These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate)	**Study Identifiers:** U1111-1111-5171, NCT01129362 **Study code:** M5A16
Title of the study: Surveillance for Rates of Pertussis Disease Among Persons Birth Through 59 Months of Age Receiving Pentacel® or Other Pertussis Vaccines	
Study center(s): 2 study centers participated in US	
Study period: Date first subject enrolled: 10/Feb/2010 Date last subject completed: 30/Dec/2014	
Phase of development: 4	

Objectives:

The study objective was to determine and compare brand-specific rates of pertussis based on WDPH (Wisconsin Division of Public Health)-reported pertussis cases with onset from 01 January 2010–31 December 2014, using data from the sample surveys to estimate brand-specific population person-time at risk.

Primary Objective: To determine the rates and relative risk of pertussis disease among Surveillance (Wisconsin) Population members who received Pentacel vaccine or another pertussis vaccine.

Observational Objective: To determine the rates and relative risks of pertussis disease for various vaccination regimens and VHs, and combinations thereof.

Methodology:

The purpose of this prospective observational surveillance study (M5A16) was to determine vaccine brand-specific rates of pertussis disease during the period of the study, among Wisconsin residents younger than 60 months of age who received no more than 4 doses of pertussis vaccine (the Surveillance [Wisconsin] Population), and to descriptively compare the rates of pertussis among persons vaccinated with Pentacel® vaccine with those among persons vaccinated with any other diphtheria, tetanus, and acellular pertussis (DTaP)-containing vaccine. The study was conducted by the Principal Investigator at UWSMPH, in collaboration with the Wisconsin State Epidemiologist from the WDPH.

Information on incident cases of pertussis and their pertussis vaccination histories (VHs; including vaccine brands received) was collected through routine pertussis surveillance procedures at WDPH. All pertussis cases were reportable by law to WDPH. De-identified pertussis case data among persons in the Surveillance (Wisconsin) Population were provided to the UWSMPH.

Brand-specific pertussis VHs during the study period among the Surveillance (Wisconsin) Population as a whole were estimated through data collected by a national sample-survey organization (M/A/R/C®) on behalf of the Sponsor in Study M5A17, which used telephone sampling surveys to identify eligible persons for the Surveillance (Wisconsin) Population and gather (with parental consent) their pertussis VHs, including brand(s) received, from the provider records. For survey recipients in Study M5A17, duration of study participation was approximately 1 month (from the date of telephone interview to the date of immunization records receipt by M/A/R/C), but may have been shorter or longer depending on the time needed to collect vaccine information from the person's Health Care Provider.

De-identified data (i.e., gender, age, race/ethnic origin, household income, and state/county/zip code) from Study M5A17 were provided to the UWSMPH. These data were used to estimate vaccine brand exposure (i.e., denominator) data for the Surveillance (Wisconsin) Population.

Based on the definition of the Surveillance (Wisconsin) Population, both cases and surveys were collected in a staggered manner, with increasing upper age limits over the 5-year period (< 24, < 36, < 48, ≤ 59, and ≤ 59 months of age, by year of study), to include only children born after the approval date of Pentacel vaccine.

Number of subjects:

Evaluated: Actual: 1195 persons

Diagnosis and criteria for inclusion:

Persons were under surveillance for this study whenever the following 4 conditions were true:
(1) the individual resided in Wisconsin for 1 or more days within the 5-year surveillance period (01 January 2010–31 December 2014),
(2) individual was between 0 and 59 months old inclusive,
(3) the individual was born after licensure and initial launch of Pentacel vaccine (assumed to be 01 January 2009), and
(4) the individual received between 1 to 4 doses of pertussis vaccines.

Study treatments: Not applicable

Duration of observation: 10 months

Criteria for evaluation:

Occurrence of confirmed or probable pertussis disease, as determined by the WDPH

Statistical methods:

Statistical Methods for the Primary Objective:

Rates of pertussis disease were evaluated and compared between pairs of vaccination groups using model-assisted survey sampling methods that accounted for the survey design structure of the M5A17 study. Since the samples of the M5A17 study were obtained using a survey sampling study design, model parameters and the corresponding variances were estimated using methodologies developed for complex survey data.

