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Effectiveness of the 10-valent pneumococcal conjugate vaccine among girls, boys, preterm and low-birth-weight infants – Results from a randomized, double-blind vaccine trial

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ABSTRACT

Background: Several studies have shown differences in susceptibility to infections and immune response to vaccines by sex. Prematurely born infants are at higher risk for pneumococcal diseases, with lower effectiveness for some vaccines compared to term infants. We have reported the effectiveness of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) on several endpoints in the Finnish Invasive Pneumococcal disease (FinIP) vaccine trial. Now, we present the results of a post-hoc analysis evaluating PHiD-CV10 effectiveness in subgroups by sex, gestational age, and birth weight.

Methods: The FinIP trial was a phase III/IV cluster-randomized, double-blind trial. Infants enrolled < 7 -months of age received PHiD-CV10 in two thirds of clusters (3 + 1 or 2 + 1 schedule) and hepatitis B vaccine as control in remaining third. Outcome data included invasive pneumococcal disease, pneumonia, tympanostomy tube placements, and antimicrobial purchases collected through national, routinely used health registers. Negative binomial model was used in the incidence and vaccine effectiveness estimation, and differences in incidences between subgroups were tested among control children.

Results: Of the 30,527 infants enrolled 51% were boys. The incidences of hospital-diagnosed pneumonia and otitis-related outcomes were higher among boys in control groups. There were no significant sex differences in the vaccine effectiveness estimates.

Altogether, 1519 (5%) infants were born before 37th gestational week. The incidences of pneumonia outcomes were higher among premature infants when compared to term infants.

The vaccine effectiveness estimates among preterm infants were not statistically significant except for antimicrobial purchases, but all point estimates were at the same level among preterm infants as among term infants. There was no significant difference between 2 + 1 and 3 + 1 schedules in any of the subgroups analysed.

Conclusion: PHiD-CV10 had a similar effectiveness in both sexes, and seemed to be protective in preterm infants.

Trial registration: ClinicalTrials.gov NCT00861380 and NCT00839254

1. Introduction

Several studies have shown differences in the susceptibility to infections and immune response to microbes and vaccines by sex [1–3]. The incidences of invasive pneumococcal disease (IPD), pneumonia and otitis media have been reported to be higher in males [4–8]. In immunological studies girls have had higher antibody levels after pneumococcal conjugate vaccine (PCV) than boys [2].

Multiple risk groups for pneumococcal diseases have been defined. Also premature infants are more susceptible to pneumococcal diseases than term infants [9,10]. The immunogenicity of PCVs among preterm infants has been somewhat lower than

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among term infants [11–14]. So far, only a few published studies have reported the effectiveness or efficacy of the 7-valent PCV against IPD among preterm and low-birth-weight infants [14,15]. Also the best possible vaccination schedule for preterm infants is still under research [16,17]. In Finland, about 5% (nearly 3 000 yearly) of all infants are born preterm [18]. The vaccinations are administered to preterm and low-birth-weight infants according to the same programme as to term infants.

We have previously reported the impact of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) on several outcomes in the Finnish Invasive Pneumococcal disease (FinIP) vaccine trial [19–24]. In this post-hoc exploratory analysis we evaluated the vaccine effectiveness (VE) by sex, by gestational age, and by birth weight.

2. Methods

The FinIP trial was a nationwide phase III/IV cluster-randomised double-blind field trial. The enrolment period extended from February 2009 to October 2010. Enrolment was ended when PCV was introduced into the National Vaccination Programme. The aim of the FinIP trial was to investigate the direct and indirect effects of PHiD-CV10 (Synflorix, GSK) against pneumococcal diseases. The trial design has been previously described [19]. Briefly, all children aged <19 months residing in the study area covering most of Finland were eligible if they had not received and were not expected to receive any of the study vaccines. A written informed consent to participation was obtained from parents or legal guardians of the children. For the current analyses we included only children belonging to the infant group, i.e. if enrolment and first vaccination took place before the age of 7 months. Children received two or three primary doses, and a booster dose after 11 months of age (2 + 1 and 3 + 1 schedules, respectively) of either PHiD-CV10 or hepatitis B vaccine (Engerix-B, GSK). Study was blinded and cluster-randomized. However, the vaccination schedules were not blinded. The blinded follow-up lasted from the first vaccine dose to the 31st December 2011 for all outcomes, except laboratory-confirmed IPD for which the follow-up was extended to last until the 31st January 2012.

