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Vaccine effectiveness of the pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) against clinically suspected invasive pneumococcal disease: a cluster-randomised trial

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Summary

Background
Vaccine effectiveness of pneumococcal conjugate vaccines against culture-confirmed invasive pneumococcal disease has been well documented. In the Finnish Invasive Pneumococcal disease (FinIP) trial, we reported vaccine effectiveness and absolute rate reduction against laboratory-confirmed invasive pneumococcal disease (confirmation by culture or antigen or DNA detection irrespective of serotype). Here, we assessed vaccine effectiveness of PHiD-CV10 against clinically suspected invasive pneumococcal disease in children by use of diagnoses coded in hospital discharge registers.

Methods
For this phase 3/4 cluster-randomised, double-blind trial, undertaken between Feb 18, 2009, and Dec 31, 2011, in municipal health-care centres and the Tampere University Vaccine Research Centre (Finland), we randomly assigned (2:2:1:1) 78 clusters into PHiD-CV10 three plus one, PHiD-CV10 two plus one, control three plus one, control two plus one groups (26:26:13:13 clusters) to give PHiD-CV10 in either three plus one or two plus one schedule (if enrolled before 7 months of age; infant schedules), two plus one (if enrolled between 7 and 11 months; catch-up schedules), and two doses at least 6 months apart (if enrolled between 12 and 18 months; catch-up schedules). Children were eligible if they had not received and were not anticipated to receive any of the study vaccines and had no general contraindications to vaccinations. We collected all inpatient and outpatient discharge notifications from the national hospital discharge register with International Classification of Diseases (ICD) 10 diagnoses compatible with invasive pneumococcal disease or unspecified sepsis, and verified data with patient files. We excluded invasive pneumococcal disease cases confirmed by positive culture or DNA/RNA detection from normally sterile body fluid. The primary objective was to estimate vaccine effectiveness against all register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis and patient-file verified non-laboratory-confirmed invasive pneumococcal disease in infants younger than 7

months at enrolment. Masked follow-up lasted from the date of the first vaccination to Dec 31, 2011. Vaccine effectiveness was calculated against all episodes. This trial is registered with ClinicalTrials.gov, numbers NCT00861380 and NCT00839254.

Findings
We enrolled 47 366 children. On the basis of ICD-10 diagnoses, we recorded 264 episodes of register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis, of which 102 were patient-file verified non-laboratory-confirmed invasive pneumococcal disease. The vaccine effectiveness was 50% (95% CI 32–63) in the 30 527 infants with three plus one and two plus one schedules combined and the absolute incidence rate reduction was 207 episodes per 100 000 person-years (95% CI 127–286). The vaccine effectiveness against the patient-file verified non-laboratory-confirmed invasive pneumococcal disease was 71% (95% CI 52–83) in infant three plus one and two plus one schedules combined. The absolute rate reduction was 142 episodes per 100 000 person-years (95% CI 91–191) in infant cohorts.

Interpretation
This vaccine-probe analysis is the first report showing the effect of pneumococcal conjugate vaccines on clinically suspected invasive pneumococcal disease. The absolute rate reduction was markedly higher compared with laboratory-confirmed invasive pneumococcal disease, which implies low sensitivity of the laboratory-based case definitions and subsequently higher public health effect of pneumococcal conjugate vaccines against invasive pneumococcal disease than previously estimated.

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Introduction

High vaccine effectiveness of pneumococcal conjugate vaccines against culture-confirmed invasive pneumococcal disease has been well documented both in clinical trials[1] and observational studies.[2,3] However, culture-confirmed invasive pneumococcal disease is a highly specific endpoint and to what extent all true invasive pneumococcal disease cases are detected is unknown.

The sensitivity of case detection of culture-confirmed invasive pneumococcal disease might be poor because patient care seeking might be very early during the disease process or delayed with spontaneous recovery; primary care referral to proper diagnosis can be missed and antimicrobial treatment started without study of causes; and hospital blood culture practices might be suboptimum. Furthermore, the sensitivity of the laboratory detection by culture is not perfect and might be further reduced by antimicrobial treatment or inappropriate processing. Lastly, reporting of cases to registers can be missed if high-quality procedures are not established. Consequently, assessments of the vaccine effect on the basis of culture-confirmed invasive pneumococcal disease most probably underestimate the public health burden averted by vaccination programmes.

