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Effectiveness of the 10-valent Pneumococcal *Haemophilus influenzae* protein D Conjugate Vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial

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SUMMARY

Background
The **Fin**nish **I**nvasive **P**neumococcal disease (FinIP) vaccine trial was designed to demonstrate the vaccine effectiveness (VE) of 10-valent PHiD-CV (GlaxoSmithKline) against invasive pneumococcal disease (IPD).

Methods
In this cluster-randomised, double-blind trial, children aged <19 months received PHiD-CV10 in two thirds of clusters (N=52) or hepatitis vaccines as control in 26 clusters. Infants aged <7 months at the first vaccination received either a 3+1 or a 2+1 vaccination schedule, children aged 7-11 months received a 2+1 schedule and children 12-18 months a two-dose schedule. The primary and secondary objectives were to demonstrate VE against culture-confirmed IPD due to any of the 10 vaccine serotypes for the 3+1 and 2+1 schedules, respectively, in children who received at least one PHiD-CV10 dose <7 months of age. Blinded IPD follow-up lasted from the first vaccination (from February 2009 through October 2010) to January 31, 2012. IPD data were retrieved from data accumulated in the National Infectious Diseases Register. This trial and nested AOM trial are registered at ClinicalTrials.gov, NCT00861380/NCT00839254.

Findings
Altogether, 47 366 children were enrolled. In 30 527 subjects evaluated for the primary objective, 13 culture-confirmed vaccine-type IPD cases were detected: 0 in the PHiD-CV10 3+1, 1 in PHiD-CV10 2+1, and 12 in control groups. The VE estimates were 100% (95%CI 83-100) for PHiD-CV10 3+1, and 92% (58-100) for PHiD-CV10 2+1 groups. Two cases of any culture-confirmed IPD irrespective of serotype were detected in combined PHiD-CV10 infant cohorts compared to 14 in the corresponding control cohorts (VE 93%, 75-99). In catch-up cohorts, seven IPD cases were reported; all in the control group; 2 in the children enrolled 7-11 months and 5 in children enrolled 12-18 months of age (VE 100%, 79-100).

Interpretation
This nationwide trial demonstrated high PHiD-CV10 effectiveness against IPD when given in different schedules. For the first time, effectiveness of a 2+1 schedule in infants was confirmed in a clinical trial.

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Panel: Research in context

Systematic review
We searched PubMed and Cochrane Library for reports published in English before September 17, 2012, with the following search terms in title or abstract text: “efficacy” or “effectiveness” and “pneumococcal”, “conjugate vaccine”, “clinical trial”, ”infants”, and “invasive”. In total, 4 clinical trials with PCV7 or PCV9 in the USA and Africa were identified. No clinical trial data were published with 2+1 infant schedule. Observational effectiveness data for both schedules of PCV7 (3+1, 2+1), used in national vaccination programmes has accumulated from several countries, but only one published report is available for PHiD-CV10.

Interpretation
The pneumococcal conjugate vaccine PHiD-CV10 given either in 3+1 or 2+1 infant schedule protects from invasive pneumococcal disease with high vaccine effectiveness (VE) of 93% (95% confidence interval 75 to 99). Catch-up vaccination schedules of children 7-11 and 12-18 months at first dose were also shown to be effective against IPD with 100% VE. This is the first European double blind randomised controlled trial to document PCV effectiveness against IPD and the first globally demonstrating the effectiveness of an infant 2+1 schedule as well as effectiveness of the catch-up vaccinations.

Disclosure of results before publication
The data have been partially presented at the 30th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) at Thessaloniki, Greece, May 8-12, 2012.

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INTRODUCTION

Widespread use of the first 7-valent pneumococcal CRM-conjugate vaccine (PCV7, Prevenar/Prevnar™, Pfizer Inc) has resulted in significant reduction of invasive pneumococcal disease (IPD) among vaccinated children on several continents.[1–6] IPD has also decreased among unvaccinated populations (herd protection). However, an increase in IPD caused by pneumococcal serotypes other than those contained in the vaccine (replacement) has been detected both in vaccinated and unvaccinated populations.[4-7]

Another pneumococcal vaccine containing ten serotype-specific polysaccharides conjugated to *Haemophilus influenzae* protein D, tetanus toxoid and diphtheria toxoid as the carrier proteins was developed (PHiD-CV10).[8–10] It was licensed in EU in March 2009 (Synflorix™, GlaxoSmithKline Vaccines) based on PHiD-CV10 immunological data according to criteria recommended by WHO[11] for licensure for protection against IPD, PHiD-CV10 safety data, and efficacy results of the 11-valent precursor formulation against acute otitis media.[12]

The Finnish Invasive Pneumococcal disease (FinIP) vaccine trial was designed to demonstrate the clinical vaccine effectiveness (VE) of PHiD-CV10 against IPD. To enable unbiased evaluation of the total effectiveness in vaccinated children and subsequently the indirect effectiveness in unvaccinated populations we used a cluster randomised clinical field-trial design.

Here, we report the PHiD-CV10 effectiveness against IPD in vaccinated children.

