The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 111442 (10PN-PD-DIT-043)

Title: Evaluation of effectiveness of GSK Biologicals' pneumococcal conjugate vaccine GSK1024850A against invasive disease.
Synflorix™ - GSK1024850A (10Pn): GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* (*H. influenzae)* protein D conjugate vaccine.

Rationale: The purpose of this study was to evaluate the vaccine effectiveness (VE) of the 10Pn vaccine against invasive disease (ID) by measuring the effects both in vaccinated children (direct and indirect effects, i.e. total effects) and in unvaccinated population (indirect effects, i.e. herd immunity). Effectiveness of immunization according to a 2-dose or 3-dose primary schedule followed by a booster dose in children < 12 months of age and in a 2-dose plus booster and 2-dose in older children (7-11 and 12-18 months respectively) was assessed. The study also evaluates vaccine impact on the incidence of hospital-diagnosed pneumonia, as well as the vaccine impact on tympanostomy tube placement and outpatient antimicrobial prescriptions .
Approximately 6000 subjects were enrolled in a nested study 10PN-PD-DIT-053 (112595) who contributed to the objectives of the 111442 study. In addition, a descriptive evaluation with regard to vaccination impact on carriage, acute otitis media (AOM), safety and immunogenicity (in a subset of subjects) was performed in the nested 112595 study.
Control vaccines were GSK Biologicals' *Engerix B*™, in children below 12 months of age, and *Havrix 720 Junior*™, in children aged 12 months and above.
Please refer also to the 112595 CTRS for the study details and results for objectives related to the 112595 study only.
Havrix™ *720 Junior* (HAV): GSK Biologicals' Hepatitis A vaccine.
Engerix™ *B* (HBV): GSK Biologicals' Hepatitis B vaccine.

Phase: III/IV

Study Period:
111442 study: 04 May 2009 (Study start) to

- 31 January 2012 (End time point for the Primary Objective and Outcome analysis common to both 111442 and 112595 studies)
- 05 October 2013 (End of 18-month period after study unblindning, for which SAEs notified via passive surveillance were reported)

Nested 112595 study: 18 February 2009 (Study start) to

- 22 December 2011 (Last Subject Last Visit in the 112595 study)
- 31 January 2012 (End time point for the Primary Objective and Outcome analysis common to both 111442 and 112595 studies)
- 05 October 2013 (End of 18-month period after study unblinding, for which SAEs notified via passive surveillance were reported)

Study Design: Double-blind, cluster-randomized, controlled study with 4 parallel groups of clusters* (2:2:1:1)
For the purpose of this cluster-randomized study, the municipalities of the participating health care centres were mapped into 72 clusters with average yearly birth cohort, ranging from around 400 to 1350 subjects. 6 further clusters of municipalities recruited solely to the nested 112595 study. Effectiveness analyses were performed on total 78 clusters and are presented below.
**Refer to the Treatment section for study cluster definitions.*

Centres:

- 111442 study: 651 vaccination centres in Finland (Well baby clinics)
- 112595 study: 15 centres in Finland

Indication: Active immunization against *S. pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F and *H. influenzae*.

Treatment:
Municipalities were organised into the following 4 parallel groups of clusters (2:2:1:1):

- 10Pn3+1 group of clusters (N = 26): Subjects enrolled in the 10Pn3+1 clusters received 10Pn vaccine. Children enrolled in these clusters between 6 weeks and 6 months of age received a 3-dose primary vaccination schedule.
- 10Pn 2+1 group of clusters (N = 26): Subjects enrolled in the 10Pn 2+1 clusters received 10Pn vaccine. Children enrolled in these clusters between 6 weeks and 6 months of age received a 2-dose primary vaccination schedule.
- Control 3+1 group of clusters (N = 13): subjects enrolled in the Control 3+1 clusters received HBV vaccine if < 12 months of age at the time of first study vaccination, or HAV vaccine if ≥ 12 months of age at the time of first study

vaccination. Children enrolled in these clusters between 6 weeks and 6 months of age received a 3-dose primary vaccination schedule.

- Control 2+1 group of clusters (N = 13): subjects enrolled in the Control 2+1 clusters received HBV vaccine if < 12 months of age at the time of first study vaccination, or HAV vaccine if ≥ 12 months of age at the time of first study vaccination. Children enrolled in these clusters between 6 weeks and 6 months of age received a 2-dose primary vaccination schedule.

Vaccination schedules and study groups depended on the age at enrolment:

- Infants enrolled between 6 weeks and 6 months of age: 3-dose primary vaccination with 10Pn vaccine ("10Pn3+1 Schedule") or HBV vaccine ("Ctrl3+1 Schedule") with an interval of at least 4 weeks, or 2-dose primary vaccination with 10Pn vaccine ("10Pn2+1 Schedule") or HBV vaccine ("Ctrl2+1 Schedule") with an interval of at least 8 weeks, followed by a booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months).
  This age group is also referred to as the "Infant cohort".
- Catch-up infants enrolled between 7 and 11 months of age: 2-dose primary vaccination with either 10Pn ("Catch-up 7-11M-10Pn") or HBV vaccine ("Catch-up 7-11M-Ctrl") with an interval of at least 4 weeks, followed by a booster dose of the same vaccine with an interval of preferably 6 months since the previous vaccine dose (minimum 4 months) ("7-11M Schedule").
- Catch-up toddlers enrolled between 12 and 18 months of age: 2-dose vaccination with 10Pn ("Catch-up 12-18M-10Pn") or HAV vaccine ("Catch-up 12-18M-Ctrl") with an interval of at least and preferably 6 months between doses ("12-18M Schedule").
  The age group between 7 and 18 months of age is also referred to as the "Catch-up cohort"

All study vaccines were administered intramuscularly in the thigh, or in the deltoid region of upper arm in children aged ≥ 12 months, provided the muscle size was adequate.
In addition to the above, please also note that the populations analysed in this study also included an Unvaccinated population. Please refer to the Statistical Methods and Study Population sections for details.

Objectives:

- To demonstrate the effectiveness of 10Pn vaccine in preventing culture-confirmed Invasive Pneumococcal Disease (IPD) due to vaccine pneumococcal serotypes in children vaccinated with at least one dose of 10Pn within the first 7 months of life in clusters assigned to a 3-dose primary vaccination course.
  Criterion for effectiveness:
  Vaccine effectiveness (VE) in preventing culture-confirmed IPD due to the 10 vaccine serotypes was demonstrated if the 2-sided p-value calculated for the null hypothesis H0 = (vaccine-type [VT] IPD VE = 0%) was lower than 5%)

Primary Outcome/Efficacy Variable:
In children starting vaccination within the first 7 months of life in clusters assigned to a 3-dose primary vaccination course:

- Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.

Secondary Outcome/Efficacy Variable(s):
In children starting vaccination within the first 7 months of life in clusters assigned to a 2-dose primary vaccination course:

- Occurrence of culture-confirmed IPD due to any of the 10 pneumococcal vaccine serotypes.

In the vaccinated population:

- Occurrence of culture-confirmed ID caused by any of the bacterial pathogens listed below:
  - any and each of the 10 pneumococcal vaccine serotypes
  - any and each of the vaccine-related pneumococcal serotypes
  - any and each of the other pneumococcal serotypes
  - any and each of the *Haemophilus influenzae* types
  - any other bacterial pathogen
- Occurrence of probable cases of ID caused by the bacterial pathogens as listed above
- Occurrence of hospital-diagnosed pneumonia cases
- Occurrence of hospital-diagnosed pneumonia cases with abnormal pulmonary infiltrates on the chest X-ray (CXR pneumonia) based on the CXR reading according to World Health Organization (WHO) criteria
- Occurrence of hospital-diagnosed pneumonia cases with alveolar consolidation/pleural effusion on the CXR (CXR-AC pneumonia) based on the CXR reading according to WHO criteria
- Occurrence of hospital-diagnosed pneumonia cases without alveolar infiltrates or pleural effusion on the CXR (CXR-NAC pneumonia) based on the CXR reading according to WHO criteria
- Occurrence of tympanostomy tube placement
- Occurrence of outpatient antimicrobial prescriptions
- Antimicrobial susceptibility of *S. pneumoniae* and *H. influenzae* isolated from ID*