We have previously reported that the PHiD-CV10 vaccine effectiveness against laboratory-confirmed invasive pneumococcal disease (collected through the National Infectious Diseases Register [NIDR] in the Finnish Invasive Pneumococcal disease [FinIP] trial) was 94% (95% CI 77–99) and the absolute rate reduction (ie, vaccine-preventable incidence) was 75 per 100 000 person-years.[4]

To estimate the effect of pneumococcal conjugate vaccines on invasive pneumococcal disease more comprehensively taking into account the potential suboptimum sensitivity of laboratory-based detection, we set to assess vaccine effectiveness of the pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10, Synflorix, GlaxoSmithKline, Belgium) against clinically suspected invasive pneumococcal disease with hospital discharge register data.

Methods

Trial design and participants

The FinIP trial was a nationwide phase 3/4 cluster- randomised, double-blind field trial done by the National Institute for Health and Welfare (THL, Finland). The trial was done in municipal health-care centres and their local well-baby clinics (N=651). The Tampere University Vaccine Research Centre (TAUVRC) undertook a parallel trial with the same design for acute otitis media, and its participants were also followed up for the outcomes of this study.[5]

The trial design has been previously described.[4] Briefly, children younger than 19 months could be enrolled if they had not received and were not anticipated to receive any of the study vaccines and had no general contraindications to vaccinations.

The study protocols were approved by the relevant ethics review boards and competent authorities before trial start. Written consent was obtained from a parent or guardian of all participants. The full protocol is available online (www.finip.fi).

Randomisation and masking

The areas of the health-care centres participating in the trial were divided geographically into 72 study clusters. TAUVRC contributed to the study in 44 of these clusters and enrolled participants in six additional clusters. The treatment was allocated into the 78 clusters (2:2:1:1) into PHiD-CV10 three plus one, PHiD-CV10 two plus one, control three plus one, and control two plus one groups (26:26:13:13 clusters) and stratified according to the birth cohort size (lower or higher than average), TAUVRC trial enrolment (50 of 78 clusters), and urbanity (24 urban and 54 rural clusters).[4] Details of the masking have been presented previously.[4]

Procedures

The PHiD-CV10 vaccine contains ten pneumococcal serotype polysaccharides (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) individually conjugated to carrier proteins: protein D of non-typeable H

influenzae, tetanus, or diphtheria toxoids. We used hepatitis B virus vaccine (10 μg/0•5 mL ENGERIX-B, GlaxoSmithKline, Belgium) as a control vaccine for children enrolled younger than 12 months and hepatitis A virus vaccine (Havrix 720 Junior, 0•5 ml GlaxoSmithKline, Belgium) for children enrolled at the age of 12 months or older.

Enrolled children were vaccinated according to either three plus one or two plus one schedule if enrolled before 7 months of age (infant schedules), two plus one if enrolled between 7 and 11 months, and two doses at least 6 months apart if enrolled between 12 and 18 months of age (catch-up schedules) as described in detail previously.[4]

The outcome data were collected from the nationwide administrative Care Register for Health Care maintained at THL (see http://www.thl.fi/en_US/web/en/ statistics/information/register_ descriptions/careregister_healthcare). The Care Register included all notifications of inpatient and outpatient care provided in all public and private hospitals in Finland. The register data included hospital and patient identification (by unique and permanent personal identity codes assigned to all long-term residents in Finland), the initial and final ICD-10 diagnoses, admission, and discharge dates, the place admitted from and discharged to, and also whether the patient survived or not. The hospitals, obliged by law, submit these data to THL in yearly batches. The completeness of the register in covering all inpatient and outpatient diagnoses in Finnish hospitals is very good although no validation studies of paediatric infectious diseases are available.[6]

We collected all discharge notifications of inpatient or outpatient care with available primary or either of the first two secondary diagnoses of ICD-10 codes compatible with clinical syndromes of invasive pneumococcal disease (ICD-10 codes A40.3, B95.3, G00.1, or M00.1) or unspecified sepsis (ICD-10 codes A40.9, A41.9, A49.9, G00, G00.9, I30.1, M00, M00.9, or B95.5) from the Care Register (panel 1 and table 1). To ensure that repeated hospital visits and admissions due to the same illness were not counted more than once in the analyses, we applied a 90-day episode rule; a new episode was judged to start on the day that the patient visited the hospital provided that at least 90 days had elapsed from the beginning of the previous episode fulfilling the criteria for the case definition.

