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Sponsor: Sanofi Pasteur	**Study Identifiers:** NCT00855855
Drug substance(s): Hib-containing vaccines approved in the U.S.	**Study code:** M5A15
Title of the study: Surveillance for Rates of Hib Disease Among Persons 0 Through 59 Months of Age Receiving Pentacel or Other Hib Vaccines	

Study Locations:

Surveillance for Hib disease was conducted by the Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance (ABCs) Program in its catchment areas for 2009–2014.

Estimates of Hib vaccine use within the surveillance population, specific to age group, time period, and vaccine brand were obtained using sample survey methodology by M/A/R/C®, a national telephone survey organization.

Study period:

Date of study start date/first survey participant enrolled: 01/Jan/2009

Date of study end date/last survey participant completed: 21/Dec/2014

Study Status: Completed

Objectives:

The purpose of this prospective observational study was to estimate Hib-containing vaccine brand specific incidence rates of invasive Hib disease among children residing in the CDC ABCs Program catchment areas.

Methodology:

This was an observational study, and it did not alter in any way the medical care received by any person. Persons under surveillance received Pentacel vaccine or another Hib-containing vaccine as part of routine care.

There were no study-mandated specimens. Any specimens collected were collected by the treating physicians or public health staff as part of their ordinary activities.

Persons living within the ABCs Program catchment areas were under surveillance for invasive Hib disease in this study when both of the following conditions were true: the individual's age was less than 5 years and the calendar year was 2009–2014 inclusive.

Prospective active population-based surveillance for invasive Hib disease was routinely conducted by the ABCs Program within diverse geographic regions representing 12% of the United States (US) and provided invasive Hib disease case-occurrence (numerator) data. Medical history data were collected by the ABCs Program for children diagnosed with invasive Hib disease.

The ABCs Program and the National Center for Health Statistics provided annual estimates of the number of persons under surveillance, by age group, within the ABCs Program catchment areas.

During the period of this study, the ABCs Program annually reported data regarding identified cases of invasive Hib disease within the surveillance population including the number and timing of Hib vaccine doses received by the child and the brand of Hib vaccine administered.

To estimate the usage of Hib vaccines by vaccine brand, the Sponsor contracted M/A/R/C, a national sample-survey organization, to collect brand-specific vaccine exposure data within the ABCs Program catchment areas. During the study period, telephone surveys were conducted to collect immunization histories on approximately 2400 children 2–23 months of age per year (i.e., approximately 200 per month).

To ensure an accurate estimate of Hib vaccine brand usage in the ABCs Program catchment areas, survey sampling conducted by the national sample-survey organization included collection of immunization records from the child's health care provider.

The duration of participation for persons in the sample survey was the time needed to respond to a single data collection request. Following the initial contact and verbal approval by parents for collection of their child's immunization history, survey packets were mailed to parents that included an instruction sheet and a verbal consent confirmation form. To minimize loss to follow-up for the vaccine usage survey, parents were contacted by M/A/R/C at 3, 5, and 7 weeks after survey packets were mailed. Once parents returned their survey, survey packets were sent to their health care providers that contained instructions, verbal consent confirmation of parent, and an immunization history collection form to be completed via a secure online website or faxed back to M/A/R/C. If necessary, physician offices also were contacted to remind them to submit the requested vaccine information.

Number of survey participants: 16,120 children with eligible participant and relevant Hib vaccine brand information supplied in the immunization history form.

Survey participant selection criteria:

Persons born after licensure and initial launch of Pentacel vaccine (assumed to be 01 January 2009) were eligible for inclusion in the sample survey for Hib vaccine brand usage in this study if the following 4 conditions were true: (1) residence within the geographic scope of the ABCs Program (operated by the CDC) during the period of surveillance; (2) aged 2 through 23 months (prior to 2nd birthday) on the day of inclusion; (3) calendar years 2009–2014, inclusive; and (4) agreement to complete the required sample survey.

Study Products:

Marketed vaccine lots were documented as used. Product descriptions of Hib-containing vaccines used are provided herein solely for information, to support correct categorization of exposures.