All study vaccines were licensed in Finland before the trial began but they were not included in the National Vaccination Programme at the time of enrolment except for specified risk groups which did not include preterm infants. Thus, preterm and low-birth-weight infants were eligible for the trial enrolment.

The outcome data were collected from routinely used national health registers. Laboratory-confirmed and serotyped IPD cases were obtained from National Infectious Diseases Register, clinically suspected IPD, pneumonia and tympanostomy tube placements (TTPs) were collected from the Care Register for Health Care in which all hospitals notify the visits and/or admissions of in- and outpatient visits (Table 1). TTPs were performed in public hospitals and also in private clinics. The data of the TTPs in private clinics were obtained from the Social Insurance Institution benefits register from which we also obtained the data on antimicrobial purchases of the children. The ICD-10 diagnoses and ATC-codes used for defining outcomes are described in Table 1.

The gestational age and birth weight were obtained from the Birth Register. Preterm infants were defined as babies born at gestational age of <37 weeks. Low-birth-weight infants were defined as infants weighing <2500 g at birth.

2.1. Statistical methods

The sample size of the study was based on the primary objective of the trial, evaluation of VE against laboratory-confirmed IPD [19].

For these exploratory analyses, the incidences of the outcomes were estimated for boys and girls, term and preterm infants, and infants with low or normal birth weight, separately in PHiD-CV10 and control groups. VE was estimated by using negative binomial model in order to allow for possible overdispersion due to cluster design. This method allows differential vaccine effect on risk groups to be evaluated with interactions. Each outcome frequencies were grouped by cluster and the cluster-specific person-years were used as weights in the analysis. The factors included in each model were treatment, binary term for gender (girl/boy), gestational age (below/above 37 weeks), or birth weight (below/above 2500 g), and an interaction term between the two. In addition, the factors used for stratified randomization were included. The difference in incidences between subgroups was tested among control children from a regression model without treatment effect.

VE was considered significant if the 95% confidence interval (CI) did not include zero. In addition, the difference in VE between the subgroups was considered significant if the p-value for the interaction parameter was<0.05. The study was randomized into 3 + 1 and 2 + 1 schedules in both PHiD-CV10 and control groups (2:2:1:1), and the two control groups were combined for the effectiveness analyses. VE was assessed separately for the infant PHiD-CV10 3 + 1, 2 + 1 schedules, as well as for the two PHiD-CV10 schedules combined.

The study protocols were approved by the relevant ethical review boards and competent authorities prior to trial start. The trials are registered at ClinicalTrials.gov (main trial NCT00861380 and the nested carriage and acute otitis media trial NCT00839254).

3. Results

Altogether 30 527 infants participated in the FinIP trial, of which 15 503 (50.8%) were boys, 1 519 (5.0%) were born before 37th gestational week and 1 086 (3.6%) had birth weight <2 500 g (Table 2). The data on the gestational age and birth weight were missing in 56 and 13 children, respectively. The median age at first vaccination for the preterm and low-birth-weight infants was 16 weeks for PHiD-CV10 recipients and 14 weeks for control vaccine recipients (Table 2).

4. Sex

The incidences of hospital-diagnosed pneumonia, tympanostomy tube placements and antimicrobial purchases in the control groups were significantly higher in boys than in girls (Fig. 1). The point estimates of the incidences of laboratory-confirmed IPD, clinically suspected non-laboratory-confirmed IPD, and hospital-treated primary pneumonia tended to be higher among boys, but differences between sexes were not statistically significant (Supplement table). The VE estimates were generally slightly higher for girls than boys for the outcomes evaluated, but we did not find any significant differences between the sexes (Fig. 2, Supplement table). The 2 + 1 and 3 + 1 schedules performed equally well in both sexes (Supplement table).