We used the NIDR to identify laboratory-confirmed cases of invasive pneumococcal disease (culture-confirmed [ie, positive for *Streptococcus pneumoniae* in culture in any normally sterile body fluid] and probable [ie, positive for *S pneumoniae* in demonstration of nucleic acid or antigen detection tests but negative for *S pneumoniae* in culture]). We matched these laboratory-confirmed cases of invasive pneumococcal disease found in NIDR with cases detected in the Care Register with personal identity codes and the date of diagnosis and sampling. We excluded all laboratory- confirmed episodes of invasive pneumococcal disease, but not invasive diseases due to other bacteria, from the analyses. The results of laboratory-confirmed invasive pneumococcal disease according to NIDR have been published previously.[4]

Patient files of all identified episodes of non-laboratory- confirmed invasive pneumococcal disease or unspecified sepsis were collected from the hospitals and the data for the following variables were extracted: the final diagnoses set by the treating physician (ICD-10 code); blood culture sample available (yes or no); result of blood culture test; any other aetiological tests including both bacterial and viral assays; first and highest C-reactive protein; and first and highest blood leucocyte counts. To increase the specificity of the outcome and to validate the register-based diagnoses, we scrutinised all the clinical and aetiological patient data to classify the cases in different clinical categories (panel 1 and table 2) by two physician researchers independently of each other (AAP and HN). For the purpose of the classification, invasive pneumococcal disease was defined as any acute disease resulting in any ICD-10 diagnosis listed in table 1 during the hospital period and the patient file details (especially the final discharge diagnosis, relevant studies of causes, and the comments by the treating paediatrician) suggested pneumococcus as the most probable causative agent for the disease. When the two reviewers established discordant categories, the case was classified independently by a third physician (RS) whose verdict established the final category if it coincided with the classification of either of the two primary reviewers. In case all three reviews produced different conclusions, the consensus was established by a panel including all three. This review was done after the trial was unmasked, but the vaccination details could not have been described in the patient files during the masked study period

and the vaccination data were not included in the datasets extracted for review.

Outcomes

The primary objectives of this study were to estimate both incidence rate ratio (vaccine effectiveness) and incidence rate difference (vaccine preventable incidence) between treatment and control groups for register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis and patient-file verified non-laboratory-confirmed invasive pneumococcal disease in infants who received at least one dose of either three plus one or two plus one schedule before age 7 months. The sample size estimation for the FinIP trial was based on the primary objective of the trial—ie, to show effectiveness against laboratory-confirmed invasive pneumococcal disease.[4]

Statistical analysis

Intention-to-treat follow-up for each participant started at the date of the first vaccination (trial enrolment from Feb 18, 2009, to Oct 5, 2010) and ended on Dec 31, 2011. The trial randomisation code was opened in April, 2012. We estimated vaccine effectiveness against all episodes. We calculated incidences as arithmetic mean of cluster-specific incidences in PHiD-CV10 and control groups.

To account for between-cluster variability in the incidence, we used a negative binomial model for the analysis of the vaccine effectiveness.[7] We grouped frequencies of episodes by cluster and used the cluster-specific person-years as weights in the analysis. When estimating the effectiveness by infant schedule, we used a treatment variable in the model as three-level factor (PHiD-CV10 three plus one, PHiD-CV10 two plus one, and control). We included factors used for stratified randomisation in the model as explanatory variables. We used the profile likelihood method to estimate the 95% CIs for the treatment parameter. We calculated vaccine effectiveness as 1 minus the incidence rate ratio.

Incidence rate difference (ie, vaccine-preventable incidence), was calculated as the difference of incidence rate estimates in the PHiD-CV10 and control groups. We used a non-parametric bootstrap method to calculate the confidence intervals.[8] We used stratified bootstrap sampling based on levels of the stratification factors used for randomisation.

This trial and the nested acute otitis media trial are registered at ClinicalTrials.gov, NCT00861380 and NCT00839254.

Role of the funding source

This collaborative study was mainly funded by GlaxoSmithKline Biologicals SA and co-funded by the National Institute for Health and Welfare (THL). Both parties were involved in all stages of the study planning, conduct, data collection, analyses, and manuscript development. All authors had access to all the data and accept responsibility for its validity. All authors agreed on the final decision to submit for publication.