Pentacel Vaccine, Sanofi Pasteur Ltd.

ActHIB® Vaccine, Sanofi Pasteur, SA

TriHIBit®, Sanofi Pasteur Inc.

Comvax®, Merck & Co, Inc.

PedvaxHIB® vaccine, Merck & Co, Inc.

Duration of study: The duration of participation for persons in the sample survey was the time needed to respond to a single data collection request. The duration of the study was 6 years.

Criteria for evaluation and definitions:

The primary endpoint was the occurrence of invasive Hib disease among persons within the population monitored by the ABCs Program.

The observational endpoint was Hib vaccine brand usage rates based on survey sampling data.

Hib breakthrough cases were defined as those who were born on or after 01 January 2009 AND, if under 4 months of age, received at least 1 dose of Hib vaccine, OR, if 4 months to under 6 months of age, received at least 2 doses of Hib vaccine, OR, if 6 months to under 16 months of age, either received at least 2 doses of a PRP-OMPC vaccine or received at least 3 doses of any Hib vaccine, OR, if 16 months of age or greater, received at least 3 doses of a PRP-OMPC vaccine or 4 doses of any Hib vaccine

Vaccine exposure groups were defined as follows: Group 1: received Pentacel only; Group 2: received ActHIB only or ActHIB 3 doses + TriHIBit 4th dose; Group 3: received PRP-OMPC only (Comvax or PedvaxHIB); Group 4a: received mixed vaccination history with at least one Pentacel dose and no unknown doses; Group 4b: received mixed vaccination history without Pentacel and no unknown doses; Group 4c: received partially or completely unknown vaccination history

Statistical methods:

The analysis population included the survey samples (Hib vaccine brand usage) in the Surveillance [ABCs] Population catchment areas) and the eligible breakthrough invasive Hib disease cases (i.e., cases occurring among vaccinated persons) reported by the CDC's ABCs Program (Case Population).

To generate population vaccine brand usage estimates in the Surveillance (ABCs) Population catchment areas, the study survey sample data were weighted using an iterative proportional fitting algorithm. Specifically, the survey sample data were weighted to balance vs. US Census data on 3 variables: (1) age-gender combination, (2) ethnicity, and (3) household income.

Analyses

Incidence rates (per 1 000 000 person-years) of invasive Hib disease breakthrough cases over the 6-year surveillance period were calculated for each vaccination group along with the corresponding 95% confidence intervals (CIs). Rate ratios of incidence rates of invasive Hib disease breakthrough cases between vaccination groups were calculated along with the corresponding 2-sided 95% CIs.

In an alternate analysis, the Poisson estimation method was used to compare the expected number of invasive Hib disease cases to the observed number of cases for Group 1 compared with each reference group (Group 2, Group 3, Group 4a, Group 4b, and Group 4c).

Summary:

Invasive Hib Disease Case Population

The Case Population consisted of a total of 5 breakthrough invasive Hib disease cases with the date of positive Hib test between 2009 and 2014: 1 case in a child who received only Pentacel vaccine (Group 1), 2 cases in children who received only PedvaxHIB vaccine (Group 3), 1 case in a child who received mixed Hib vaccines (Group 4a; Dose 1 and 4, ActHIB vaccine and Dose 2 and 3, Pentacel vaccine), and 1 case in a child who received unknown Hib vaccine (Group 4c; noted as HibTITER [Wyeth Pharmaceuticals Inc], although unlikely to be correct as this brand of Hib vaccine was discontinued in the United States prior to start of study).

Hib Vaccine Brand Sample Survey Population

In the Surveillance (ABCs) Population catchment areas, the overall person-time estimate for Hib vaccine exposure was 9 304 270 person-years. The person-time estimates were 3 460 183 person-years for Group 1; 3 034 112 person-years for Group 2; 889 753 person-years in Group 3; 1 160 795 person-years in Group 4a; 270 570 person-years in Group 4b; and 488 857 person-years in Group 4c.

Demographic and Baseline Characteristics

Apart from age, no demographic data were provided by the CDC for invasive Hib disease cases.