5. Gestational age and birth weight

The incidences of both pneumonia outcomes were significantly higher among preterm infants than among term infants (Fig. 3). The VE estimates among the preterm infants were not statistically significant except for antimicrobial purchases, but all point estimates were at the same level among preterm infants as among term infants (Table 3). The results for the low-birth-weight infants were similar to the results for the preterm infants (Table 4), yet the VE for tympanostomy tube placements among the low-birth-

Table 1
The outcomes, case definitions, follow-up, episode duration and data sources used in the evaluation of pneumococcal diseases in the Finnish Invasive Pneumococcal disease vaccine trial.

Disease	Outcome	Case definition	Days between two episodes	Data source
Invasive pneumococcal disease (IPD)	Laboratory-confirmed IPD	Disease where *S. pneumoniae* isolated by culture or detected by antigen or nucleic acid test from normally sterile body fluid.	90	National Infectious Diseases Register*
	Clinically suspected, non-laboratory-confirmed IPD or unspecified sepsis (Non-lab IPD)	Any register-based event with an ICD-10 diagnosis compatible with IPD: A40.3, B95.3, G00.1, M00.1; or unspecified sepsis: A40.9, A41.9, A49.9, G00, G00.9, I30.1, M00, M00.9, B95.5. Laboratory-confirmed IPD excluded.	90	National Care Register§
Pneumonia	Hospital-diagnosed pneumonia	Any register-based event in with ICD-10 diagnosis of pneumonia: J10.0, J11.0, J12 to J18, J85.1 or J86.	90	National Care Register
	Hospital-treated primary pneumonia	Hospitalization with primary ICD-10 diagnosis of pneumonia at discharge: J10.0, J11.0, J12 to J18, J85.1 or J86.	90	National Care Register
Otitis media	Tympanostomy tube placements (TTP)	An event of TTP with the applicable NOMESCO code DCA20.	1	National Care Register **and** Benefits Register of Social Insurance Institution#
	Antimicrobial purchases	Antimicrobial prescription for antibacterials recommended for otitis media, ATC codes: J01CA04, J01CR02, J01CE02, J01DC02, J01DC04, J01EE02, J01FA09 or J01FA10.	1	Benefits Register of Social Insurance Institution

Follow-up: from first vaccine dose to 31st January 2012 (laboratory-confirmed IPD) or to 31st December 2011 (all other outcomes).
* Infectious disease laboratory notifications; serotyped at the reference laboratory of National Institute for Health and Welfare (THL).
§ In- and outpatient discharge notifications from all Finnish hospitals.
# Reimbursements paid for care in private clinics.

Table 2
Baseline characteristics and vaccination data of the study participants.