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METHODS

Trial design

The FinIP vaccine trial was a controlled, cluster-randomised, double-blind field trial conducted in Finnish health care centres (HCC) designed to demonstrate effectiveness of the PHiD-CV10 against IPD in infants. A parallel acute otitis media (AOM) trial conducted by the Tampere University Vaccine Research Centre (TAUVRC) had the same cluster-randomised design and its subjects were also evaluated in this study. [13]

Participants

In fall 2008, public municipal HCCs of mainland Finland (212 out of 237) were invited to participate excluding Northern Lapland and small HCCs for logistic reasons. Altogether 139 HCCs covering 77% (46,000/60,000) of the national birth cohort accepted the invitation. Enrolment and vaccinations were performed in local well-baby clinics (WBC, N=651) by the nurses (N>2,200) who are responsible for routine health follow-up and immunisations. The WBC visits are scheduled at 1/2/3/4/5/6/8/10/12/18/24 months of age, including physician's check-up at 1/4/8/18 months. Practically all infants attend WBCs regularly.

The National Institute for Health and Welfare (THL) sent study information letters to Finnish- and Swedish-speaking parents/legal guardians of all children born in the study area from December 2007 through May 2010. WBC nurses (and physicians when needed) gave oral information and obtained the written informed consent from the parent/legal guardian. TAUVRC enrolled subjects at 15 different dedicated study clinics. The child could be enrolled from 6 weeks to 18 months of age provided that he/she had not received, and was not anticipated to receive any of the study vaccines, nor had any study vaccine-specific or general contraindications to immunisations.

The enrolment ended, as planned, when PCV was introduced in the Finnish National Vaccination Programme (NVP) in September 2010 for children born on June 1, 2010 or later.

Study vaccines

The pneumococcal study vaccine consisted of 1 µg of each capsular polysaccharide (PS) for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 µg for serotype 4 each individually conjugated to protein D of nontypeable *Haemophilus influenzae*, 3 µg of capsular polysaccharide of serotypes 18C and 19F conjugated to tetanus and diphtheria toxoids, respectively.

Hepatitis B virus (HBV) vaccine (ENGERIX-B 10 µg/0·5 ml™) was used as a control vaccine for children enrolled under 12 months of age and hepatitis A virus (HAV) vaccine (Havrix 720 Junior™) for children enrolled at the age of 12 months or older. All study vaccines were manufactured by GSK Vaccines.

Vaccinations

Children enrolled under 7 months of age received 3 (minimum 4-week intervals) or 2 (minimum 8-week interval) primary vaccinations followed by a booster dose at least 4 months after the last primary dose, not earlier than at 11 months of age. Children enrolled between 7 to 11 months of age received two doses at least 4 weeks apart and a booster dose at least 4 months after the second primary dose. Children enrolled between 12 to 18 months of age received two doses at least 6 months apart. The study vaccines were administered concomitantly with the NVP vaccines (Appendix table 1) at the scheduled visits.

Cluster randomisation and masking

The areas of the participating HCCs were divided geographically into 72 clusters taking into account administrative structures (WBC/HCC/municipality) and the birth cohort size, which ranged from 322 to 1127 (mean 636) per cluster. Eleven municipalities covered exclusively by TAUVRC were divided

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into 6 additional clusters with yearly birth cohorts ranging from 785 to 1472 (total birth cohort 7600). The treatments were allocated to the 78 clusters using two infant schedules (3+1/2+1) and a randomisation ratio of 2:2:1:1 (PHiD-CV10-3+1:PHiD-CV10-2+1:Control-3+1:Control-2+1, Figure 1). Treatment allocation was stratified according to the size of the birth cohort (below/above average), TAUVRC trial enrolment (50 of 78 clusters), and urbanity (24 urban, 54 rural clusters). Balance was also ensured in the six additional TAUVRC clusters and in six clusters in Southwest Finland (Turku area) assigned for detailed respiratory infection assessment. Minimisation algorithm[14] was used to obtain a reasonable 2:2:1:1 treatment balance according to the stratification factors.

In each cluster and each WBC, all children received either PHiD-CV or control vaccine as the blinded study vaccine. If the child moved from one cluster to another, the original vaccination series was continued without unblinding.

Each WBC was provided with two boxes of identical study vaccine vials: one for children enrolled before 12 months (PHiD-CV10 or HBV) and another for children enrolled at an older age (PHiD-CV10 or HAV). Each cluster was assigned a unique randomisation code. TAUVRC trial used a different tool for randomisation with individual randomisation codes, which were aligned with the randomisation of the main study based on subject's residence. Any medical need for vaccinations against pneumococcal disease or hepatitis were handled in a double-blind fashion by allocating the hepatitis vaccination to those randomised to the PHiD-CV10 group and vice versa. The number or the borders of the clusters were not revealed to participants or WBC nurses and physicians. The clinicians diagnosing and treating IPD were not otherwise involved in the trial conduct. The investigators were kept blinded to the subject and cluster details of the IPD cases occurring during the study.