- Occurrence of Lower respiratory tract infections (LRTIs) (in a subset of ± 1500 subjects in Turku area)[£]
- Occurrence of Upper respiratory tract infections (URTIs), including AOM (in a subset of ± 1500 subjects in Turku area)[£]

In the unvaccinated population:

- Occurrence of culture-confirmed ID caused by the bacterial pathogens as listed above[$]
- Occurrence of probable cases of ID caused by the bacterial pathogens as listed above[%]
- Occurrence of hospital-diagnosed pneumonia cases
- Occurrence of tympanostomy tube placement (only in children ≤ 7 years of age)*
- Occurrence of outpatient antimicrobial prescriptions (only in children ≤ 7 years of age)*

[£]*Refer to the 112595 CTRS for these results.*

[$]*Only culture-confirmed invasive pneumococcal disease (IPD) results are reported in this summary. As very few cases of ID linked to other bacteria were reported, the analysis of ID caused by other pathogens was cancelled.*

[%]*Results for this outcome are not presented: the analysis of the indirect effectiveness for probable ID cases has been cancelled due to the unavailability of the data.*

**Results for these outcomes were not available at the time of writing of this CTRS; they will be posted when they become available.*

Statistical Methods:

The analyses were performed on the Infant Vaccinated cohort, on the Catch-up Vaccinated cohort and on the Unvaccinated cohort:

- The Infant Vaccinated cohort included all subjects vaccinated with first dose of study vaccine below 7 months of age.
- The Catch-up Vaccinated cohort included all subjects vaccinated with first dose of study vaccine at or above 7 months of age.
- The Unvaccinated cohort included all persons not enrolled in the study but who lived in the study cluster areas.

Analysis of Effectiveness in the Vaccinated Population

The analysis was performed on the Infant Vaccinated cohort and the Catch-up Vaccinated cohort including all subjects enrolled, correctly randomized in this 111442 study and in the 112595 study, who received at least one study vaccine dose.

Effectiveness against IDs

The analysis of VE was firstly based on comparisons of numbers of culture-confirmed IPD, considering events occurring in the follow-up time from Dose 1 in children starting vaccination within the first 7 months of life. The number of subjects with IPD in each cluster was compared between groups in a sequential manner. 10Pn3+1 clusters were first compared to the combined Control 3+1 and Control 2+1 clusters in order to demonstrate positive vaccine effectiveness. If positive vaccine effectiveness was demonstrated, the 10Pn 2+1 clusters were subsequently compared to the combined Control 3+1 and Control 2+1 clusters.

These comparisons were done applying the following algorithm:

1. using a negative binomial log-linear model favouring correction for the cluster effect by taking into account for over-dispersion associated to cluster. The model included the group and the stratification factors as covariates.
2. In case of convergence issue with the first model (namely failure to find a maximum likelihood or over-dispersion null), a negative binomial log-linear model including only the group as covariate was applied.
3. If the over-dispersion was null (i.e. convergence to a Poisson model), the above models were replaced by a standard Poisson model including the group and stratification factors as covariates.

Statistical difference between groups was based on a 2-sided log-likelihood ratio p-value for the null hypothesis of no group difference < 5%. Any of these models was applied to derive the VE defined as 1 minus Relative Risk (RR). Incidence rates were derived considering the total number of years of follow-up as denominator.

Consequently, the 4 following methods were subsequenty used for the calculation of P-value/95% CI in vaccine effectiveness analysis:

- Method 1 = 2-sided profile log-likelihood ratio using a Negative Binomial regression model with strata
- Method 2 = 2-sided profile log-likelihood ratio using a Negative Binomial regression model without strata
- Method 3 = 2-sided profile log-likelihood ratio using a classical log linear Poisson regression with strata
- Method 4 = 2-sided profile log-likelihood ratio using a classical log linear Poisson regression without strata

Note that calculation of p-value using these above methods did not take into account the multiplicity of the endpoints.

Vaccine effectiveness was also calculated in terms of comparisons of culture-confirmed ID (if relevant number of cases) and in terms of pooled pneumococcal confirmed and probable cases in the Infant cohort for children assigned to a 3-dose and a 2-dose primary vaccination course and in the Catch-up cohort for pooled groups stratified per age range (7-11M and 12-18M).

Effectiveness against hospital-diagnosed pneumonia and hospital-diagnosed pneumonia classified based on CXR reading (CXR pneumonia).

The calculation of VE for hospital-diagnosedand hospital-diagnosed CXR pneumonia was performed similarly as that for VE against ID. The follow-up period considered was the period between the administration of Dose 1 to the cut-off date of 31 December 2011.
Hospital-diagnosed pneumonia cases were identified based on hospital discharge diagnosis using the following International Classification of Disease (ICD)-10 diagnosis codes. J10.0 (Influenza with pneumonia, other influenza virus identified), J11.0 (Influenza with pneumonia, virus not identified), J12 (Viral pneumonia, not elsewhere classified), J13 (Pneumonia due to *S. pneumoniae*), J14 (for Pneumonia due to *H. influenzae*), J15 (all pneumonia, not elsewhere classified), J16 (Pneumonia due to other infectious organisms, not elsewhere classified), J17 (Pneumonia in diseases classified elsewhere), J18 (Pneumonia, organism unspecified), J85.1 (Abscess of lung with pneumonia), and J86 (Pyothorax (including empyema)).
CXR pneumonia was defined as a hospital-diagnosed pneumonia case with the presence of abnormal pulmonary infiltrates on the CXR as per the judgement of the independent review panel using WHO methodology. Abnormal pulmonary infiltrates could be either with (Consolidated pneumonia) or without (Non-consolidated pneumonia) alveolar consolidation/pleural effusion.
New cases of hospital-diagnosed and hospital-diagnosed CXR pneumonia were defined based on a 30-day rule, meaning that a new episode was considered if at least a 30-day interval elapsed (i.e. a difference of 30 days or more) from the onset of the previous episode.

Effectiveness in prevention of outpatient antimicrobial prescriptions and tympanostomy tube placement.
The calculation of VE for tympanostomy tube placement and antimicrobial prescriptions episodes occurring respectively in the Infant cohort for children assigned to a 3-dose and a 2-dose primary vaccination course and in the Catch-up cohort for pooled groups stratified per age range (7-11 months and 12-18 months) was performed similarly as that for VE against ID. The follow-up period was from the administration of Dose 1 to the cut-off date of 31 December 2011.
Tympanostomy tube placement and antimicrobial prescriptions episodes were defined as follows:

- A tympanostomy tube placement episode was defined as a tympanostomy tube placement episode classified under the DCA 20 code in the Finnish National Institute of Health and Welfare (THL) and Social Insurance Institution of Finland (KELA) registers, using the Nordic Centre for Classifications in Health Care (NOMESCO) Classification of Surgical Procedures (NCSP), version 1.12. from January 2008, and could refer to either an unilateral or a bilateral TTP procedure.
- An antimicrobial prescriptions episode was defined as an episode of antimicrobial prescription to an infant/child falling under the following Anatomic Therapeutic Chemical [ATC] codes: J01 (Antimicrobial prescription) and the following codes for antimicrobial prescriptions usually recommended for otitis media and RTI: J01CA04 (Amoxicyllin), J01CR02 (Amoxicyllin with enzyme inhibitor), J01CE02 (Phenoxymethylpenicillin), J01DC02 (Cefuroxime), J01DC04 (Cefaclor), J01EE02 (Sulfadiazine and trimethoprim), J01FA09 (Clarithromycin), and J01FA10 (Azithromycin).

New episodes of antimicrobial treatment were analyzed according to a 2-day rule meaning that a new episode was considered if at least 2-day interval elapsed from the onset of the previous episode. New episodes of tympanostomy tube placement defined according to a 30-day rule meaning that a new episode was considered if at least 30-day interval elapsed from the onset of the previous episode.