	Girls				**Boys**			
	PHiD-CV			**Control****	**PHiD-CV**			**Control****
	2 + 1	**3 + 1**	**Total**		**2 + 1**	**3 + 1**	**Total**	
Number of participants	4882	5155	10,037	4987	5172	5118	10,290	5213
Gestational age < 37 weeks, %	4.8	4.3	4.5	4.5	6.1	4.9	5.5	5.3
Birth weight < 2500 g, %	3.8	3.6	3.7	4.0	3.8	2.8	3.3	3.3
Age at first dose of study vaccine, weeks, median (range)	14 (5–30)	14 (6–31)	14 (5–31)	14 (6–30)	14 (6–30)	14 (6–30)	14 (6–30)	14 (6–30)
Follow-up time, months, mean*	23.8	24.2	24.0	24.1	23.8	24.2	24.0	24.3
	Premature infants (gestational age < 37 weeks)				**Term infants (gestational age ≥ 37 weeks)**			
	PHiD-CV			**Control****	**PHiD-CV**			**Control****
	2 + 1	**3 + 1**	**Total**		**2 + 1**	**3 + 1**	**Total**	
Number of participants	547	474	1021	498	9478	9784	19,262	9690
Male gender, %	57.6	53.0	55.4	55.2	51.0	49.7	50.4	50.9
Gestational age, weeks, median (range)	35 (25–36)	35 (27–36)	35 (25–36)	35 (26–36)	40 (37–43)	40 (37–43)	40 (37–43)	40 (37–43)
Birth weight < 2500 g, %	49.7	44.9	47.5	49.4	1.2	1.2	1.2	1.3
Birth weight, kg, median (range)	2.5 (0.5–4.9)	2.6 (1.0–5.5)	2.5 (0.5–5.5)	2.5 (0.7–5.0)	3.6 (1.7–5.7)	3.6 (1.8–5.7)	3.6 (1.7–5.7)	3.6 (1.8–5.5)
Age at first dose of study vaccine, weeks, median (range)	16 (7–30)	15 (6–30)	16 (6–30)	14 (6–30)	14 (5–30)	14 (6–31)	14 (5–31)	14 (6–30)
Follow-up time, months, mean*	23.5	24.3	23.9	24.1	23.8	24.2	24.0	24.2
	Infants with birth weight < 2500 g				**Infants with birth weight ≥ 2500 g**			
	PHiD-CV			**Control****	**PHiD-CV**			**Control****
	2 + 1	**3 + 1**	**Total**		**2 + 1**	**3 + 1**	**Total**	
Number of participants	383	329	712	374	9665	9940	19,605	9823
Male gender, %	51.2	42.9	47.3	46.3	51.4	50.1	50.7	51.3
Birth weight, kg, median (range)	2.2 (0.5–2.5)	2.2 (1.0–2.5)	2.2 (0.5–2.5)	2.2 (0.7–2.5)	3.5 (2.5–5.7)	3.5 (2.5–5.7)	3.5 (2.5–5.7)	3.6 (2.5–5.5)
Gestational age < 37 weeks, %	71.3	65.3	68.5	66.0	2.8	2.6	2.7	2.6
Gestational age, weeks, median (range)	35 (25–41)	35 (27–41)	35 (25–41)	35 (26–41)	40 (32–43)	40 (32–43)	40 (32–43)	40 (31–43)
Age at first dose of study vaccine, weeks, median (range)	17 (7–30)	15 (7–30)	16 (7–30)	14 (6–29)	14 (5–30)	14 (6–30)	14 (5–30)	14 (6–30)
Follow-up time in, months, mean*	23.7	24.4	24.0	24.0	23.7	24.2	24.0	24.2

* Follow-up time for all other outcomes but laboratory-confirmed invasive pneumococcal disease, for which the follow-up was one month longer.
** Combined 2 + 1 and 3 + 1 schedules