Results

47 366 children were enrolled from Feb 18, 2009, to Oct 5, 2010. 45 974 participants received at least one dose of correctly assigned vaccine and were included in the intention-to-treat analyses (figure 1). The baseline and vaccination data have been published previously.[4]

We identified 264 episodes of register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis. Table 1 shows the diagnosis codes. Five children had two episodes and one child had three episodes.

Table 2 shows the final diagnoses of all episodes on the basis of patient-file review. We noted 102 episodes (including one child with three episodes) of patient-file verified non-laboratory-confirmed invasive pneumococcal disease.

Table 3 shows the baseline characteristics and clinical features of patients with register-based or patient-file verified non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis in comparison with patients with laboratory-confirmed invasive pneumococcal disease.[4] We recorded no fatal cases in any of the patient groups. The clinical courses of all non-laboratory-confirmed case

definition groups were very similar to laboratory-confirmed invasive pneumococcal disease with respect to the duration of treatment in hospital and C-reactive protein and leucocyte count values during hospital stay. Only the highest leucocyte levels were higher and C-reactive protein values at admission tended to be lower in laboratory-confirmed episodes than in the non-laboratory-confirmed invasive pneumococcal disease episodes (table 3). 21 of 264 (8%) episodes of register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis had a final ICD-10 diagnosis of pneumonia, which was much lower than laboratory-confirmed invasive pneumococcal disease, in which the clinical syndrome was pneumonia in 28% (eight of 29) of the episodes. Acute otitis media was listed as a final diagnosis at discharge from the hospital in 39 of 264 (15%) episodes of register-based non-laboratory- confirmed invasive pneumococcal disease or unspecified sepsis. This finding was similar in the laboratory- confirmed episodes (five of 29 [17%]).

The vaccine effectiveness for the register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis was 50% for both infant three plus one and two plus one schedules combined (95% CI 32–63) and combined catch-up groups (95% CI 14–71; table 4). The absolute rate reduction was similar in infant groups (207 episodes per 100 000 person-years) and in combined catch-up groups (203 episodes).

The more specific case definition of register-based non-laboratory-confirmed invasive pneumococcal disease gave higher vaccine effectiveness estimates but the incidence rate reductions were lower than for the register- based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis (table 5). The vaccine effectiveness was similar for the patient-file verified non-laboratory-confirmed invasive pneumococcal disease (71% [95% CI 52–83] in infant three plus one and two plus one schedules combined and in combined catch-up groups (69%, 95% CI 32–86; table 6). The absolute rate reduction was 142 episodes per 100 000 person-years in infant groups and 111 episodes in catch-up groups.

The vaccine effect was already seen at 6–11 months of age and persisted at least up to 29 months of age (figure 2). We further explored the relative and absolute effect of PHiD-CV10 with various C-reactive protein and blood leucocyte cutoff amounts (first and highest during admittance to hospital) in the case definitions for the infant cohort. High C-reactive protein value cutoffs gave successively increased vaccine effectiveness estimates, nearly reaching those shown for laboratory-confirmed invasive pneumococcal disease. However, as expected, the absolute reduction decreased with the less sensitive endpoint definitions (appendix). The blood leucocyte concentration cutoffs did not have a consistent effect on vaccine effectiveness estimates (data not shown).

The addition of the vaccine-preventable incidence of culture-confirmed and probable invasive pneumococcal disease (75 episodes per 100 000 person-years) reported earlier from the same trial[4] to that of the register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis of our analysis (table 4) resulted in vaccine-preventable incidence of 282 episodes per 100 000 person-years. This finding would translate into a number needed to vaccinate of 178 for the infant cohorts per 2-year follow-up to prevent one case of laboratory-confirmed or non-laboratory- confirmed invasive pneumococcal disease.

If we assumed the same vaccine effectiveness for the undetected invasive pneumococcal disease as reported for culture-confirmed or probable invasive pneumococcal disease, irrespective of serotype (vaccine effectiveness point estimate 94%),[4] the incidence of the register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis attributable to pneumococcus would be estimated at 220 episodes per 100 000 person-years (207/0•94) in the infant control group. Thus, the total incidence of clinical invasive pneumococcal disease including both laboratory-confirmed and non-confirmed invasive pneumococcal disease episodes would be 300 per 100 000 person-years. Therefore, this vaccine-probe design suggests that the sensitivity of the laboratory-based detection of invasive pneumococcal disease in the present routine hospital care setting was 27% (80 / [80 + 220]).