Analysis of Safety in the Vaccinated Population
For the period till the end of the blinded ID Follow-Up, the analysis was performed on the Infant Vaccinated cohort and on the Catch-up Vaccinated cohort defined based on subjects enrolled in the 111442 study only.
Safety analysis was based on SAEs reported via passive surveillance considering data reported through Finnish registers – passive surveillance consisting of collection of spontaneous reports of SAES reported post-vaccination with complementary national registers check in Finnish population for fatal cases SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and reported according to MedDRA Preferred Term. The number and percentage of subjects with SAE(s) were tabulated by treatment cluster group for infants and each catch-up group separately up to the end of the blinded ID Follow-Up period. The same tabulation was performed for fatal SAEs and for SAEs considered by the investigators to be causally related to vaccination for the same period.
For the period from the end of the blinded ID Follow-Up period up to 05 October 2013, end of 18-month period after study unblinding, the numbers of subjects from both, 111442 and 112595, studies for which at least one SAE was reported via passive surveillance were summarized. This summary also includes outcome of SAEs (fatal, non-fatal) and causal relationship with vaccination as assessed by the investigators.

Analysis of Indirect effects in the Unvaccinated Population
The analysis was performed on the Unvaccinated cohort. The calculation of VE for culture-confirmed IPD and for hospital-diagnosed pneumonia was performed similarly as that for VE against ID in the Vaccinated Population. The follow-up periods considered were the years 2010, 2011 and 2012 (periods starting 1st of January to 31st December of the considered year).
New cases of IPD/hospital-diagnosed pneumonia were analyzed according to a 30-day rule, meaning a new episode was

considered if it at least a 30-day interval elapsed (i.e. a difference of 30 days or more) from the onset of the previous episode. Results are presented for age range 5 years and above.

Study Population:

Vaccinated Population

Children between, and including, 6 weeks to 18 months of age at the time of the first vaccination. Subjects were excluded if they had a history of previous vaccination with any pneumococcal vaccine other than the study vaccine, or with Hepatitis A or B virus vaccine during the study period, or if such use was planned during the study period, or if they presented high risk of pneumococcal infections (such as anatomic or functional asplenia, HIV infection, chronic cardiac or respiratory disease (not asthma), diabetes, cochlear implant, CSF fistula or with significant immunodeficiency) or with any medical condition that would contraindicate the initiation of routine immunization outside a clinical trial context. Written informed consent was obtained from the parent/guardian of the subject prior to study entry.

Unvaccinated Population

All persons not enrolled in the study but who lived in the study cluster areas. No informed consent was obtained from these persons; however, permission for use of the aggregated data from the health registers was obtained before data extraction..

Number of subjects

Note regarding the tables presented here below: After the analysis had been performed, an error in treatment number allocation was identified in the 112595 study nested within the 111442 study. For 3 subjects, new subject numbers were allocated after administration of the first dose without excluding the initially allocated subject numbers from the Total Vaccinated cohort. Thus, for these 3 initially enrolled subjects, 2 subject numbers per each subject were used, while actually there were 3 subjects less enrolled among the 47369 subject numbers allocated. Therefore the actual total number of subjects enrolled was 47366 subjects with 45974 subjects in the Total Vaccinated cohort. This corresponds to 30527 subjects in the Infant Vaccinated cohort, 5787 in the Catch-up 7-11 Months Vaccinated cohort and 9660 in the Catch-up 12-18 Months Vaccinated cohort instead of the 30528, 5788 and 9661 subjects respectively presented in the demographic tables below. As these 3 subjects were part of separate age cohorts, the error would not be expected to have a significant impact on the overall data analysis; therefore re-analysis was not performed. The results presented below are based on the analysis including the 6 subject numbers pertaining to 3 enrolled subjects.

Infants Enrolled between 6 Weeks and 6 Months of Age

Number of subjects	111442 only			Total (111442 & 112595)		
	10Pn3+1 Group	10Pn2+1 Group	Ctrl Group	10Pn3+1 Group	10Pn2+1 Group	Ctrl Group
Planned, N	Not available	Not available	Not available	12180	12180	12180
Randomised, N (Infant Vaccinated cohort)	8427	9112	8872	10273	10054	10201
Completed, n (%)	Not available	Not available	Not available	Not available	Not available	Not available
Total Number Subjects Withdrawn, n (%)	Not available	Not available	Not available	Not available	Not available	Not available
Withdrawn due to Adverse Events n (%)	Not available	Not available	Not available	Not available	Not available	Not available
Withdrawn due to Lack of Efficacy n (%)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons n (%)	Not available	Not available	Not available	Not available	Not available	Not available
Demographics	10Pn3+1 Group	10Pn2+1 Group	Ctrl Group	10Pn3+1 Group	10Pn2+1 Group	Ctrl Group
N (Infant Vaccinated cohort)	8427	9112	8872	10273	10054	10201
Females: Males	4239:4188	4399:4713	4351:4521	5159:5114	4883:5171	4995:5206
Mean Age, months (SD)	3.4 (1.30)	3.4 (1.31)	3.3 (1.31)	3.2 (1.32)	3.3 (1.32)	3.2 (1.32)
Race, n (%)	Not available	Not available	Not available	Not available	Not available	Not available

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with HBV vaccine
10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with HBV vaccine

Subjects Enrolled between 7 Months and 18 Months of Age

Number of subjects	111442 only		Total (111442 & 112595)	
	7-11 Months	12-18 Months	7-11 Months	12-18 Months

	10Pn Group	Ctrl Group	10Pn Group	Ctrl Group	10Pn Group	Ctrl Group	10Pn Group	Ctrl Group
Planned, N	Not available	Not available	Not available	Not available	4698	2349	6832	3416
Randomised, N (Catch-up Vaccinated cohort)	3689	1812	6249	3020	3880	1908	6535	3126
Completed, n (%)	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available
Total Number Subjects Withdrawn, n (%)	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available
Withdrawn due to Adverse Events, n (%)	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available
Demographics	10Pn Group	Ctrl Group	10Pn Group	Ctrl Group	10Pn Group	Ctrl Group	10Pn Group	Ctrl Group
N (Catch-up Vaccinated cohort)	3689	1812	6249	3020	3880	1908	6535	3126
Females: Males	Not available	Not available	Not available	Not available	1888:1992	925:983	3197:3338	1530:1596
Mean Age, months (SD)	Not available	Not available	Not available	Not available	8.8 (1.36)	8.8 (1.34)	14.5 (2.46)	14.5 (2.39)
Race, n (%)	Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available

Groups in the 7-11 months age range

- 10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
- Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine

Groups in the 12-18 months age range:

- 10Pn Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of 10Pn vaccine
- Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of HAV vaccine

Primary Outcome Results: Vaccine effectiveness (with p-value) in prevention of culture confirmed Vaccine Type-Invasive Pneumococcal Disease anytime after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 3+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE			
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95%CI		P-value*
							LL	UL		LL	UL	
Vaccine serotypes (vaccine type-Invasive Pneumococcal Disease)	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100.0	82.8	100.0	<0.0001
	Ctrl	10201	10	12	21294.18	0.564	0.291	0.984	-	-	-	-

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a culture-confirmed ID
n+ = number of clusters with at least one event culture-confirmed ID n/T = percentage of subjects reporting a culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for P-value/95% CI calculation: 2-sided profile log-likelihood ratio 95% CI/P-value using a classical log linear Poisson regression with strata. Calculation of the p-value did not take into account the multiplicity of the endpoints.
**Criterion for evaluation of the objective: VE in preventing culture-confirmed IPD due to the 10 vaccine serotypes demonstrated if p-value < 5%.*

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of culture-confirmed Invasive Disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 3+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Culture-confirmed ID	10Pn3+1	10273	2	2	21501.88	0.093	0.011	0.336	89.1	62.1	98.3
	Ctrl	10201	14	18	21294.18	0.845	0.501	1.336	-	-	-
Pneumococcal ID (IPD)	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	85.6	100
	Ctrl	10201	11	14	21294.18	0.657	0.359	1.103	-	-	-
Serotype 4	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	-	-	-
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 6B	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	54.9	100
	Ctrl	10201	5	5	21294.18	0.235	0.076	0.548	-	-	-
Serotype 7F	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	-	-	-
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 14	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	39.6	100
	Ctrl	10201	4	4	21294.18	0.188	0.051	0.481	-	-	-
Serotype 18C	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-541.5	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Serotype 19F	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-379.2	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Serotype 23F	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-643.3	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Cross-reactive serotypes	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-51.8	100
	Ctrl	10201	2	2	21294.18	0.094	0.011	0.339	-	-	-
Serotype 6A	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-379.2	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Serotype 19A	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-381.1	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Other pneumococcal serotypes (non vaccine non cross-reactive serotypes)	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	-	-	-
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 3	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	-	-	-
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 15C	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	-	-	-
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
H. influenzae	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-774.6	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Non-typeable (NTHi)	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-774.6	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Other bacteria	10Pn3+1	10273	2	2	21501.88	0.093	0.011	0.336	50.7	-152.8	93.2
	Ctrl	10201	4	4	21294.18	0.188	0.051	0.481	-	-	-
Neisseria meningitidis	10Pn3+1	10273	2	2	21501.88	0.093	0.011	0.336	-115.4	-4553.1	79.5
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Streptococcus pyogenes	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-46.5	100
	Ctrl	10201	2	2	21294.18	0.094	0.011	0.339	-	-	-
Moraxella catarrhalis	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	-774.6	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a culture-confirmed ID
n+ = number of clusters with at least one event culture-confirmed ID
n/T = percentage of subjects reporting a culture-confirmed ID expressed in 1000-child year

95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata.