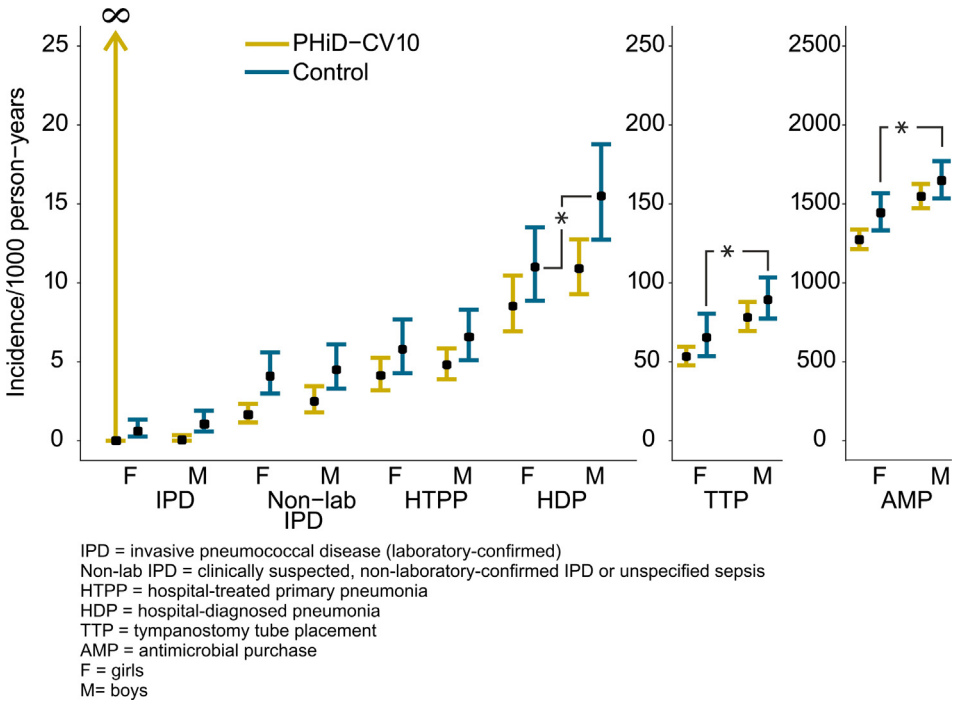

Fig. 1. Incidences of the pneumococcal disease outcomes in girls and boys in the PHiD-CV10 and control groups. Note different y-axes for the different outcomes. * statistically different incidence between groups, p-values 0.019, 0.013 and 0.017 for HDP, TTP and AMP, respectively.

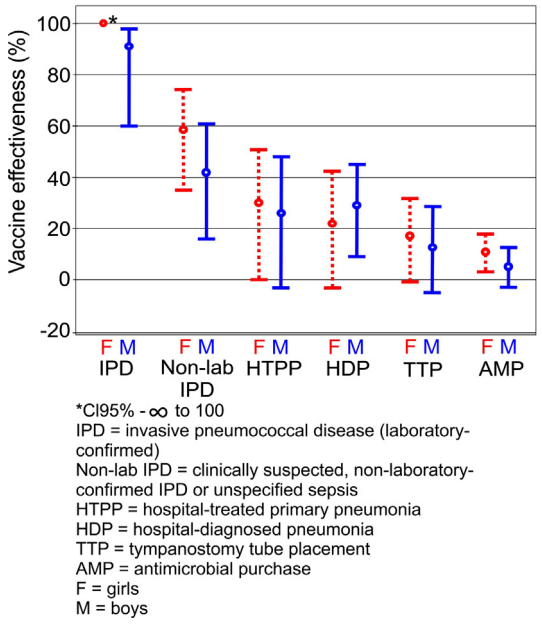

Fig. 2. Vaccine effectiveness for the pneumococcal disease outcomes in girls and boys.

weight infants was as high as 39% (95% CI 11–58). The 2 + 1 and 3 + 1 schedules performed equally well in preterm and low-birth-weight infants for all outcomes (Tables 3–4).

6. Discussion

In this double-blind randomized controlled trial the incidences of pneumococcal diseases were higher in boys when compared to girls in all the outcomes evaluated, but the differences were statistically significant only for the most common outcomes: hospital-diagnosed pneumonia, tympanostomy tube placements and antimicrobial purchases. Pneumonia incidences were higher among preterm infants when compared to term infants. There were no differences in vaccine effectiveness estimates between sexes. The VE point estimates for preterm and low-birth-weight infants suggested protection, although the VE estimates were not statistically significant due to the small subsets.

Our results are compatible with the earlier studies showing higher incidences of pneumococcal infections in boys [4–8]. There were no significant sex differences in the VE for any of the outcomes. Our results were in line with the Gambian trial in which a nine-valent PCV was evaluated in the prevention of IPD and pneumonia [5]. In a Brazilian surveillance study the VE of PHiD-CV10 against pneumonia was significantly higher in girls [8]. The higher incidence of otitis and slightly lower (non-significant) effectiveness of PCV among boys was reported also in the Kaiser Permanente trial [25]. From a public health perspective the potentially lower relative VE in boys should be considered in light of the higher incidence of pneumococcal diseases in boys resulting in a considerable absolute reduction of disease burden due to vaccination. However, further studies of the sex differences are needed to confirm these results.

IPD and pneumonia incidences have previously been reported to be higher among preterm than term infants [10,14]. In this study the number of cases among preterm and low-birth-weight children was too low for evaluation of the IPD incidence but the pneumonia incidences were significantly higher in preterm and low-birth weight infants when compared to term infants. The positive VE point estimates suggest PHiD-CV10 effectiveness in protection of preterm and low-birth-weight infants even though the only statistically significant result was the VE against antimicrobial purchases among preterm infants and against tympanostomy tube placements in low-birth-weight infants. The effectiveness of the PCVs against other than laboratory-confirmed IPD among preterm infants has not, to our knowledge been previously reported.