This low sensitivity can partly be explained by failure to obtain blood-culture test (15% of the episodes) and the antimicrobial exposure at admission (12% in the non- laboratory-confirmed episodes and 0% in laboratory- confirmed). If only episodes with blood culture obtained and no exposure to antimicrobials are included (69 of 87 episodes in the infant control cohorts), we estimate the sensitivity

of the laboratory-based detection of invasive pneumococcal disease as 31% (80 / [80 + 174]).

Table 2 shows the final categories of acute infections resulting in ICD-10 coding compatible with invasive pneumococcal disease or unspecified sepsis during hospital visit or admittance to hospital. We recorded seven episodes for which the patient-file review resulted in classification of no acute infection (table 2). In two of these episodes, sepsis was suspected during admittance to hospital, but another non-infectious disease was ultimately diagnosed. In two episodes, there was a previous admittance to hospital with a sepsis diagnosis and a follow-up visit later than 90 days after the admittance; with our definition, we calculated these as two episodes. Finally, we noted three episodes in which no obvious disease compatible with invasive pneumococcal disease or non-specified sepsis were mentioned in the source data available. Thus, the misclassification proportion based on erroneous register data entry would be estimated at maximum 1% (three of 264).

The study design also allowed the estimation of the completeness of the National Infectious Diseases Register (NIDR), which collects data for culture- confirmed invasive pneumococcal disease and probable invasive pneumococcal disease detected by DNA or RNA detection (29 cases).[4] Blood culture had been taken in 225 of 264 (85%) episodes of register-based non- laboratory-confirmed invasive pneumococcal disease or unspecified sepsis, all negative for *Streptococcus pneumoniae* in patient-file review. Thus, in this dataset with ICD-10 diagnoses compatible with invasive pneumococcal disease and unspecified sepsis, the completeness of the reporting of positive cases to NIDR was 100% (29 / [29 + 0]).

Discussion

Our report is the first to show the effect of a pneumococcal conjugate vaccine on a clinical syndrome compatible with invasive pneumococcal disease that remains non-confirmed by laboratory assays, and implies much higher public health value of pneumococcal conjugate vaccines than previously reported. All previous clinical trials have relied on laboratory-based microbiological case definitions. All infant and catch-up vaccination schedules showed high effectiveness, although the results for catch-up schedule with enrolment at 7–11 months' age were not statistically significant. The vaccine effectiveness point estimates were actually higher for the infant two plus one schedule than for the three plus one schedule, but the confidence intervals were overlapping. Furthermore, we have reported comparable vaccine effectiveness estimates for the infant three plus one and two plus one schedules for all other study outcomes of culture-confirmed invasive pneumococcal disease,[4] pneumonia,[9] and antimicrobial purchases.[10]

We are aware of only two published studies[11,12] by Simonsen and colleagues in which the same kind of discharge register-based endpoint was used (panel 2). In these observational studies, the investigators used register-based invasive pneumococcal disease treatment in hospital from a hospital discharge register as the endpoint, but they did not have data for whether these cases were culture-confirmed. However, incidences of the register-based invasive pneumococcal disease endpoint were only about half of those reported for culture- confirmed disease with treatment in hospital.[2,13] These data suggested that most of the cases were actually blood-culture positive. Nevertheless, researchers noted a large relative reduction during the 7-valent pneumococcal conjugate vaccine vaccination era compared with the baseline before the vaccinations and further reduction after the introduction of the 13-valent pneumococcal conjugate vaccine.[11,12]

Additionally, pneumococcal conjugate vaccines have reduced other pneumococcus-related clinical endpoints such as pneumonia and acute otitis media both in clinical trials and in observational studies.[1,14,15] The vaccine probe design[16] used in this report has also been exploited in circumstances in which information about disease cause was difficult to obtain or was deemed to have low sensitivity. Examples include estimation of vaccine- preventable invasive disease and pneumonia caused by *H influenzae*[17] and the exploration of pneumococcal vaccine-preventable pneumonia burden by use of various different case definitions.[18]