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of culture confirmed Invasive Disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 2+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Culture-confirmed ID	10Pn2+1	10054	4	4	20646.64	0.194	0.053	0.496	77.2	38.7	93.4
	Ctrl	10201	14	18	21294.18	0.845	0.501	1.336	-	-	-
Pneumococcal ID (IPD)	10Pn2+1	10054	2	2	20646.64	0.097	0.012	0.350	85.8	49.1	97.8
	Ctrl	10201	11	14	21294.18	0.657	0.359	1.103	-	-	-
Vaccine serotypes (VT-IPD)	10Pn2+1	10054	1	1	20646.64	0.048	0.001	0.270	91.8	58.3	99.6
	Ctrl	10201	10	12	21294.18	0.564	0.291	0.984	-	-	-
Serotype 4	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	-	-	-
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 6B	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	54.5	100
	Ctrl	10201	5	5	21294.18	0.235	0.076	0.548	-	-	-
Serotype 7F	10Pn2+1	10054	1	1*	20646.64	0.048	0.001	0.270	-1.85E13	-124E306	83.2
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 14	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	43.3	100
	Ctrl	10201	4	4	21294.18	0.188	0.051	0.481	-	-	-
Serotype 18C	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-330.7	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Serotype 19F	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-470.8	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Serotype 23F	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-788.4	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Cross-reactive serotypes	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-77.3	100
	Ctrl	10201	2	2	21294.18	0.094	0.011	0.339	-	-	-
Serotype 6A	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-470.8	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Serotype 19A	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-536.3	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Other pneumococcal serotypes (non vaccine non cross-reactive serotypes)	10Pn2+1	10054	1	1	20646.64	0.048	0.001	0.270	-6637637	-5.41E13	99.6
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 3	10Pn2+1	10054	1	1	20646.64	0.048	0.001	0.270	-6637637	-5.41E13	99.6
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
Serotype 15C	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	-	-	-
	Ctrl	10201	0	0	21294.18	0.000	0.000	0.173	-	-	-
H. influenzae	10Pn2+1	10054	1	1	20646.64	0.048	0.001	0.270	-10.5	-2711.4	95.7
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Non-typeable (NTHi)	10Pn2+1	10054	1	1	20646.64	0.048	0.001	0.270	-10.5	-2711.4	95.7
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Other bacteria	10Pn2+1	10054	1	1	20646.64	0.048	0.001	0.270	79.0	-58.6	99.1
	Ctrl	10201	4	4	21294.18	0.188	0.051	0.481	-	-	-
Neisseria meningitidis	10Pn2+1	10054	1	1	20646.64	0.048	0.001	0.270	2.7	-2488.5	96.8
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-
Streptococcus pyogenes	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-154.0	100
	Ctrl	10201	2	2	21294.18	0.094	0.011	0.339	-	-	-
Moraxella catarrhalis	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-795.8	100
	Ctrl	10201	1	1	21294.18	0.047	0.001	0.262	-	-	-

10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine

Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from both studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a culture-confirmed ID
n+ = number of clusters with at least one event culture-confirmed ID
n/T = percentage of subjects reporting a culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata
**The culture-confirmed VT-IPD case due to serotype 7F occurred 12 days after administration of Dose 1.*

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of culture-confirmed invasive disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 7-11M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Culture-confirmed ID	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	100	30.1	100
	Ctrl	1908	2	2	4480.73	0.446	0.054	1.612	-	-	-
Pneumococcal ID (IPD)	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	100	30.1	100
	Ctrl	1908	2	2	4480.73	0.446	0.054	1.612	-	-	-
Vaccine serotypes (VT-IPD)	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	100	30.1	100
	Ctrl	1908	2	2	4480.73	0.446	0.054	1.612	-	-	-
Serotype 4	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 6B	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 7F	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	100	-156.3	100
	Ctrl	1908	1	1	4480.73	0.223	0.006	1.243	-	-	-
Serotype 14	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	100	-148.6	100
	Ctrl	1908	1	1	4480.73	0.223	0.006	1.243	-	-	-
Serotype 18C	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 19F	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 23F	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Cross-reactive serotypes	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 6A	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 19A	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Other pneumococcal serotypes (non vaccine non cross-reactive serotypes)	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 3	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Serotype 15C	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
H. influenzae	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Non-typeable (NTHi)	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Other bacteria	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-

10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine

Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from both studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a culture-confirmed ID
n+ = number of clusters with at least one event culture-confirmed Invasive Disease
n/T = percentage of subjects reporting a culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata.

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of culture confirmed Invasive Disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 12-18M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95%CI	
							LL	UL		LL	UL
Culture- confirmed ID	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	79.0	100
	Ctrl	3126	5	5	7421.16	0.674	0.219	1.572	-	-	-
Pneumococcal ID (IPD)	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	79.0	100
	Ctrl	3126	5	5	7421.16	0.674	0.219	1.572	-	-	-
Vaccine serotypes (VT-IPD)	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	73.1	100
	Ctrl	3126	3	3	7421.16	0.404	0.083	1.181	-	-	-
Serotype 4	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	-665.8	100
	Ctrl	3126	1	1	7421.16	0.135	0.003	0.751	-	-	-
Serotype 6B	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	-255.5	100
	Ctrl	3126	1	1	7421.16	0.135	0.003	0.751	-	-	-
Serotype 7F	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Serotype 14	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Serotype 18C	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Serotype 19F	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	-170.6	100
	Ctrl	3126	1	1	7421.16	0.135	0.003	0.751	-	-	-
Serotype 23F	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Cross-reactive serotypes	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Serotype 6A	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Serotype 19A	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Other pneumococcal serotypes (non vaccine non cross-reactive serotypes)	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	23.9	100
	Ctrl	3126	2	2	7421.16	0.269	0.033	0.974	-	-	-
Serotype 3	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	-142.6	100
	Ctrl	3126	1	1	7421.16	0.135	0.003	0.751	-	-	-
Serotype 15C	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	-146.5	100
	Ctrl	3126	1	1	7421.16	0.135	0.003	0.751	-	-	-
H. influenzae	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Non-typeable (NTHi)	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Other bacteria	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-

10Pn Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of 10Pn vaccine
Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of HAV vaccine

VE (%) = Vaccine effectiveness
N = total number of subjects from both studies 111442 and 112595
T (year) = sum of follow-up period expressed years
n = number of subjects reporting a culture-confirmed ID
n+ = number of clusters with at least one event culture-confirmed ID
n/T = percentage of subjects reporting a culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of probable or culture-confirmed Invasive Disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 3+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95%CI	
							LL	UL		LL	UL
Probable cases of ID	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	7.6	100
	Ctrl	10201	2	3	21294.18	0.141	0.029	0.412	-	-	-
Confirmed or probable cases of IPD	10Pn3+1	10273	0	0	21501.88	0.000	0.000	0.172	100	87.8	100
	Ctrl	10201	11	17	21294.18	0.798	0.465	1.278	-	-	-

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from both studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a probable or culture-confirmed ID
n+ = number of clusters with at least one event probable or culture-confirmed ID
n/T = percentage of subjects reporting a probable or culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Methods for 95% CI calculation:

- Probable cases of ID: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata
- Confirmed or probable cases of IPD: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model without strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of probable or culture-confirmed Invasive Disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 2+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95%CI	
							LL	UL		LL	UL
Probable cases of IPD	10Pn2+1	10054	0	0	20646.64	0.000	0.000	0.179	100	-9.6	100
	Ctrl	10201	2	3	21294.18	0.141	0.029	0.412	-	-	-
Confirmed or probable cases of IPD	10Pn2+1	10054	2	2	20646.64	0.097	0.012	0.350	87.7	54.6	98.1
	Ctrl	10201	11	17	21294.18	0.798	0.465	1.278	-	-	-