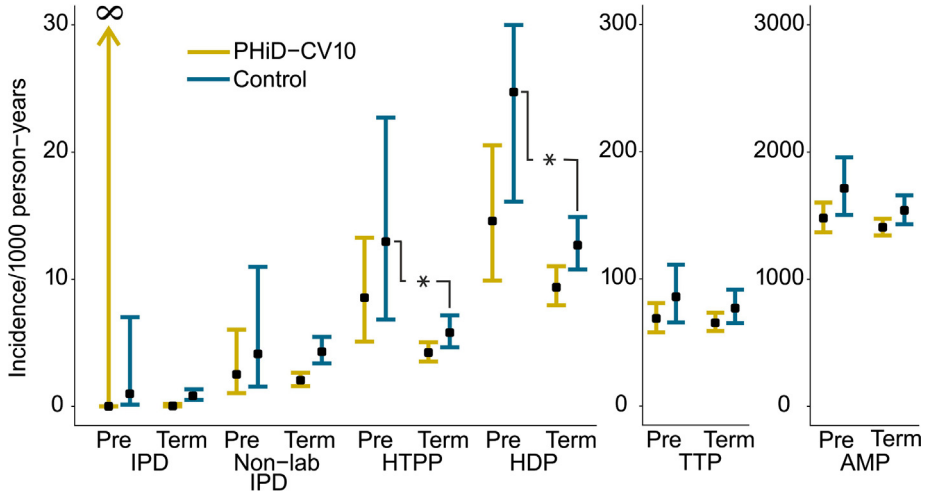

Fig. 3. Incidences of the pneumococcal disease outcomes in preterm and term infants in the PHiD-CV10 and control groups. Note different y-axes for the different outcomes. * statistically different incidence between groups. p-values 0.0034 and 0.0066 for HTPP and HDP, respectively.

Table 3
Incidences of the pneumococcal disease outcomes, and vaccine effectiveness (VE) estimates among preterm and term infants.

	Preterm infants			Term infants		
Treatment group	N	Incidence/1000 py*	VE (95% CI)	N	Incidence/1000 py*	VE (95% CI)
Invasive pneumococcal disease (IPD)						
Control	1	0.9		16	0.8	
PHiD-CV10	0	0	100 (−∞ to 100)	2	0.1	94 (73 to 99)
PHiD-CV10 2 + 1	*0*	*0*	*100 (−∞ to 100)*	*2*	*0.1*	*88 (46 to 97)*
PHiD-CV10 3 + 1	*0*	*0*	*100 (−∞ to 100)*	*0*	*0*	*100 (−∞ to 100)*
Non-laboratory-confirmed IPD**						
Control	4	3.9		83	4.3	
PHiD-CV10	6	2.9	28 (−185 to 79)	80	2.1	51 (32 to 65)
PHiD-CV10 2 + 1	*3*	*2.7*	*32 (−211 to 87)*	*29*	*1.6*	*64 (44 to 77)*
PHiD-CV10 3 + 1	*3*	*3.1*	*23 (−252 to 85)*	*51*	*2.6*	*39 (12 to 58)*
Hospital-treated primary pneumonia						
Control	13	12.8		111	5.7	
PHiD-CV10	18	8.6	33 (−42 to 67)	158	4.1	27 (4 to 45)
PHiD-CV10 2 + 1	*10*	*9.0*	*29 (−63 to 70)*	*74*	*4.0*	*30 (3 to 50)*
PHiD-CV10 3 + 1	*8*	*8.1*	*36 (−54 to 75)*	*84*	*4.3*	*25 (−5 to 46)*
Hospital-diagnosed pneumonia						
Control	24	24		248	13	
PHiD-CV10	30	14	39 (−8 to 65)	367	10	26 (6 to 41)
PHiD-CV10 2 + 1	*16*	*14*	*39 (−18 to 69)*	*178*	*10*	*27 (3 to 45)*
PHiD-CV10 3 + 1	*14*	*14*	*40 (−17 to 70)*	*189*	*10*	*25 (4 to 41)*
Tympanostomy tube placements						
Control	87	86		1543	80	
PHiD-CV10	141	67	21 (−9 to 43)	2597	68	14 (−3 to 29)
PHiD-CV10 2 + 1	*75*	*67*	*21 (−14 to 46)*	*1238*	*66*	*14 (−6 to 30)*
PHiD-CV10 3 + 1	*66*	*67*	*20 (−17 to 46)*	*1359*	*69*	*15 (−7 to 32)*
Antimicrobial purchases						
Control	1705	1683		30,278	1560	
PHiD-CV10	3133	1495	12 (1 to 21)	54,823	1431	8 (−2 to 16)
PHiD-CV10 2 + 1	*1678*	*1508*	*10 (−2 to 21)*	*26,342*	*1411*	*8 (−3 to 17)*
PHiD-CV10 3 + 1	*1455*	*1481*	*13 (0 to 25)*	*28,481*	*1450*	*8 (−4 to 18)*