Outcomes

The invasive disease outcome data were collected through the National Infectious Diseases Register (NIDR) at THL, which is a laboratory-based surveillance system for collection of cases of diseases due to defined pathogens. Reporting of diagnostic findings for blood and/or cerebrospinal fluid cultures all around Finland to this register is mandatory for all laboratories and performed electronically. It is also obligatory to send the bacterial isolates of defined species to the THL laboratory for species verification, archiving and further typing. For *S. pneumoniae,* serotyping by multiplex-PCR supplemented with the Quellung reaction when needed is routinely conducted.[15] Culture-confirmed IPD was defined as any disease where *S. pneumoniae* was isolated from normally sterile body fluids by culture. Probable IPD was defined by demonstration of *S. pneumoniae* based on nucleic acid and/or antigen detection tests only, without isolation by culture.

Serious and/or unexpected adverse reactions following immunisation were collected from the national vaccine adverse reaction register maintained at THL. WBCs nurses were specifically requested to report all deaths, which were also searched from the Population Information System. Results of safety follow-up from the TAUVRC trial will be reported separately.

Cohorts and follow-up definitions

Infant cohorts in the 3+1 and 2+1 clusters comprised of infants who received the first vaccine dose before 7 months of age. The two control groups with 3+1 and 2+1 schedules were combined for the effectiveness analyses. There were two catch-up cohorts: children receiving the first study vaccination at 7-11 months of age and those receiving it at 12-18 months of age.

Intention-to-treat (ITT) follow-up started at the date of the first vaccination. According-to-protocol (ATP) follow-up period defined only for infants enrolled before 7 months of age started two weeks after the last primary dose. Subjects with protocol violation were eliminated from the ATP follow-up. Both blinded follow-up periods for IPD ended on January 31, 2012.

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Sample size estimation and statistical analysis

The primary objective was to demonstrate VE against culture-confirmed IPD due to any of the 10 vaccine serotypes in children who received at least one PHiD-CV10 dose <7 months of age in the 3+1 schedule. The trial was powered to show a significant difference (alpha=0·05) in vaccine-type IPD rate between 3+1 PHiD-CV10 and control arms in the infant cohort. NIDR data from years 2004-2008, grouped according to age and trial clusters, was used to estimate vaccine-type IPD rates and between-cluster variability. Between-cluster coefficient of variation (CV)[16] was estimated as 0·12 and calculations at the end of recruitment with final number of enrolled subjects showed that 12 vaccine-type IPD cases were expected to occur in the control group by the end of January 2012. The study power was estimated through simulation to be 91%, assuming 12 vaccine-type IPD cases to occur in the control clusters, VE of 90%, and 0·12 between-cluster CV. CV of 0·12 indicates low or at most moderate between-cluster variability.[17]

Negative binomial model, allowing for possible overdispersion due to cluster design,[16] was the method chosen prior to unblinding for the primary analysis. IPD frequencies were grouped by cluster and the cluster-specific person-years were used as weights in the analysis. Factors used for stratified randomisation were included in the model as explanatory variables. In case of non-convergence, the model without stratification factors was applied and in case of non-convergence of the over-dispersion parameter (i.e. negligible design effect), Poisson regression was used. Likelihood ratio (LR) test[18] between models with and without the treatment variable was used as the test for significance. In order to match with the LR-test and to account for zero cases in the treatment group, profile likelihood method[18] was used to estimate the 95% confidence interval for the treatment parameter. VE was calculated as 1 minus rate ratio.

The study protocols were submitted to the relevant ethical review boards and competent authorities prior to trial start. The protocol is available at www.finip.fi. This trial and nested AOM trial are registered at ClinicalTrials.gov, NCT00861380 and NCT00839254.

Role of the funding source

GlaxoSmithKline Biologicals SA was the main funding source and National Institute for Health and Welfare (THL) co-funded this collaborative study.

Both parties were involved in all stages of the study planning, conduct, data collection, analysis and manuscript development. In terms of Good Clinical Practice, GSK had the role of the sponsor and THL researchers had the role of the investigator.

All authors had access to all the data in the study and accepted responsibility for its validity. All authors agreed on the final decision to submit for publication.

RESULTS

Participant flow and baseline data

From February 18, 2009 through October 5, 2010, a total of 47 366 children were enrolled; 41 188 children at the well-baby clinics and 6 178 at the TAUVRC clinics. Of the roughly 125 000 children invited to participate, 38% were finally enrolled. The enrolment proportion ranged from 21-61% in the 72 WBC clusters and from 8-16% in the six TAUVRC-only clusters.

All 45 974 subjects who received at least one dose of correct vaccine were included in ITT analyses. 1392 children were excluded from effectiveness analysis: 1 381 children did not receive the treatment assigned to their cluster due to an error in the TAUVRC trial randomisation at the beginning of the study; 10 subjects did not receive any study vaccinations; and one subject was excluded due to lost source documentation (Figure 2).
The mean follow-up was 25 months (range 15-35) for infants and 28 months (range 14-35) for subjects in the catch-up groups. The baseline and vaccination data presented in Table 1 shows similarity between the groups.