10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from both studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a probable or culture-confirmed ID
n+ = number of clusters with at least one event probable or culture-confirmed ID
n/T = percentage of subjects reporting a probable or culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Methods for 95% CI calculation:

- Probable cases of IPD: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata
- Confirmed or probable cases of IPD: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model without strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of probable or culture confirmed Invasive Disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 7-11M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95%CI	
							LL	UL		LL	UL
Probable cases of IPD	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	-	-	-
	Ctrl	1908	0	0	4480.73	0.000	0.000	0.823	-	-	-
Confirmed or probable cases of IPD	10Pn	3880	0	0	9000.95	0.000	0.000	0.410	100	30.1	100
	Ctrl	1908	2	2	4480.73	0.446	0.054	1.612	-	-	-

10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from both studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a probable or culture-confirmed ID
n+ = number of clusters with at least one event probable or culture-confirmed ID
n/T = percentage of subjects reporting a probable or culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in the prevention of probable or culture confirmed Invasive Disease any time after the administration of first vaccine dose till the end of the blinded ID Follow-up period – 12-18M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Probable cases of IPD	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	-	-	-
	Ctrl	3126	0	0	7421.16	0.000	0.000	0.497	-	-	-
Confirmed or probable cases of IPD	10Pn	6535	0	0	15361.00	0.000	0.000	0.240	100	79.0	100
	Ctrl	3126	5	5	7421.16	0.674	0.219	1.572	-	-	-

10Pn Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of 10Pn vaccine
Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of HAV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from both studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of subjects reporting a probable or culture-confirmed ID
n+ = number of clusters with at least one event probable or culture-confirmed ID
n/T = percentage of subjects reporting a probable or culture-confirmed ID expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 3+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Hospital-diagnosed pneumonia	10Pn3+1	10273	25	209	20629.98	10.131	8.804	11.601	26.7	4.9	43.5
	Ctrl	10200	26	283	20426.75	13.854	12.287	15.566	-	-	-

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year

95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 2+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Hospital-diagnosed pneumonia	10Pn2+1	10054	26	201	19793.32	10.155	8.800	11.660	29.3	7.5	46.3
	Ctrl	10200	26	283	20426.75	13.854	12.287	15.566	-	-	-

10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 7-11M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Hospital-diagnosed pneumonia	10Pn	3880	42	89	8671.64	10.263	8.242	12.630	33.2	3.0	53.4
	Ctrl	1907	22	68	4316.83	15.752	12.232	19.970	-	-	-

10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 12-18M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Hospital-diagnosed pneumonia	10Pn	6534	39	138	14803.91	9.322	7.832	11.013	22.4	-8.7	44.8
	Ctrl	3126	24	84	7155.85	11.739	9.363	14.533	-	-	-

10Pn Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of 10Pn vaccine
Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of HAV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia with CXR reading according WHO criteria any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 3+1

Schedule (Infant Vaccinated cohort)

Event Type	Group	N	n+	n	T (year)	Person-year rate			VE		
						n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Consolidated pneumonia	10Pn3+1	10273	22	45	20629.98	2.181	1.591	2.919	45.0	19.8	62.8
	Ctrl	10200	23	81	20426.75	3.965	3.149	4.929	-	-	-
Non-consolidated pneumonia	10Pn3+1	10273	18	60	20629.98	2.908	2.219	3.744	-2.2	-72.9	38.8
	Ctrl	10200	18	60	20426.75	2.937	2.241	3.781	-	-	-
Consolidated or non-consolidated pneumonia	10Pn3+1	10273	24	105	20629.98	5.090	4.163	6.161	26.0	-5.1	47.9
	Ctrl	10200	25	141	20426.75	6.903	5.810	8.141	-	-	-

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation:

- Consolidated pneumonia: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model without strata
- Non-consolidated pneumonia/Consolidated or non-consolidated pneumonia: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia with CXR reading according WHO criteria any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 2+1
Schedule (Infant Vaccinated cohort)

Event Type	Group	N	n+	n	T (year)	Person-year rate			VE		
						n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Consolidated pneumonia	10Pn2+1	10054	20	45	19793.32	2.273	1.658	3.042	43.9	19.6	61.4
	Ctrl	10200	23	81	20426.75	3.965	3.149	4.929	-	-	-
Non-consolidated pneumonia	10Pn2+1	10054	19	52	19793.32	2.627	1.962	3.445	11.9	-44.6	46.2
	Ctrl	10200	18	60	20426.75	2.937	2.241	3.781	-	-	-
Consolidated or non-consolidated pneumonia	10Pn2+1	10054	23	97	19793.32	4.901	3.974	5.978	31.0	4.0	50.6
	Ctrl	10200	25	141	20426.75	6.903	5.810	8.141	-	-	-

10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation:

- Consolidated pneumonia: 2-sided profile log-likelihood ratio 95% CI using a a classical log linear Poisson regression with strata
- Non-consolidated pneumonia/Consolidated or non-consolidated pneumonia/No pneumonia/Uninterpretable: 2-sided profile log-likelihood ratio 95%CI using Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia with CXR reading according WHO criteria any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 7-11M
Schedule (Catch-up Vaccinated cohort)

Event Type	Group	N	n+	n	T (year)	Person-year rate			VE		
						n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Consolidated pneumonia	10Pn	3880	14	17	8671.64	1.960	1.142	3.139	56.3	15.6	77.5

	Ctrl	1907	13	19	4316.83	4.401	2.650	6.873	-	-	-
Non-consolidated pneumonia	10Pn	3880	19	29	8671.64	3.344	2.240	4.803	29.7	-36.5	63.5
	Ctrl	1907	13	21	4316.83	4.865	3.011	7.436	-	-	-
Consolidated or non-consolidated pneumonia	10Pn	3880	30	46	8671.64	5.305	3.884	7.076	42.6	9.0	63.9
	Ctrl	1907	18	40	4316.83	9.266	6.620	12.618	-	-	-

10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation:

- Consolidated pneumonia/Uninterpretable:2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata
- Non-consolidated pneumonia/Consolidated or non-consolidated pneumonia/No pneumonia: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in reducing hospital-diagnosed pneumonia with CXR reading according WHO criteria any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 12-18M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Consolidated pneumonia	10Pn	6534	18	27	14803.91	1.824	1.202	2.654	48.2	0.6	73.1
	Ctrl	3126	13	25	7155.85	3.494	2.261	5.157	-	-	-
Non-consolidated pneumonia	10Pn	6534	27	42	14803.91	2.837	2.045	3.835	5.3	-71.7	45.0
	Ctrl	3126	11	21	7155.85	2.935	1.817	4.486	-	-	-
Consolidated or non-consolidated pneumonia	10Pn	6534	31	69	14803.91	4.661	3.626	5.899	26.5	-17.8	53.1
	Ctrl	3126	17	46	7155.85	6.428	4.706	8.574	-	-	-

10Pn Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of 10Pn vaccine
Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of HAV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of hospital-diagnosed pneumonia
n+ = number of clusters with hospital-diagnosed pneumonia
n/T = percentage of hospital-diagnosed pneumonia expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation:

- No pneumonia: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model without strata
- Consolidated pneumonia/Non-consolidated pneumonia/Consolidated or non-consolidated pneumonia/Uninterpretable: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all tympanostomy tube placements any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 3+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Tympanostomy tube placement	10Pn3+1	10273	26	1418	20629.98	68.735	65.203	72.408	13.2	-6.0	29.0
	Ctrl	10200	26	1624	20426.75	79.504	75.683	83.467	-	-	-

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of tympanostomy tube placements

n+ = number of clusters with a tympanostomy tube placement
n/T = percentage of tympanostomy tube placements expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all tympanostomy tube placements for the infants enrolled between 6 weeks and 6 months of age any time after the administration of the first vaccine dose till 31 December 2011 – 2+1 Schedule (30-day rule) (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Tympanostomy tube placement	10Pn2+1	10054	26	1308	19793.32	66.083	62.550	69.764	13.0	-4.7	27.5
	Ctrl	10200	26	1624	20426.75	79.504	75.683	83.467	-	-	-