CI = Confidence interval.
* Person-years.
** Clinically suspected, non-laboratory-confirmed IPD or unspecified sepsis.

Table 4
Incidences of the pneumococcal disease outcomes, and vaccine effectiveness (VE) estimates among low-birth-weight infants and infants with birth weight at least 2500 g.

	Low-birth-weight			Birth weight at least 2500 g		
Treatment group	N	Incidence/1000 py*	VE (95% CI)	N	Incidence/1000 py*	VE (95% CI)
Invasive pneumococcal disease (IPD)						
Control	1	1.3		16	0.8	
PHiD-CV10	0	0	100 (−∞ to 100)	2	0.05	94 (74 to 99)
PHiD-CV10 2 + 1	*0*	*0*	*100 (−∞ to 100)*	*2*	*0.1*	*88 (46 to 97)*
PHiD-CV10 3 + 1	*0*	*0*	*100 (−∞ to 100)*	*0*	*0*	*100 (−∞ to 100)*
Non-laboratory-confirmed IPD**						
Control	3	4.0		84	4.3	
PHiD-CV10	2	1.4	65 (−112 to 95)	84	2.2	50 (29 to 64)
PHiD-CV10 2 + 1	*2*	*2.7*	*34 (−302 to 91)*	*30*	*1.6*	*63 (43 to 77)*
PHiD-CV10 3 + 1	*0*	*0*	*100 (98 to 100)*	*54*	*2.7*	*36 (13 to 56)*
Hospital-treated primary pneumonia						
Control	6	8.1		118	6.0	
PHiD-CV10	9	6.3	21 (−139 to 72)	167	4.3	28 (4 to 46)
PHiD-CV10 2 + 1	*5*	*6.7*	*17 (−180 to 76)*	*79*	*4.2*	*30 (3 to 50)*
PHiD-CV10 3 + 1	*4*	*6.0*	*26 (−165 to 81)*	*88*	*4.4*	*25 (−5 to 47)*
Hospital-diagnosed pneumonia						
Control	11	15		261	13	
PHiD-CV10	18	13	14 (−92 to 60)	379	10	27 (8 to 42)
PHiD-CV10 2 + 1	*10*	*13*	*9 (−122 to 63)*	*184*	*10*	*28 (5 to 45)*
PHiD-CV10 3 + 1	*8*	*12*	*19 (−103 to 69)*	*195*	*10*	*26 (6 to 42)*
Tympanostomy tube placements						
Control	69	93		1561	79	
PHiD-CV10	79	56	39 (11 to 58)	2659	68	13 (−5 to 29)
PHiD-CV10 2 + 1	*39*	*52*	*44 (12 to 64)*	*1274*	*67*	*13 (−8 to 30)*
PHiD-CV10 3 + 1	*40*	*60*	*34 (−4 to 59)*	*1385*	*69*	*14 (−9 to 32)*
Antimicrobial purchases						
Control	1223	1643		30,760	1563	
PHiD-CV10	2074	1462	10 (−2 to 19)	55,882	1433	8 (−1 to 16)
PHiD-CV10 2 + 1	*1116*	*1488*	*7 (−6 to 19)*	*26,904*	*1414*	*8 (−2 to 17)*
PHiD-CV10 3 + 1	*958*	*1434*	*12 (−2 to 23)*	*28,978*	*1452*	*8 (−3 to 17)*

CI = Confidence interval.
* Person-years.
** Clinically suspected, non-laboratory-confirmed IPD or unspecified sepsis.