During the period of the study, overall person-time estimates for the population under surveillance in the ABCs Program catchment areas were 4 745 178 person-years for males and 4 559 092 person-years for females. The overall person-time estimate was highest for persons of non-Hispanic ethnicity (7 463 086 person-years) and White (6 715 792person-years). There were differences in the person-time estimates by geographic region, ranging from 535 088 person-years for New York to 1 662 310 person-years for Georgia. Person-time estimates were highest for children aged 12–23 months (5 396 476) and for 3 doses (4 197 679 person-years).

Invasive Hib Disease Incidence Rates and Incidence Rate Ratios

The distribution of breakthrough invasive Hib disease cases by vaccine group and estimated incidence rates based on person-time with corresponding 95% CI are shown below. For the comparison of interest (Group 1 vs. Group 2), the risk ratio was not calculable due to the absence of cases in Group 2.

Group	Number of Breakthrough Hib Cases	Hib Incidence Rate (per 1,000,000 person-years)	95% Confidence Interval
Group 1	1	0.29	0-2.16
Group 2	0	0	0-1.27*
Group 3	2	2.25	0-12.56
Group 4a	1	0.86	0-6.45
Group 4b	0	0	0-14.2*
Group 4c	1	2.05	0-15.32

Comparison	Risk Ratio	95% Confidence Interval
Group 1 vs. Group 2	NE	NE
Group 1 vs. Group 3	0.13	0.01-1.42
Group 1 vs. Group 4a	0.34	0.02-5.36
Group 1 vs. Group 4b	NE	NE
Group 1 vs. Group 4c	0.14	0.01-2.26
Group 3 vs. Group 4a	2.61	0.24-28.78
Group 3 vs. Group 4b	NE	NE
Group 3 vs. Group 4c	1.1	0.1-12.12
Group 4a vs. Group 4b	NE	NE
Group 4a vs. Group 4c	0.42	0.03-6.73

*: Upper 95% confidence bound is based on non-survey based Wilson-score method
NE: Not estimable
Group 1: Pentacel only
Group 2: ActHIB only or ActHIB 3 doses + TriHIBit 4th dose
Group 3: PRP-OMPC only (Comvax or PedvaxHIB)
Group 4a: Mixed vaccination history with at least one Pentacel dose and no unknown doses
Group 4b: Mixed vaccination history without Pentacel and no unknown doses
Group 4c: Partially or completely unknown vaccination history

Poisson Estimation

The results of applying the Poisson estimation method, showing expected vs. observed cases by vaccine group, are provided below.

Comparisons of Number of Hib Cases between Group 1 vs. Group 2, Group 1 vs. Group 3, Group 1 vs. Group 4a, Group 1 vs. Group 4b and Group 1 vs. Group 4c Based on Poisson Approach

Comparison	Reference Group	Number of Observed Cases Reference Group	Number of Observed Cases Group 1	Expected Number of Cases*	Upper One-sided 95% CI Bound†	Expected Number of Cases* > Upper One-sided 95% CI Bound?
Group 1 vs. Group 2	**Group 2**	0	1	0.88	3	No
Group 1 vs. Group 3	**Group 3**	2	1	0.26	6.3	No
Group 1 vs. Group 4a	**Group 4a**	1	1	0.34	4.7	No
Group 1 vs. Group 4b	**Group 4b**	0	1	0.08	3	No
Group 1 vs. Group 4c	**Group 4c**	1	1	0.14	4.7	No

*: Expected number of Hib cases in the reference group, based on Group 1 Hib case incidence rate
†: Upper one-sided 95% CI bound for number of Hib cases in reference group based on Poisson distribution
Group 1: Pentacel only
Group 2: ActHIB only or ActHIB 3 doses + TriHIBit 4th dose
Group 3: PRP-OMPC only (Comvax or PedvaxHIB)
Group 4a: Mixed vaccination history with at least one Pentacel dose and no unknown doses
Group 4b: Mixed vaccination history without Pentacel and no unknown doses
Group 4c: Partially or completely unknown vaccination history

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