10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of tympanostomy tube placements
n+ = number of clusters with a tympanostomy tube placement
n/T = percentage of tympanostomy tube placements expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all tympanostomy tube placements any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 7-11M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Tympanostomy tube placement	10Pn	3880	52	591	8671.64	68.153	62.769	73.876	10.7	-8.1	25.9
	Ctrl	1907	26	345	4316.83	79.920	71.708	88.814	-	-	-

10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of tympanostomy tube placements
n+ = number of clusters with a tympanostomy tube placement
n/T = percentage of tympanostomy tube placements expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all tympanostomy tube placements any time after the administration of the first vaccine dose till 31 December 2011 (30-day rule) – 12-18M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Tympanostomy tube placement	10Pn	6534	52	841	14803.91	56.809	53.034	60.782	-0.6	-20.5	15.9
	Ctrl	3126	26	422	7155.85	58.973	53.480	64.877	-	-	-

10Pn Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of 10Pn vaccine
Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of HAV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of tympanostomy tube placements
n+ = number of clusters with a tympanostomy tube placement
n/T = percentage of tympanostomy tube placements dose expressed in 1000-child year
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all antimicrobial prescriptions any time after the

administration of the first vaccine dose till 31 December 2011 (2-day rule) – 3+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Antimicrobial prescriptions (ATC code J01)	10Pn3+1	10273	26	32855	20629.98	1592.585	1575.411	1609.901	6.7	-1.4	14.1
	Ctrl	10200	26	34852	20426.75	1706.194	1688.328	1724.202	-	-	-
Antimicrobial prescriptions for antibacterial usually recommended for otitis media and for respiratory infections (ATC codes: J01CA04, J01CR02, J01CE02, J01DC02, J01DC04, J01EE02, J01FA09 and J01FA10)	10Pn3+1	10273	26	29937	20629.98	1451.141	1434.749	1467.674	7.5	-1.1	15.4
	Ctrl	10200	26	31982	20426.75	1565.692	1548.579	1582.947	-	-	-

10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of antimicrobial prescriptions
n+ = number of clusters with antimicrobial prescription(s)
n/T = percentage of antimicrobial prescriptions expressed in 1000 child-years
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all antimicrobial prescriptions any time after the administration of the first vaccine dose till 31 December 2011 (2-day rule) – 2+1 Schedule (Infant Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Antimicrobial prescriptions (ATC code J01)	10Pn2+1	10054	26	30729	19793.32	1552.493	1535.183	1569.950	7.5	-0.4	14.6
	Ctrl	10200	26	34852	20426.75	1706.194	1688.328	1724.202	-	-	-
Antimicrobial prescriptions for antibacterial usually recommended for otitis media and for respiratory infections (ATC codes: J01CA04, J01CR02, J01CE02, J01DC02, J01DC04, J01EE02, J01FA09 and J01FA10)	10Pn2+1	10054	26	28027	19793.32	1415.983	1399.453	1432.659	7.8	-0.6	15.5
	Ctrl	10200	26	31982	20426.75	1565.692	1548.579	1582.947	-	-	-

10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 or 3 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of antimicrobial prescriptions
n+ = number of clusters with antimicrobial prescription(s)
n/T = percentage of antimicrobial prescriptions expressed in 1000 child-years
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all antimicrobial prescriptions any time after the administration of the first vaccine dose till 31 December 2011 (2-day rule) – 7-11M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Antimicrobial prescriptions (ATC code J01)	10Pn	3880	52	13325	8671.64	1536.618	1510.637	1562.934	3.3	-5.0	10.8
	Ctrl	1907	26	7120	4316.83	1649.360	1611.269	1688.124	-	-	-
Antimicrobial prescriptions for	10Pn	3880	52	12061	8671.64	1390.856	1366.143	1415.903	3.7	-5.0	11.6

antibacterial usually recommended for otitis media and for respiratory infections (ATC codes: J01CA04, J01CR02, J01CE02, J01DC02, J01DC04, J01EE02, J01FA09 and J01FA10)	Ctrl	1907	26	6474	4316.83	1499.713	1463.401	1536.698	-	-	-

10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of antimicrobial prescriptions
n+ = number of clusters with antimicrobial prescription(s) n/T = percentage of antimicrobial prescriptions expressed in 1000 child-years
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation:

- Antimicrobial prescriptions linked to ATC code J01CA04 (Amoxicyllin): 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata
- Other cases: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Vaccine effectiveness (VE) in prevention of all antimicrobial prescriptions any time after the administration of the first vaccine dose till 31 December 2011 (2-day rule) – 12-18M Schedule (Catch-up Vaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T (year)	n/T (Per 1000)	95% CI		%	95% CI	
							LL	UL		LL	UL
Antimicrobial prescriptions (ATC code J01)	10Pn	6534	52	19481	14803.91	1315.936	1297.521	1334.547	4.0	-3.5	10.9
	Ctrl	3126	26	10174	7155.85	1421.774	1394.280	1449.675	-	-	-
Antimicrobial prescriptions for antibacterial usually recommended for otitis media and for respiratory infections (ATC codes: J01CA04, J01CR02, J01CE02, J01DC02, J01DC04, J01EE02, J01FA09 and J01FA10)	10Pn	6534	52	17435	14803.91	1177.729	1160.312	1195.343	3.5	-4.6	10.9
	Ctrl	3126	26	9097	7155.85	1271.268	1245.277	1297.665	-	-	-

10Pn Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of 10Pn vaccine
Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers receiving 2 doses of HAV vaccine
VE (%) = Vaccine effectiveness
N = total number of subjects from studies 111442 and 112595
T (year) = sum of follow-up period expressed in years
n = number of antimicrobial prescriptions
n+ = number of clusters with antimicrobial prescription(s)
n/T = percentage of antimicrobial prescriptions expressed in 1000 child-years
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Method for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Indirect effects – vaccine effectiveness in prevention of invasive pneumococcal disease in 5 to 99+ years old population in year 2010 (Unvaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T(year)	n/T (per 100000)	LL	UL	%	LL	UL
Any serotype IPD	Ind-10Pn	2626735	48	385	2626735	14.657	13.229	16.197	-7.6	-28.5	9.6
	Ind-Ctrl	1354702	24	184	1354702	13.582	11.691	15.693	-	-	-
Vaccine serotype IPD	Ind-10Pn	2626735	47	222	2626735	8.452	7.376	9.639	-10.6	-40.3	12.2
	Ind-Ctrl	1354702	22	103	1354702	7.603	6.206	9.221	-	-	-
Vaccine-related IPD	Ind-10Pn	2626735	31	43	2626735	1.637	1.185	2.205	9.7	-49.8	44.4
	Ind-Ctrl	1354702	15	25	1354702	1.845	1.194	2.724	-	-	-
Non-vaccine & non-vaccine-related	Ind-10Pn	2626735	39	105	2626735	3.997	3.269	4.839	-18.6	-74.0	18.0
	Ind-Ctrl	1354702	20	45	1354702	3.322	2.423	4.445	-	-	-

serotype IPD											

Ind-10Pn Group = Non-vaccinated persons living in the study cluster areas, in which study participants received 10Pn vaccine
Ind-Ctrl Group = Non-vaccinated persons living in the study cluster areas, in which study participants received HAV or HBV vaccine
VE (%) = Vaccine effectiveness = (1 minus Relative Risk)*100
N = total number of persons from studies 111442 and 112595
n = number of persons reporting an IPD in given category
n+ = number of clusters with IPD in given category
T(year) = sum of follow up period expressed in years
n/T (per 100000) = percentage of persons reporting an invasive pneumococcal disease expressed in 100000 person-years
Methods for 95% CI calculation:

- Non-vaccine & non-vaccine-related serotype IPD: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata
- Any serotype IPD/Vaccine serotype IPD/Vaccine-related IPD: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata

Secondary Outcome Variable(s): Indirect effects – vaccine effectiveness in prevention of invasive pneumococcal disease in 5 to 99+ years old population in year 2011 (Unvaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T(year)	n/T (per 100000)	LL	UL	%	LL	UL
Any serotype IPD	Ind-10Pn	2636783	48	382	2636783	14.487	13.071	16.015	-5.5	-26.7	12.1
	Ind-Ctrl	1360966	24	187	1360966	13.740	11.841	15.857	-	-	-
Vaccine serotype IPD	Ind-10Pn	2636783	47	206	2636783	7.813	6.782	8.955	-0.6	-29.1	21.4
	Ind-Ctrl	1360966	22	106	1360966	7.789	6.377	9.420	-	-	-
Vaccine-related IPD	Ind-10Pn	2636783	29	61	2636783	2.313	1.770	2.972	-13.0	-88.5	32.2
	Ind-Ctrl	1360966	16	27	1360966	1.984	1.307	2.886	-	-	-
Non-vaccine & non-vaccine-related serotype IPD	Ind-10Pn	2636783	42	110	2636783	4.172	3.429	5.028	-5.7	-50.3	24.3
	Ind-Ctrl	1360966	19	54	1360966	3.968	2.981	5.177	-	-	-

Ind-10Pn Group = Non-vaccinated persons living in the study cluster areas, in which study participants received 10Pn vaccine
Ind-Ctrl Group = Non-vaccinated persons living in the study cluster areas, in which study participants received HAV or HBV vaccine
VE (%) = Vaccine effectiveness = (1 minus Relative Risk)*100
N = total number of persons from studies 111442 and 112595
n = number of persons reporting an IPD in given category
n+ = number of clusters with IPD in given category
T(year) = sum of follow up period expressed in years
n/T (per 100000) = percentage of persons reporting an invasive pneumococcal disease expressed in 100000 person-years
Methods for 95% CI calculation:

- Any serotype IPD/Vaccine serotype IPD/Vaccine-related IPD: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata
- Non-vaccine & non-vaccine-related serotype IPD: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model without strata

Secondary Outcome Variable(s): Indirect effects – vaccine effectiveness in prevention of invasive pneumococcal disease in 5 to 99+ years old population in year 2012 (Unvaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T(year)	n/T (per 100000)	LL	UL	%	LL	UL
Any serotype IPD	Ind-10Pn	2654010	48	372	2654010	14.017	12.628	15.516	7.0	-12.0	22.5
	Ind-Ctrl	1367343	24	206	1367343	15.066	13.079	17.269	-	-	-
Vaccine serotype IPD	Ind-10Pn	2654010	40	157	2654010	5.916	5.026	6.917	31.0	11.1	46.1
	Ind-Ctrl	1367343	23	117	1367343	8.557	7.077	10.255	-	-	-
Vaccine-related IPD	Ind-10Pn	2654010	36	79	2654010	2.977	2.357	3.710	-44.6	-126.3	4.9
	Ind-Ctrl	1367343	18	28	1367343	2.048	1.361	2.960	-	-	-
Non-vaccine & non-vaccine-related serotype IPD	Ind-10Pn	2654010	43	133	2654010	5.011	4.196	5.939	-16.4	-62.2	15.6
	Ind-Ctrl	1367343	22	59	1367343	4.315	3.285	5.566	-	-	-

Ind-10Pn Group = Non-vaccinated persons living in the study cluster areas, in which study participants received 10Pn vaccine

Ind-Ctrl Group = Non-vaccinated persons living in the study cluster areas, in which study participants received HAV or HBV vaccine
VE (%) = Vaccine effectiveness = (1 minus Relative Risk)*100
N = total number of persons from studies 111442 and 112595
n = number of persons reporting an IPD in given category
n+ = number of clusters with IPD in given category
T(year) = sum of follow up period expressed in years
n/T (per 100000) = percentage of persons reporting an IPD expressed in 100000 person-years
Methods for 95% CI calculation:

- Any serotype IPD/Vaccine serotype IPD/Non-vaccine & non-vaccine-related serotype IPD: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata
- Vaccine-related IPD: 2-sided profile log-likelihood ratio 95% CI using a classical log linear Poisson regression with strata

Secondary Outcome Variable(s): Indirect effects – vaccine effectiveness in prevention of hospital-diagnosed pneumonia in 5 to 99+ years old population in year 2010 (30-day rule) (Unvaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T(year)	n/T (per 1000)	LL	UL	%	LL	UL
Hospital-diagnosed pneumonia	Ind-10Pn	2626735	48	24214	2626735	9.218	9.103	9.335	0.3	-8.8	8.8
	Ind-Ctrl	1354702	24	12480	1354702	9.212	9.052	9.375	-	-	-

Ind-10Pn Group = Non-vaccinated persons living in the study cluster areas, in which study participants received 10Pn vaccine
Ind-Ctrl Group = Non-vaccinated persons living in the study cluster areas, in which study participants received HAV or HBV vaccine
VE (%) = Vaccine effectiveness = (1 minus Relative Risk)*100
N = total number of persons from studies 111442 and 112595
n = number of reported hospital-diagnosed pneumonia according to the 30-day rule
n+ = number of clusters with hospital-diagnosed pneumonia
T(year) = sum of follow up period expressed in years
n/T (per 1000) = percentage of reported hospital-diagnosed pneumonia according to the 30-day rule expressed in 1000 person-years
Methods for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Indirect effects – vaccine effectiveness in prevention of hospital-diagnosed pneumonia in 5 to 99+ years old population in year 2011 (30-day rule) (Unvaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T(year)	n/T (per 1000)	LL	UL	%	LL	UL
Hospital-diagnosed pneumonia	Ind-10Pn	2636783	48	27687	2636783	10.500	10.378	10.624	-0.8	-10.0	7.8
	Ind-Ctrl	1360966	24	14193	1360966	10.429	10.259	10.601	-	-	-

Ind-10Pn Group = Non-vaccinated persons living in the 1114422 and 112595 study cluster areas, in which study participants received 10Pn vaccine
Ind-Ctrl Group = Non-vaccinated persons living in the 1114422 and 112595 study cluster areas, in which study participants received HAV or HBV vaccine
VE (%) = Vaccine effectiveness = (1 minus Relative Risk)*100
N = total number of persons from studies 111442 and 112595
n = number of reported hospital-diagnosed pneumonia according to the 30-day rule
n+ = number of clusters with hospital-diagnosed pneumonia
T(year) = sum of follow up period expressed in years
n/T (per 1000) = percentage of reported hospital-diagnosed pneumonia according to the 30-day rule expressed in 1000 person-years
Methods for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Secondary Outcome Variable(s): Indirect effects – vaccine effectiveness in prevention of hospital-diagnosed pneumonia in 5 to 99+ years old population (by 5 years step and total) in year 2012 (30-day rule) (Unvaccinated cohort)

						Person-year rate			VE		
Event Type	Group	N	n+	n	T(year)	n/T (per 1000)	LL	UL	%	LL	UL
Hospital-diagnosed pneumonia	Ind-10Pn	2654010	48	26852	2654010	10.118	9.997	10.239	-2.3	-11.9	6.5
	Ind-Ctrl	1367343	24	13565	1367343	9.921	9.755	10.088	-	-	-

Ind-10Pn Group = Non-vaccinated persons living in the study cluster areas, in which study participants received 10Pn vaccine

Ind-Ctrl Group = Non-vaccinated persons living in the study cluster areas, in which study participants received HAV or HBV vaccine
VE (%) = Vaccine effectiveness = (1 minus Relative Risk)*100
N = total number of persons from studies 111442 and 112595
n = number of reported hospital-diagnosed pneumonia according to the 30-day rule
n+ = number of clusters with hospital-diagnosed pneumonia
T(year) = sum of follow up period expressed in years
n/T (per 1000) = percentage of reported hospital-diagnosed pneumonia according to the 30-day rule expressed in 1000 person-years
Methods for 95% CI calculation: 2-sided profile log-likelihood ratio 95% CI using a Negative Binomial regression model with strata

Safety Results: Number (%) of subjects with SAEs reported in the 111442 study from study start to the end of the blinded ID Follow-Up period – Subjects enrolled aged 6 weeks to 6 months (Infant Vaccinated cohort)

Serious adverse event, n (%) [n assessed by the investigator to be related to study medication]