Statistical analysis was conducted using SAS software (SAS Institute, Cary, NC), version 9.4. SAS procedures for the analysis of complex survey data were used when conducting the analyses.

Rates of pertussis per 100,000 person-years and the corresponding 90% confidence intervals (CIs) were calculated for the following vaccination groups:

- Group 1
- Group 2

Rate ratios and the corresponding 90% CIs were calculated for the following comparison:

- Group 1 vs. Group 2

A Poisson regression model for complex survey data was used to estimate the rate ratios adjusted by VH group (VH1–VH8), geographic region (Northeastern, Northern, Southeastern, Southern, and Western), and surveillance study periods (6-months periods between 01 January 2010 and 31 December 2014). The adjusted rate ratios and the corresponding 90% CIs were calculated for the following comparison:

- Group 1 vs. Group 2

Statistical Methods for the Observational Analyses:

Comparison of Rate Ratios for Rates of Confirmed or Probable Pertussis Between Vaccination Groups

Analyses for the observational objective followed the same methods as described for the primary objective to calculate rates of pertussis, rate ratios, and their respective 90% CIs.

Rates of pertussis per 100,000 person-years and the corresponding 90% CIs were calculated for the following vaccination groups:

- Group 1

- Group 2
- Group 2-Tripedia
- Group 2-Daptacel
- Group 2-Infanrix
- Group 2-Pediarix
- Group 3

Unadjusted and adjusted rate ratios and the corresponding 90% CIs were calculated for the following comparisons:

- Group 1 vs. Group 3
- Group 2 vs. Group 3
- Group 1 vs. each defined subgroup within Group 2
- Group 3 vs. each defined subgroup within Group 2
- Each defined subgroup within Group 2 vs. each other defined vaccine subgroup in Group 2

Other Subgroup Analyses:

Subgroup analyses followed the same methods as described for the primary objective to calculate rates of pertussis, rate ratios, and their respective 90% CIs. The vaccination groups and vaccination group comparisons (with the addition of Group 1 vs. Group 2) listed above were also used for the subgroups.

For the Confirmed Case Population, analyses were conducted for the overall population and stratified by VH, vaccination timeliness, geographic region, 6-month surveillance study period, and study year. Furthermore, adjusted rates and rate ratios for confirmed cases only were calculated using a Poisson regression model for complex survey data.

Summary:

Population characteristics:

Case population: The Case Population consisted of a total of 1195 persons with confirmed or probable pertussis as categorized by WDPH from January 2010–December 2014. Pertussis cases were reported in 436 persons in Group 1, 449 persons in Group 2, and 310 persons in Group 3. In the Group 2 subgroups, pertussis cases were reported in 17 persons in Group 2-Daptacel, 15 persons in Group 2-Infanrix, and 417 persons in the Group 2-Pediarix. No pertussis cases were reported for the Group 2-Tripedia subgroup.

Surveillance (Wisconsin) Population: In the Surveillance (Wisconsin) Population, the overall person-time estimate was 1,133,403 person-years. The person-time estimates were 440,279 person-years for Group 1, 466,520 person-years for Group 2 (of which 422,598 person-years were for the Group 2-Pediarix subgroup), and 226,604 person-years in Group 3.

Demographic and Baseline Characteristics: Overall, there were more males (52.2%) in the Case Population. The majority of persons across all groups were of non-Hispanic ethnicity and White (67.1%). There were differences in the proportion of cases across groups by age at onset of cough, with the largest differences occurring between Group 3 and the other 2 groups, which can be attributed to how persons were assigned to Group 3. Across all groups, the majority of cases (59.7%) occurred during the outbreak period. There were differences observed in the proportion of cases reported across all groups by geographic region.