Our estimates of vaccine effectiveness fall between those for culture-confirmed invasive pneumococcal disease[1,4] and radiologically confirmed pneumonia.[19] Similar to pneumonia, the vaccine effect was the net reduction in disease due to the ten vaccine serotypes combined, and potentially also

due to cross-reactive vaccine-related serotypes, plus the net increase because of replacement by non-vaccine serotypes. Non-typeable *H influenzae* is a rare cause of invasive-like disease, and despite protein D carrier in the vaccine, is unlikely to contribute to our findings. The high vaccine effectiveness we recorded (especially for the patient-file verified non- confirmed invasive pneumococcal disease), further augmented with various C-reactive protein cutoff concentrations, clinical features, and health-care utilisation indistinguishable from culture-confirmed invasive pneumococcal disease, suggested that we had discovered true cases of invasive pneumococcal disease that had gone undetected despite collection of blood for appropriate culture. In this vaccine-probe analysis, we also noted that the paediatricians in Finnish hospitals could accurately recognise the vaccine-preventable clinical syndrome of pneumococcal bacteraemia. It could be argued that because of the non-specificity of the endpoints, the case definitions included other pneumococcal disease syndromes, such as lower and upper respiratory infections. However, only a small proportion of non-laboratory-confirmed invasive pneumococcal disease episodes also had the primary discharge diagnosis of pneumonia or acute otitis media. Thus, the effect on the endpoints cannot be solely explained by vaccine effect on clinical pneumonia and upper respiratory infections, especially because the reported vaccine effectiveness estimates against clinical pneumonia[9] and respiratory tract infections[10] were far below those for non-confirmed invasive pneumococcal disease in our study.

For the most sensitive endpoint of register-based non- confirmed invasive pneumococcal disease or unspecified sepsis, the vaccine effectiveness estimates were lower than for other endpoints because of the lower specificity of this endpoint (table 2). However, the rationale of this definition was to be highly sensitive to capture the vaccine-preventable disease incidence as completely as possible. Indeed, the absolute reduction for this outcome was higher than for other endpoints, which suggests that more episodes of true vaccine-preventable cases were captured with this endpoint than with the more stringent endpoints.

The vaccine-preventable incidence can be seen as the most pertinent estimate in the assessment of the public health effect of the vaccine. The vaccine-preventable incidence of non-laboratory-confirmed invasive pneumococcal disease in this study was 1•1–2•8 times higher than that of culture-confirmed or probable invasive pneumococcal disease reported earlier from the same trial setting.[4] The main reason for this additional disease burden seems to be the low sensitivity of the blood culture. Even if a blood culture was taken in most of the episodes, the samples remained culture-negative. In a study of adults with presentation of severe sepsis, the blood culture was positive in 45% of cases.[20] In more than half of the culture-negative cases an infectious cause was suspected, although not confirmed. In a paediatric study of clinical syndromes compatible with invasive pneumococcal disease (mainly pneumonia), the blood culture was positive for pneumococcus in 4% of cases, but real-time PCR on whole blood sample was positive in up to 24% (ie, 5•5 times higher).[21]

This was a nationwide, double-blind randomised trial with a large enrolment proportion (38% of age-eligible birth cohorts). We collected outcome data from a nationwide established register. The Care Register collects discharge notifications of routine care for all hospital individual outpatient visits and inpatient ward admissions. We collected data for all discharge notifications including emergency room discharge notifications. Therefore, our dataset included the first working diagnoses at emergency rooms with the first suspicion of diagnoses at admission, not only the final diagnoses assigned after further clinical assessment and follow-up at discharge from the hospital, which further increased the sensitivity of the case detection.

To address the potential non-specificity of the clinical diagnoses assigned, we verified all clinical patient-file data to establish classification considering all clinical data for the whole period of treatment in hospital and to identify the most probable cases of non-laboratory- confirmed invasive pneumococcal disease (table 2). As expected, the vaccine effectiveness estimates were higher for the patient-file verified endpoint than for other endpoints suggesting higher specificity. However, the effect of the patient-file verification was not crucial because the register-based endpoints also gave high vaccine effectiveness estimates and we recorded the highest vaccine-preventable incidence for the most sensitive register-based outcome.

The data linkage for enrolled participants and their register notifications was done with the Personal

Identity Code, which is unique and permanent for all Finnish citizens and long-term residents. Therefore, all nationwide notifications can be linked to a participant with this code. The Personal Identity Code includes a check digit (see http://www.vrk.fi/default. aspx?id=45) preventing false entries and is correct in 99•5% of all discharge notifications.[6] Therefore, we might have missed only a few episodes diagnosed and treated abroad outside of the Finnish hospitals. However, we might have missed cases if the appropriate ICD-10 code was not entered in the discharge notification. In this case of suboptimum sensitivity of case detection, the estimates of vaccine effectiveness would probably not be affected in the randomised design, but the incidence of non-confirmed invasive pneumococcal disease, and also vaccine preventable disease incidence, would be even higher than we recorded.