Vaccine effectiveness against IPD

From the administration of the first dose of study vaccine until the end of the blinded follow-up, a total of 26 culture-confirmed IPD cases were reported. Of these, three (serotypes 6B, 14 and 19A) occurred in the erroneously randomised TAUVRC infants and were therefore excluded from further analyses. All three received control vaccine instead of PHiD-CV10 vaccine.

No vaccine-type IPD cases occurred after the first vaccine dose in the PHiD-CV10 3+1 infant group compared to 12 cases in the control group. Thus, VE was 100% (95% confidence interval 83-100%, table 2). One vaccine-type IPD due to serotype 7F was reported in a child receiving 2+1 infant schedule with PHiD-CV10, with VE of 92% (58-100%) compared to control group. This only case of vaccine-type IPD in any of the PHiD-CV10 cohorts occurred 12 days after the first vaccine dose given at 4 months of age. For the ATP follow-up period in the infant cohort, there were 11 cases of vaccine-type IPD in the control group compared to zero in the combined PHiD-CV10 groups meaning 100% VE (91-100%).

There were two cases of vaccine-related type IPD (6A and 19A) in the control infant group and one non-vaccine type IPD (serotype 3) in a fully vaccinated child in the PHiD-CV10 infant groups (table 3). Any culture-confirmed IPD irrespective of serotype were reported for two subjects in combined PHiD-CV10 infant cohorts compared to 14 in the corresponding control cohorts (VE 93%, 75-99). With the incidence of 66 per 100 000 person-years in the control group for any culture-confirmed IPD, the absolute rate reduction was 61 per 100 000 person-years.

Five cases of IPD due to serotype 6B were detected in the control infant cohorts compared to none in the PHiD-CV10 cohorts in the ITT follow-up (VE 100%, 77-100%). For serotype 14, the corresponding figures were 4 and 0, respectively (VE 100%, 71-100%). For other serotypes, only single cases were found (table 3).

In addition to culture-confirmed cases, there were 3 probable, culture-negative IPD cases detected by AccuProbe (GEN-PROBE, San Diego, USA) directly from the blood-culture bottles, all in the control clusters (table 2). No sample was available for serotyping for these cases.

For the catch-up cohorts, there were 7 cases of IPD, all in the control group. Of these, 2 and 5 were reported in children vaccinated with the first dose at 7-11 months of age and at 12-18 months of age, respectively (VE 100%, 79-100% for the latter cohort, Table 3, Appendix table 2).

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All IPD cases were diagnosed at hospital emergency rooms and treated in hospital. There were neither fatal nor meningitis cases. Two of the cases in the control group were treated at intensive care unit. Further clinical details are available in Appendix table 2.
In addition, there were eight cases of invasive diseases due to other bacteria, see Appendix table 3.

Adverse events
Twelve children died during the blinded follow-up of the FinIP trial. The deaths were equally distributed between the treatment groups (four in each of the PHiD-CV10 3+1, the PHiD-CV10 2+1 and the combined control groups) and none were temporally associated with study vaccinations or considered related to trial participation. Causes of death in the control group were accidental asphyxiation (2), traffic accident (1), and Reye's syndrome (1) and in the PHiD-CV10 groups genetic diseases (2), sudden death of unknown cause (2), and accidental asphyxiation, enteroviral disease, myocarditis, and sudden infant death syndrome (one of each).

Additionally, non-fatal serious adverse events suspected to be vaccine-related by the reporting health care professional were reported for 18 children, nine of them the investigator categorised as possibly or definitely related to study vaccine. Among those, there were two febrile convulsions in the PHiD-CV10 group and three in the control group, one hypotonic hyporesponsive episode in the control group, one local reaction with irritability and two cases of Kawasaki's disease both in the PHiD-CV10 group. Of the remaining nine cases, two IPD cases, one cystitis and one unspecified infection occurred in the control clusters, and two diarrhoea cases, one tonsillitis, one parotitis and one eczema with fever in the PHiD-CV10 clusters.

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DISCUSSION

The FinIP trial demonstrated excellent effectiveness of the PHiD-CV10 vaccine against invasive pneumococcal disease for all vaccination schedules assessed. The convincing effectiveness of the infant 2+1 schedule used in many national programmes was demonstrated for the first time in a clinical trial setting. Effectiveness was also shown against the two most common serotypes 6B and 14. . We were not able to show serotype-specific effectiveness for any of the other serotypes (including serotypes 1, 5 and 7F) due to the low number or no cases.

Our results are very similar to those of the NCKP trial[1] assessing the PCV7 vaccine in 3+1 schedule in which the vaccine efficacy against vaccine-type IPD was 94% and against any IPD irrespective of serotype 89% in ITT follow-up. However, the results of the current trial and the NCKP trial compare favourably to the results of clinical trials conducted in populations with high IPD burden,[19–21] in which lower point estimates of VE ranging from 42 to 53% for ITT follow-up against any IPD have been reported. In our trial similarly to the NCKP trial[1], there was no indication of replacement disease, although the number of non-vaccine serotype IPDs was too low for inference.