In the Surveillance (Wisconsin) Population, overall person-time estimates were 578,036 person-years for males and 555,367 person-years for females. The overall person-time estimate was highest for persons of non-Hispanic ethnicity and White (714,046 person-years). There were differences in the person-time estimates across groups by age at time of telephone survey, with the largest differences occurring between Group 3 and the other 2 groups, which can be attributed to how persons were assigned to Group 3. By outbreak period, overall person-time estimates increased over time (310,664 person-years pre-outbreak, 383,580 person-years during outbreak, and 439,159 person-years post-outbreak). In Group 1, person-time estimates were highest during the outbreak period (166,260 person-years).

Pertussis Rates

Primary Analysis

Group 1 and Group 2 had similar rates of pertussis (98.94 vs. 96.16) per 100,000 person-years. The comparison of rates of pertussis between Group 1 and Group 2 resulted in an unadjusted rate ratio of 1.03 (90% CI: 0.92–1.15), indicating that the primary analysis found no significant difference between the rates of pertussis between these 2 groups.

Observational and Subgroup Analyses

Observational Analysis

In the observational analysis, the Group 2-Pediarix subgroup had a similar rate of pertussis per 100,000 person-years to Group 1 (98.59 vs. 98.94). The unadjusted rate ratio analysis indicated that there was no statistically significant difference in the rates of pertussis between Group 1 and the Group 2-Pediarix subgroup.

Subgroup Analyses

- Vaccination History and Vaccination Timeliness
    - The rates of pertussis per 100,000 person-years for Group 1, Group 2, and the Group 2 subgroups varied by vaccination group for each VH and across VHs (VH1–VH8) by vaccination group. Based on the unadjusted rate ratios, there were no statistically significant differences in the rates of pertussis for any of the VHs (VH1–VH8) between Group 1 and Group 2 or between Group 1 and the Group 2-Pediarix subgroup.
    - For Group 1, Group 2, and the Group 2-Pediarix subgroup, when the rates of pertussis among persons who had delayed vaccine doses (delayed VH) were compared with those among persons who received vaccines on time (timely VH), the rates of pertussis were substantially higher for delayed VHs, with 90% CIs for the corresponding timely VH rates that did not overlap, indicating that the difference was potentially statistically significant.
- Wisconsin Department of Public Health Geographic Regions
    - The rates of pertussis per 100,000 person-years for Group 1, Group 2, and the Group 2 subgroups varied widely

across WDPH geographic regions. The risk of pertussis varied across geographic regions with no difference in the rates of pertussis between Group 1 and Group 2 or between Group 1 and Group 2-Pediarix in the Northeastern and Northern region, lower rates of pertussis in Group 1 than in Group 2 or Group 2-Pediarix in the Southeastern and Southern regions, and a lower rate of pertussis in Group 2 and Group 2-Pediarix than in Group 1 in the Western region.