All SAEs	10Pn2+1 Group N = 9112	Ctrl2+1 Group N = 4399	10Pn3+1 Group N = 8427	Ctrl3+1 Group N = 4473
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	7 (0.08) [2]	1 (0.02) [0]	6 (0.07) [1]	7 (0.16) [2]
Pyrexia	0 (0.00) [0]	0 (0.00) [0]	2 (0.02) [1]	0 (0.00) [0]
Accidental death	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Asphyxia	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Convulsion	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [1]
Cystitis	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Death	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Diarrhoea	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Eczema	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Febrile convulsion	1 (0.01) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Foreign body	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Gaucher's disease	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Hypotonic-hyporesponsive episode	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [1]
Infection	0 (0.00) [0]	1 (0.02) [0]	0 (0.00) [0]	0 (0.00) [0]
Injection site reaction	1 (0.01) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Irritability	1 (0.01) [1]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Krabbe's disease	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Laryngitis	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Myocarditis	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Parotitis	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Pneumococcal sepsis	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Reye's syndrome	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Road traffic accident	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Sepsis	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Sudden death	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Sudden infant death syndrome	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Vomiting	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Fatal SAEs	10Pn2+1 Group N = 9112	Ctrl2+1 Group N = 4399	10Pn3+1 Group N = 8427	Ctrl3+1 Group N = 4473
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	4 (0.04) [0]	0 (0.00) [0]	4 (0.05) [0]	3 (0.07) [0]
Accidental death	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Asphyxia	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Death	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Foreign body	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Gaucher's disease	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Krabbe's disease	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Laryngitis	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]

Myocarditis	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Reye's syndrome	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Road traffic accident	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.02) [0]
Sepsis	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Sudden death	1 (0.01) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Sudden infant death syndrome	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]

10Pn2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
Ctrl2+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 2 doses and boosted with HBV vaccine 10Pn3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with 10Pn vaccine
Ctrl3+1 Group = Infants enrolled 6 weeks-6 months of age: infants primed with 3 doses and boosted with HBV vaccine

Safety Results: Number (%) of subjects with SAEs reported in the 111442 study from study start to the end of the blinded ID Follow-Up period – Subjects enrolled aged 7 to 18 months (Catch-up Vaccinated cohort)

Serious adverse event, n (%) [n assessed by the investigator to be related to study medication]

All SAEs	7-11 Months		12-18 Months	
	10Pn Group N = 3689	Ctrl Group N = 1812	10Pn Group N = 6249	Ctrl Group N = 3020
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	3 (0.08) [2]	2 (0.11) [1]	2 (0.030) [1]	2 (0.07) [1]
Febrile convulsion	1 (0.03) [1]	0 (0.00) [0]	0 (0.00) [0]	1 (0.03) [1]
Kawasaki's disease	1 (0.03) [1]	0 (0.00) [0]	1 (0.01) [1]	0 (0.00) [0]
Asphyxia	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.03) [0]
Convulsion	0 (0.00) [0]	1 (0.06) [1]	0 (0.00) [0]	0 (0.00) [0]
Diarrhoea haemorrhagic	0 (0.00) [0]	0 (0.00) [0]	1 (0.01) [0]	0 (0.00) [0]
Pneumococcal sepsis	0 (0.00) [0]	1 (0.06) [0]	0 (0.00) [0]	0 (0.00) [0]
Syncope	0 (0.00) [0]	1 (0.061) [1]	0 (0.00) [0]	0 (0.00) [0]
Tonsillitis	1 (0.03) [0]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]
Fatal SAEs	7-11 Months Age Range		12-18 Months Age Range	
	10Pn Group N = 3689	Ctrl Group N = 1812	10Pn Group N = 6249	Ctrl Group N = 3020
Subjects with fatal SAE (s), n (%) [n assessed by the investigator as related]	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.03) [0]
Asphyxia	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]	1 (0.03) [0]

Groups in the 7-11 months age range:
- 10Pn Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with 10Pn vaccine
- Ctrl Group = Catch-up infants 7-11 months of age: infants primed with 2 doses and boosted with HBV vaccine

Groups in the 12-18 months age range:
- 10Pn Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of 10Pn vaccine
- Ctrl Group = Catch-up toddlers 12-18 months of age: toddlers vaccinated with 2 doses of HAV vaccine

Safety Results: Number of subjects enrolled and vaccinated in the 111442 and 112595 study with SAEs reported via passive surveillance from the end of the blinded ID Follow-Up period up to the end of 18-month period after study unblinding – Subjects enrolled aged 6 weeks to 6 months and 7 to 18 months

From the end of the blinded ID Follow-Up period up to the end of 18-month period after study unblinding, at least one SAE was reported for 3 subjects: one subject enrolled aged 6 weeks to 6 months in the 10Pn3+1 Group (epilepsy), one subject enrolled aged 6 weeks to 6 months in the 10Pn2+1 Group (quadriplegic infantile cerebral palsy and optic atrophy), and one subject enrolled aged 12-18 months in the 10Pn2+1 Group who received 2 doses of control vaccine (due to randomisation error in the study 112595) (pneumococcal infection). None of the above SAEs were reported to have had a fatal outcome and none have been assessed by the investigators to be related to study vaccination.

Conclusions:

Effectiveness

Among subjects from both the 111442 and 112595 studies enrolled within the first 7 months of life in clusters assigned to a 3-dose primary vaccination course (3+1 Schedule), the effectiveness of the 10Pn vaccine in preventing culture-confirmed IPD due to vaccine pneumococcal serotypes was 100% (95% CI range from 82.8% to 100%). Between study start and the end of the blinded ID Follow-Up period, respectively 0 and 12 subjects in the 10Pn3+1 and Ctrl groups presented culture-confirmed IPD due to vaccine pneumococcal serotypes. The primary objective was reached as the 2-sided p-value calculated for the null hypothesis (H0) = (VT IPD VE = 0%) was lower than the defined 2-sided alpha level of 0.05 (p-value <0.0001).

Safety

From study start up to the end of ID Follow-up period, through safety passive surveillance among the subjects from the 111442 study enrolled between 6 weeks and 6 months of age (Infant Vaccinated cohort), at least one SAE was reported for a total of 21 subjects:

- 6 (0.07%) subjects assigned to the 10Pn3+1 Schedule,
- 7 (0.16%) subjects assigned to the Control 3+1 Schedule,
- 7 (0.08%) subjects assigned to the 10Pn 2+1 Schedule,
- And 1 (0.02%) subject assigned to the Control 2+1 Schedule.

Among these 21 subjects,

- Fatal SAEs were reported for 11 subjects (4 assigned to the 10Pn3+1 Schedule, 3 assigned to the Control 3+1 Schedule and 4 assigned to the 10Pn 2+1 Schedule). None of these fatal SAEs were assessed by the investigators to be causally related to vaccination.
- At least one SAEs assessed by the investigators to be causally related to vaccination was reported for 5 subjects, 2 subjects in the 10Pn2+1 Schedule, 1 subject in the 10Pn3+1 Schedule and 2 subjects in the Ctrl3+1 Schedule.

From study start up to the end of the blinded ID Follow-Up period, among the catch-up subjects from the 111442 study enrolled between 7 and 18 months of age (Catch-up Vaccinated cohort), at least one SAE was reported for a total of 9 subjects:

- 3 (0.08%) subjects assigned to the Catch-up 7-11M-10Pn Schedule,
- 2 (0.11%) subjects assigned to the Catch-up 7-11M-Ctrl Schedule,
- 2 (0.03%) subjects assigned to the Catch-up 12-18M-10Pn Schedule,
- And 2 (0.07%) subjects assigned to the Catch-up 12-18M-Ctrl Schedule,

Among these 9 subjects, at least one SAE considered by the investigators as causally related to vaccination was reported for 5 subjects assigned to the 7-11M and 12-18M schedules (2 subjects assigned to the Catch-up 7-11M-10Pn Schedule, 1 subject assigned to the Catch-up 7-11M-Ctrl Schedule, 1 subject assigned to the Catch-up 12-18M-10Pn Schedule, and 1 subject assigned to the Catch-up 12-18M-Ctrl Schedule). One fatal SAE was reported for the subject assigned to the Catch-up 12-18M-Ctrl Schedule. This SAE was assessed by the investigators as not causally related to vaccination.

From the end of the blinded ID Follow-Up period up to the end of the 18-month period after study unblinding, at least one SAE was reported in 3 subjects. None of them were reported to have had a fatal outcome or have been assessed by the investigators to be causally related to study vaccination.

Refer to the 112595 CTRS for results of the nested 112595 (10PN-PD-DIT-053) study including AOM.

Date updated: 23 January 2015