No safety concerns were observed during the FinIP trial. The number of deaths was comparable to the pre-trial baseline incidence, and balanced across treatment groups. The two cases of Kawasaki's disease in the PHiD-CV10 group are much less than the expected number of 11 in all study subjects using the incidence of 11·4 per 100 000 person-years as a reference.[22,23]

We consider our study data of high validity because of the randomised double-blind trial design with concurrent controls. The outcome data were collected from an established nationwide register. The laboratory-based surveillance has been mandatory for all hospital laboratories since 1995 and electronic reporting is used. From all reported culture-confirmed IPD cases, a bacterial isolate was available for serotyping. Furthermore, the trial follow-up was complete for all cases reported in the register as they were identified using the national Personal Identity Code, which is unique and permanent for all Finnish citizens given soon after birth or immigration.

The baseline IPD incidence prior to study start during 2004 to 2008 was 63·1 per 100 000 person-years in children under two years of age with the highest incidence in infants 10 to 21 months of age. Altogether 78% were caused by serotypes covered by the PHiD-CV10. The incidence is lower compared to US data before PCV7 but comparable to European incidence figures ranging from 54·2 to 67·7 per 100 000 person-years in the corresponding age group.[3,4, 25]

We failed to enrol high proportions of age-eligible children in all the clusters. The main reason was refusal to participate as the trial exclusion criteria mainly followed the contraindications of the NVP, coverage of which is extremely high (>95%). Based on hepatitis vaccination indications and PCV national sales statistics the commercial use of study vaccines was estimated low. The enrolment was substantially higher (44% vs. 24%) for birth cohorts of 2009 to 5/2010 compared to children born in 2008 enrolled mainly in the catch-up cohorts. The enrolment was also lower in the clusters with exclusive TAUVRC enrolment, in the urban clusters in the biggest cities and in the Swedish-speaking areas. However, the IPD incidence in the control clusters during the trial was identical with the Finnish baseline observed before the study start, which suggests no major selection bias in study participation.

Variability in the IPD incidence is associated with population characteristics, but also with diagnostic practices, especially use of blood cultures.[24,26] The Finnish population is generally homogeneous, but access to treatment and diagnostic practices may vary between areas. However, variability in the IPD

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incidence between the study clusters in 2004-2008 was low. Similar homogeneity was observed in the actual trial data. To minimise the risk of bias we chose to include high enough number of clusters to have more than one cluster in each major city and hospital district. Further assurance for comparability between treatment groups was sought through stratification of randomisation.

PCV was introduced in 2+1 schedule into the Finnish National Vaccination Programme from September 1, 2010 for infants born on June 1, 2010 or later without catch-up vaccinations. Out of the total of 13, five cases of vaccine-type IPD occurred before the start of the NVP and six cases within one year of the NVP start and only two cases thereafter. Should the NVP have had any effect on the study results, it would have diluted the VE estimates by reducing IPD incidence primarily in the control clusters with no direct protection.

Vaccine effectiveness demonstrated in our nationwide population-based field trial with considerable enrolment proportion is best fitted to predict the impact of corresponding vaccination programmes in developed country settings. Accordingly, the early national surveillance data available following the introduction of PHiD-CV10 in the NVP shows a marked reduction in infant IPD in Finland[27] and in Quebec, Canada.[28]

Vaccination with PCV7 has already shown a considerable impact on public health burden of pneumococcal diseases among the vaccine recipients in different countries. The effectiveness of PHiD-CV10 against IPD shown in the current study confirms that at least similar reduction in disease burden can be expected with this vaccine. Moreover, additional benefit for vaccinees can be anticipated through vaccine impact on pneumonia[29] and otitis media.[12]

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T.M. Kilpi contributed to the concept and study design, acquisition of data, data analysis and interpretation, drafting of the manuscript, review and final approval of manuscript.

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CONFLICT OF INTEREST:

A.A. Palmu has had travel paid for and honoraria by GlaxoSmithKline to attend expert group meetings, has had travel paid by Merck to attend expert group meetings and has received a travel grant from SanofiPasteur MSD. He is the head of Clinical Research Unit at the National Institute for Health and Welfare which has received research funding from GlaxoSmithKline.
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T. Puumalainen was an employee of GlaxoSmithKline Vaccines during the study conduct.
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TABLES

Table 1: Characteristics of study participants and vaccination data for the different treatment arms