- Six-Month Periods (01 January 2010–31 December 2014) and Study Year (2010–2014)
  - Rates of pertussis varied over 6-month study periods and by year. The highest rates of pertussis were observed during 2012 overall and in both of its 6-month study periods (during the pertussis outbreak in Wisconsin that occurred from July 2011–December 2012) and in the study period from 01 July 2014–31 December 2014.
  - The majority of the unadjusted rate ratios calculated using rates of pertussis for vaccination group comparisons by the 6-month study periods showed no statistically significant differences in the rates of pertussis between Group 1 and Group 2 or between Group 1 and the Group 2-Pediarix subgroup.
  - The unadjusted rate ratios calculated using rates of pertussis for vaccination group comparisons by the study year periods showed no statistically significant differences in the rates of pertussis between Group 1 and Group 2 or between Group 1 and the Group 2-Pediarix subgroup in study years 2011, 2012, and 2014. In 2010, the comparisons between Group 1 and Group 2 and between Group 1 and the Group 2-Pediarix subgroup indicated a lower rate of pertussis in Group 2 and Group 2-Pediarix subgroup; whereas, in 2013 these comparisons both indicated a lower rate of pertussis in Group 1.
- Wisconsin Outbreak Periods
  - The unadjusted rate ratios calculated using rates of pertussis for vaccination group comparisons by pre-, during, and post-outbreak periods between Group 1 and Group 2 and between Group 1 and the Group 2-Pediarix subgroup indicated that there were no statistically significant differences in the rates of pertussis during the outbreak period or the post-outbreak period between Group 1 and Group 2 or between Group 1 and the Group 2-Pediarix subgroup. During the pre-outbreak period, Group 2 and the Group 2-Pediarix subgroup had lower rates of pertussis compared with Group 1.
- Subgroup results for Group 2-Daptacel and Group 2-Infanrix
  - Due to the small sample sizes in the Group 2-Daptacel and Group 2-Infanrix subgroups, unadjusted rate ratios of pertussis for the vaccination group comparisons using these subgroups should be interpreted cautiously. The majority of the comparisons for VHs, vaccination timeliness, WDPH geographic regions, 6-month study periods, study year periods, and outbreak periods using these subgroups showed no statistically significant differences in the rate of pertussis based on the unadjusted rate ratios.
- Adjusted Analysis of Pertussis Rate Ratios Calculated
  - Based on the differences observed in the rates of pertussis in the subgroup analyses of VH1 through VH8, WDPH geographic regions, and 6-month study periods, the rate ratio analysis was adjusted by these important confounding factors.
  - As in the unadjusted rate ratio analysis, the adjusted rate ratio analysis found no significant difference in the rate of pertussis between Group 1 and Group 2 or between Group 1 and the Group 2-Pediarix subgroup.
  - Due to the small sample sizes in the Group 2-Daptacel and Group 2-Infanrix subgroups, adjusted rate ratios of pertussis for the vaccination group comparisons using these subgroups should be interpreted cautiously. These comparisons indicated no statistically significant differences in the rates of pertussis.
- Confirmed Pertussis Cases – Subgroup Analysis
  - The unadjusted analyses using a case definition of pertussis restricted to those categorized by WDPH as confirmed should be interpreted with caution. The difference between being a confirmed case vs. a probable case is laboratory confirmation, which varied by practice and geographic location (e.g., rural vs. urban). Vaccine brand preference also varied by practice and geographic location.

- Vaccination group comparisons in the unadjusted and adjusted rate ratio analyses indicated that there were statistically significant differences between the rates of confirmed pertussis between Group 1 and Group 2 and between Group 1 and Group 2-Pediarix subgroup, with lower rates of confirmed pertussis in Group 2 and the Group 2-Pediarix subgroup.
- For the unadjusted rate ratio analyses of VHs, 6-month study periods, study year periods, and outbreak periods using confirmed pertussis, the majority of vaccination group comparisons indicated that there was a statistically significant difference between the rates of confirmed pertussis between Group 1 and Group 2 and between Group 1 and Group 2-Pediarix subgroup, with lower rates of confirmed pertussis in Group 2 and the Group 2-Pediarix subgroup.
- For vaccination timeliness, the rates of confirmed pertussis were substantially higher for delayed VHs with 90% CIs for the corresponding timely VH rates that did not overlap, indicating that the difference was potentially statistically significant.
- The risk of confirmed pertussis varied across geographic regions with no difference in the rates of confirmed pertussis between Group 1 and Group 2 or between Group 1 and Group 2-Pediarix in the Northeastern, Northern, Southeastern, and Southern regions, and a lower rate of confirmed pertussis in Group 2 and Group 2-Pediarix than in Group 1 in the Western region.
- Due to the small sample sizes in the Group 2-Daptacel and Group 2-Infanrix subgroups, unadjusted rate ratios of confirmed pertussis for the vaccination group comparisons using these subgroups should be interpreted cautiously. The majority of the comparisons for VHs, vaccination timeliness, WDPH geographic regions, 6-month study periods, study year periods, and outbreak periods using these subgroups showed no statistically significant differences in the rates of confirmed pertussis based on the unadjusted rate ratios calculated using rates of confirmed pertussis.

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