratology Information Specialists (OTIS)

- Internationally recognized research organisation
  - Established in 1990
  - Network of university or hospital-based telephone services located throughout the U.S. and Canada
    - 17 services
    - Respond to patient and provider inquiries regarding exposures in pregnancy
    - ~ 100,000 queries per year either through direct contact with an individual service or through a national 800 number routing system
    - Conduct pregnancy outcome studies
    - Recruit exposed women as well as unexposed women during pregnancy and follow these women to delivery to compare the frequency of a range of specified outcomes
Goals of OTIS Pilot project

- **Sponsored 18 month pilot project from 1 Sep 2006 to 29 Feb 2008**
  - This was first vaccine safety study conducted by Organization of Teratology Information Services

- **Objectives**
  - Estimate the number of exposed pregnant women who can be recruited for a pregnancy outcome study
  - Provide preliminary data on pregnancy outcome for a subset of exposed women whose pregnancies are completed within the pilot project period
  - Adacel, Menactra & Fluzone
Pregnancy Follow-up by OTIS

- **Intake interview**
  - pregnancy history; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity; income category, current medication use, both prescriptive and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug use; current pregnancy complications including illnesses; names and addresses of health care providers

- **Pregnancy diary**

- **Interim interviews**

- **Outcome interviews**
  - Outcome interview for live born infants
  - Outcome interview for spontaneous or elective abortions
  - Medical Records and General Pediatric Evaluation
  - All adverse outcomes will be reported to sanofi pasteur
    - SAEs within 24 hours
    - Other AEs in annual report
Results of OTIS study, 1 Sep 06 – 29 Feb 08

Vaccine exposure among 224 caller contacts to OTIS

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>No. of Reports (%)</th>
<th>No. of Enrolled and Vaccine Confirmed (%)</th>
<th>No. of Enrolled and S-P Vaccine Confirmed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu</td>
<td>172 (76.8)</td>
<td>83 (81.4)</td>
<td>50 (72.5)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>11 (4.9)</td>
<td>2 (2.0)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Pertussis (Tdap)</td>
<td>41 (18.3)</td>
<td>17 (16.7)</td>
<td>17 (24.6)</td>
</tr>
<tr>
<td>Total</td>
<td>224</td>
<td>102</td>
<td>69*</td>
</tr>
</tbody>
</table>

*3 women enrolled for exposure to two vaccines

Of the 66 women (representing 69 exposures) who are enrolled and who have confirmed exposure to SP product, outcome obtained on 40 pregnancies

Of these, 39 have delivered live born babies and 1 pregnancy resulted in a spontaneous abortion
Case-Control Surveillance Study
“Birth Defects Study” (Slone)

- Conducted by Slone Epidemiology Center
- Cases: mothers of infants with birth defects under study
- Controls: mothers of non-malformed infants (“normals”)
- Subjects are identified through birth defect registries or hospitals and related facilities (4 regions in US – MA, Eastern PA, NY state, San-Diego County)
Vaccine Exposure among 2177 Birth Defect Surveillance Study Subjects (Slone) (September 1, 2006 – February 29, 2008)

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>No. of Reports</th>
<th>% of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu</td>
<td>452</td>
<td>20.8</td>
</tr>
<tr>
<td>Tetanus/Tdap</td>
<td>35</td>
<td>1.6</td>
</tr>
<tr>
<td>Typhoid</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>Pertussis</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>Hepatitis (A, unspec)</td>
<td>4</td>
<td>0.14</td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unspecified</td>
<td>14</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>516</td>
<td><strong>23.7</strong></td>
</tr>
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</table>
Summary of Pilot Study

- Major limitation in vaccine safety studies in pregnancy is whether relevant exposure information can be accurately captured.
- Using novel approaches, it was demonstrated that at least 8% of pregnant women receive Fluzone in pregnancy.
Summary

● Different methods used to monitor safety of vaccines in pregnancy (registries based on spontaneous reporting, active surveillance – cohort study, case-control)
● There are regional differences in requirements for establishing pregnancy registries
Thank you
Birth Defect Surveillance Study
Fluzone Validation (Slone)

- Flu vaccine was most commonly reported exposure during pregnancy
  - 452 flu vaccine recipients (20.8%)
  - 130 (28.8%) of the immunizations were received in a setting other than a health care provider

- Signed medical record releases were obtained from 266 (58.8%) subjects
  - Directly confirm 196 of the 452 reported exposures (43.4%) through a specific personal medical record
  - Additional 118 (26.1%) indirectly confirmed by obtaining general information from the provider
  - For 138, tracking was unsuccessful

- Among those confirmed, 55% received Sanofi Pasteur vaccine

- Based on 18 months’ experience, approximately 8% (174/2177) of women receive Fluzone in pregnancy