	PHiD-CV10 group		Control group	
Infants (<7 months of age)	**3+1 schedule**	**2+1 schedule**	**3+1 schedule**	**2+1 schedule**
Number of participants	N=10273	N=10054	N=4941	N=5259
Male gender, %	49•8	51•4	51•6	50•7
Gestational age, <37 weeks, %	4•6	5•5	5•2	4•6
Birth weight, <2500 g, %	3•2	3•8	4•2	3•1
Age at first dose of study vaccine, weeks, median (range)	14 (6 to 31)	14 (5 to 30)	14 (6 to 30)	14 (6 to 30)
Subjects with complete primary vaccination series schedule, %	96•7	98•5	97•3	99•3
Follow-up time in months, mean	25•1	24•6	24•7	25•3
Children (7-11 months of age)				
Number of participants	N=3880		N=1907	
Male gender, %	51•3		51•6	
Gestational age, <37 weeks, %	5•9		6•6	
Birth weight, <2500 g, %	4•3		5•2	
Age at first dose of study vaccine, weeks, median (range)	40 (30 to 52)		40 (30 to 52)	
Subjects with complete primary vaccination series schedule (2 doses), %	97•8		98•6	
Follow-up time in months, mean	27•8		28•1	
Children (12-18 months of age)				
Number of participants	N=6534		N=3126	
Male gender, %	51•1		51•1	
Gestational age, <37 weeks, %	5•9		6•2	
Birth weight, <2500 g, %	4•5		4•1	
Age at first dose of study vaccine, weeks, median (range)	63 (52 to 93)		64 (52 to 91)	
Subjects with complete 2-dose vaccination series, %	92•9		93•6	
Follow-up time in months, mean	28•2		28•5	

Table 2: Episodes of invasive pneumococcal disease (IPD) and the vaccine effectiveness for the 10-valent PHiD-CV in vaccinated infants enrolled at the age of <7 months, intention-to-treat analysis unless stated otherwise.

	Number of episodes		**Number of clusters with at least one episode**		**Follow-up time, person-years**		**Incidence, per 100 000 person-years**		**Vaccine effectiveness**	
Endpoint definition and vaccinated cohort	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	VE point estimate	95% CI
Culture-confirmed vaccine-type IPD, 3+1 schedule from dose 1	0	12	0	10	21502	21292	0	56•4	100	83-100
Culture-confirmed vaccine-type IPD, 2+1 schedule from dose 1	1	12	1	10	20647	21292	4•8	56•4	92	58-100
Culture-confirmed vaccine-type IPD, 3+1 and 2+1 schedule combined, *per protocol follow-up*	0	11	0	9	36882	18660	0	58•9	100	91-100
Culture-confirmed IPD irrespective of serotype, 3+1 and 2+1 schedule combined from dose 1	2	14	2	11	42149	21292	4•7	65•8	93	75-99
Culture-confirmed or probable IPD, 3+1 and 2+1 schedule combined from dose 1	2	17	2	11	42149	21292	4•7	79•8	94	77-99

culture-confirmed IPD, *S. pneumoniae* isolated from normally sterile body fluids by culture; probable IPD, demonstration of *S. pneumoniae* from normally sterile body fluids based on nucleic acid and/or antigen detection tests only, without isolation by culture

Table 3: Number of episodes of culture-confirmed invasive pneumococcal disease (IPD) by serotype.

Serotype	Control group, children enrolled at <7 months of age	PHiD-CV10 group, children enrolled at <7 months of age, combined*	Control group, children enrolled at 7-11 months of age	PHiD-CV10 group, children enrolled at 7-11 months of age	Control group, children enrolled at 12-18 months of age	PHiD-CV10 group, children enrolled at 12-18 months of age
Follow-up years	**21292**	**42149**	**4479**	**9001**	**7421**	**15358**
Vaccine serotypes						
1						
4					1	
5						
6B	5				1	
7F		1	1			
9V						
14	4				1	
18C	1					
19F	1		1			
23F	1					
Subtotal	**12**	**1**	**2**	**0**	**3**	**0**
Vaccine-related serotypes **						
6A	1					
19A	1					
Subtotal	**2**	**0**	**0**	**0**	**0**	**0**
Other serotypes						
3		1			1	
15C					1	
Subtotal	**0**	**1**	**0**	**0**	**2**	**0**
TOTAL	**14**	**2**	**2**	**0**	**5**	**0**

* both IPD cases in 2+1 group
** belonging into the same serogroup as vaccine serotypes

Appendix table 1: Vaccines included in the Finnish National Vaccination Programme offered for children under 36 months of age during the trial conduct which were commonly given concomitantly with the study vaccinations.

Vaccination	Vaccine	Doses	Schedule	Comments
BCG	BCG Vaccine SSI™ (Statens Serum Institut)	1	at birth	Risk groups only
Rota	RotaTeq™ (Sanofi Pasteur MSD)	3	2, 3, 5 months	Started in September 2009
DTaP/IPV/Hib	Infanrix-IPV+Hib™ (GSK Vaccines)	3	3, 5, 12 months	
MMR	M-M-RVaxPro™ (Sanofi Pasteur MSD)	1	15 to 18 months	
Influenza	several in use	1 or 2	yearly	Starting in November each year; first vaccination 2 doses, then 1 only
Pandemic Influenza AH1N1	Pandemrix™ (GSK Vaccines)	1	from 6 months onwards	Between November 2009 to March 2010

Appendix table 2: Cases of culture-confirmed and probable invasive pneumococcal disease.