The VE point estimates suggested that both 3 + 1 and 2 + 1 schedules were effective in subgroups analysed. In a previously published study, all tested vaccination schedules resulted in good immune response in premature infants, but the timing of the highest antibody concentrations varied by schedule [16]. In a review article the geometric mean antibody concentrations (GMCs) after three primary doses were higher than after two primary doses, but the difference disappeared already before the pre-booster measurement [26]. Furthermore, the increases of GMCs were similar after the booster dose regardless of the number of primary doses [26]. Both studies suggest that the optimum schedule for preterm and term infants in each country should be decided by the timing of the highest risk for pneumococcal disease. In Finland, the highest incidence of pneumococcal diseases occurs after the child's first birthday [27,28], and thus, any potential advantage of the 3 + 1 schedule compared to the currently used 2 + 1 (at 3, 5 and 12 months of age) schedule would be minor during the post priming and pre-booster period. Furthermore, development of the indirect effect would reduce any potential differences during a large-scale vaccination programme [27,28].

The FinIP trial was a cluster-randomized double-blind trial with a parallel comparison group without pneumococcal vaccinations. The subgroups evaluated were evenly distributed in the treatment groups. While the cluster-randomization is the optimal design when evaluating the indirect effectiveness, for estimation of the effectiveness in the vaccinated subgroups, the design results in lower power compared to individually-randomized design. This resulted in wide confidence intervals, especially for the infrequent outcomes, even though the number of preterm and low-birth-weight infants enrolled was substantial.

The quality of register-based studies depends on the quality of registers. Finnish registers for health care have been in routine use for decades and the reporting to them is mandatory suggesting complete capture of the events. The register data have been reported to be valid [22,29,30]. The main problem in the register-based studies is that the diagnoses are not based on standardized definitions and may include errors in entering the codes. However, any kind of systematic misclassification would probably affect all blinded treatment groups similarly, including both sexes and both term and preterm infants.

7. Conclusions

In this exploratory analysis of the controlled randomized FinIP trial, the clinical effectiveness of PHiD-CV10 was evaluated, for the first time, among different subgroups. The point estimates of vaccine effectiveness suggest protection in both sexes, and also among the preterm and low-birth-weight infants. Unfortunately, there was not enough power to get statistically significant results. There were no significant differences between the 2 + 1 and 3 + 1 schedules in any of the subgroups analysed. Based on this study, the 2 + 1 or "Nordic" schedule is sufficient also for the risk groups such as the preterm or low-birth-weight infants.

Trademark statement: *Synflorix* and *Engerix-B* are trademarks of the GSK group of companies.

8. Contributors

HN contributed to acquisition of data, data interpretation, and drafting of the manuscript. AAP contributed to the concept and study design, acquisition of data, data analysis and interpretation. HR contributed to statistical analysis and data interpretation. JJ contributed to the concept and study design, acquisition of data, statistical analysis, and data interpretation.

TP and DB contributed to the concept and study design, the study conduct, data analysis and interpretation. MM contributed to the study conduct and data interpretation. LS contributed to the study design and data interpretation. All authors have reviewed and approved the final manuscript.

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All authors attest they meet the ICMJE criteria for authorship.

Declaration of Competing Interest

HN, AAP, JJ, HR and TP are employees of National Institute for Health and Welfare which received funding for the conduct of the FinIP study from GSK group of companies. TP was an employee of the GSK group of companies during the study conduct. MM, DB and LS are employees of the GSK group of companies and own shares of the GSK group of companies.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.033.

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