List case	Study vaccine administered	Serotype	Age at enrolment, months	Age at invasive disease, months	Month and year of the case	Relevant medical history	Clinical syndrome
1	PHiD-CV10 2+1	7F	4	4	DEC2009	None	Septic arthritis
2	PHiD-CV10 2+1	3	2	17	FEB2011	None, previous Infant Respiratory Distress Syndrome	Bacteremic pneumonia
3	Control 3+1	6A	6	8	JUL2010	None	Bacteremia
4	Control 2+1	6B	3	12	FEB2011	Eczema atopic	Bacteremia
5	Control 2+1	6B	5	16	MAY2010	None	Bacteremia
6	Control 2+1	6B	4	17	FEB2011	None	Bacteremia
7	Control 2+1	6B	3	10	FEB2011	None	Bacteremic pneumonia
8	Control 3+1	6B	5	19	MAR2011	None	Bacteremia
9	Control 3+1	14	5	10	NOV2009	Eczema atopic	Bacteremia
10	Control 3+1	14	3	13	JUL2010	Food allergy	Bacteremia
11	Control 3+1	14	6	23	DEC2010	None	Bacteremia
12	Control 3+1	14	1	20	APR2011	Asthma, post-infectious	Bacteremic pneumonia
13	Control 3+1	18C	5	16	JUN2010	Low birth weight, Small for gestational age	Bacteremia
14	Control 3+1	19A	2	18	OCT2011	None	Bacteremic pneumonia/ empyema
15	Control 2+1	19F	3	21	JAN2012	None	Bacteremia
16	Control 3+1	23F	3	25	JAN2012	None	Bacteremia
17	Control 3+1	NA, probable IPD	4	15	DEC2010	None	Bacteremia
18	Control 3+1	NA, probable IPD	1	12	MAY2011	Eczema atopic	Bacteremic pneumonia

19	Control 3+1	NA, probable IPD	2	19	OCT2011	None	Bacteremic pneumonia
20	Control 3+1*	6B	2	20	OCT2010	None	Bacteremia
21	Control 3+1*	14	1	11	FEB2010	Food allergy	Bacteremic pneumonia
22	Control 3+1*	19A	2	10	NOV2009	None	Bacteremia
23	Control catch-up	7F	10	10	AUG2009	None	Bacteremia
24	Control catch-up	14	9	17	APR2010	None	Bacteremia
25	Control catch-up	3	14	44	SEP2011	None	Bacteremic pneumonia
26	Control catch-up	4	12	20	JUN2010	Food allergy	Bacteremia
27	Control catch-up	6B	18	30	OCT2010	None	Bacteremia
28	Control catch-up	15C	14	40	OCT2011	None, previously hydronephrosis	Bacteremia
29	Control catch-up	19F	18	30	OCT2010	None	Bacteremia

* subject eliminated from the ITT effectiveness analyses due to randomisation error

All cases were detected from blood culture samples; culture-confirmed IPD, *S. pneumoniae* isolated by culture; probable IPD, demonstration of *S. pneumoniae* based on nucleic acid and/or antigen detection tests only, without isolation by culture

NA- not available

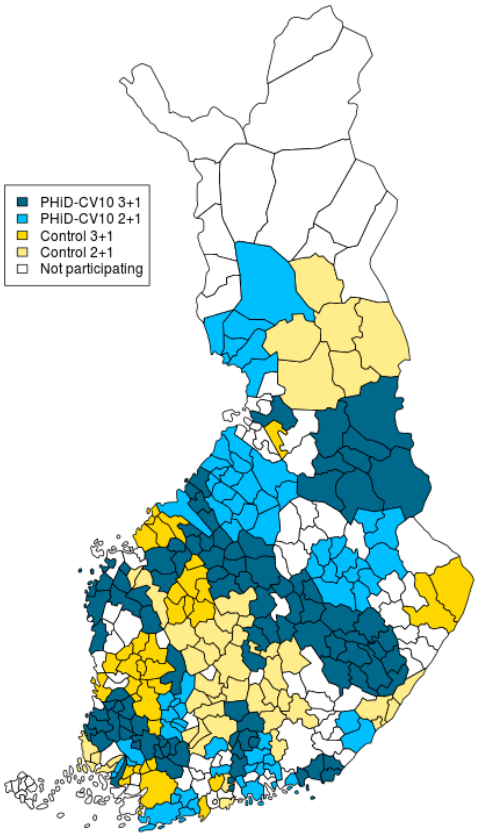
Appendix table 3: Cases of culture-confirmed invasive diseases due to other bacteria.

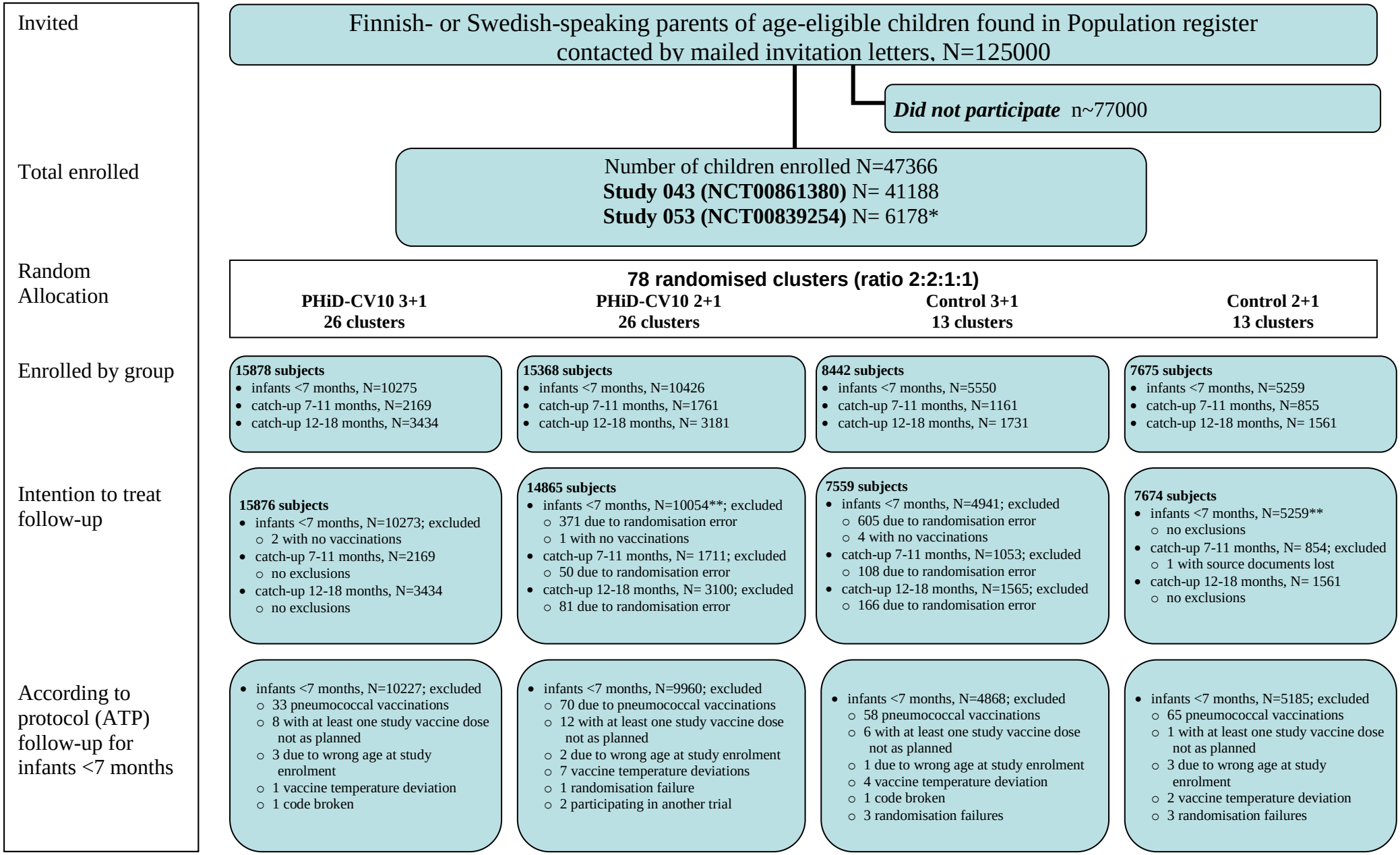
List case	Study vaccine administered	Pathogen	Age at enrolment, months	Age at invasive disease, months	Month and year of the ID case	Relevant medical history	Sample positive	Clinical syndrome
1	Control 2+1	*S. pyogenes*	5	17	MAR2010	None, varicella in a week preceding ID	Blood	Bacteremic pneumonia/ Septic arthritis
2	Control 2+1	*S. pyogenes*	2	24	MAR2011	None	Blood	Bacteremia
3	Control 2+1	*N. meningitidis*	3	3	NOV2009	None	Blood	Meningitis
4	PHiD-CV10 2+1	*N. meningitidis*	6	15	NOV2010	None	Cerebrospinal fluid and blood	Meningitis
5	PHiD-CV10 3+1	*N. meningitidis*	1	5	SEP2009	None	Blood	Bacteremia
6	PHiD-CV10 3+1	*N. meningitidis*	3	13	MAY2011	None	Cerebrospinal fluid	Meningitis
7	PHiD-CV10 2+1	*H. influenzae, non-typable*	2	20	DEC2011	Food allergy	Blood	Bacteremic pneumonia/empyema
8	Control 3+1	*H. influenzae, non-typable + M. catarrhalis*	2	23	SEP2011	None	Blood	Bacteremia

FIGURE LEGENDS

Figure 1. Map of Finland with trial municipalities and treatment groups. Treatment groups are indicated with different colors and the lines represent the boundaries of Finnish municipalities, the number of which ranged from 1 to 12 per cluster. Six biggest cities included several clusters.

Figure 2. Trial profile for the subjects


PHiD-CV10 3+1
PHiD-CV10 2+1
Control 3+1
Control 2+1
Not participating



* 3 subjects not randomised nor vaccinated

** includes one subject withdrawn from the register follow-up during the blinded follow-up period