Diagnostic practices might vary between hospitals, and the effect of this bias might be a concern in cluster- randomised trials. Finland has 20 public hospitals, which cover the whole country. 16 hospitals served both PHiD-CV10 and control clusters in our study. The remaining four hospitals, which covered roughly 10% of the study population, served PHiD-CV10 clusters only. Exclusion of these clusters from the analyses had no effect on the results (data not shown).

Our finding of additional disease burden was detected in addition to the laboratory-confirmed invasive pneumococcal disease (incidence 80 per 100 000 person- years in the infant cohort in the control clusters).[4] This finding is concordant with the national long-term average for culture-confirmed invasive pneumococcal disease before pneumococcal conjugate vaccines vaccination era of roughly 60 per 100 000 person-years in children younger than 2 years. The Finnish incidences of invasive pneumococcal disease are far higher than reported for most countries in Europe.[22] Thus, the high additional pneumococcal disease burden presented in this report is not due to poor detection of the culture-confirmed disease. In the pre-pneumococcal conjugate vaccines era invasive pneumococcal disease incidence was much higher in the USA,[2] partly because of more sensitive blood culture detection including sampling from well- appearing febrile children, so-called occult pneumococcal bacteraemia,[23] diagnosed and treated in outpatient settings. Actually, the rates of admittance to hospital with invasive pneumococcal disease in the USA[2] are concordant with the Finnish rates. Our cases might have been bacteraemic at some point during the course of illness but at the time of blood sampling, they were, by definition, negative in blood culture and almost invariably treated in the hospital.

The diagnostic, treatment, and coding practices vary substantially by country, area, and by time. However, pneumococcal disease is present everywhere. We believe that our results are generalisable and valid also for other high-income countries. Although true differences exist in the incidence of invasive pneumococcal disease, the low incidences of culture- confirmed invasive pneumococcal disease are most probably associated with low sensitivity of the case detection. Thus, on the basis of our findings, especially in countries with low incidence of culture-confirmed invasive pneumococcal disease, the effect of pneumococcal conjugate vaccines is probably much higher than would be expected on the basis of laboratory-confirmed disease.

This is the first clinical trial report showing the effect of pneumococcal conjugate vaccines on clinically suspected non-laboratory-confirmed invasive pneumococcal disease, and our data suggest a higher public health value of pneumococcal conjugate vaccines than previously estimated. Although this study might still miss a large disease burden that remains undetected because of many factors affecting care seeking and diagnostics at the primary care level, the vaccine probe design[16] enables deeper understanding of the public health value of the pneumococcal conjugate vaccines. This point should also be taken into account in the future health economic analyses of pneumococcal conjugate vaccines.

Contributors

AAP, JJ, ER, TP, LS, DB, and TMK contributed to the concept and study design. AAP, JJ, HN, RS, ER, and TMK contributed to acquisition of data. JJ analysed the data. AAP, JJ, and TMK drafted the manuscript. All authors interpreted the data and reviewed and approved the final version of the report.

Declaration of interests

AAP has had travel paid for and honoraria by GlaxoSmithKline group of companies to attend expert group meetings, has had travel paid by Merck to attend expert group meetings, and has received a travel grant from Sanofi Pasteur MSD. He is the head of the Clinical Research Unit at the National Institute for Health and Welfare, which has received research funding from the GlaxoSmithKline group of companies. JJ is the head of Vaccine Research Unit at the National Institute for Health and Welfare, which has received research funding from the GlaxoSmithKline group of companies. HN is an employee of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from the GlaxoSmithKline group of companies. RS is an employee of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from the GlaxoSmithKline group of companies. ER is an employee of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from the GlaxoSmithKline group of companies. TP was an employee of the GlaxoSmithKline group of companies during the study conduct. MM and LS are employees of the GlaxoSmithKline group of companies and have stock ownership of the GlaxoSmithKline group of companies. DB is an employee of the GlaxoSmithKline group of companies and has stock and stock options ownership of the GlaxoSmithKline group of companies. TMK is director of the Department of Vaccination and Immune Protection at the National Institute for Health and Welfare, which has received research funding from the GlaxoSmithKline group of companies.

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Panel 1: Definitions of outcomes

Register-based non-laboratory-confirmed invasive pneumococcal disease or unspecified sepsis

- Defined as an episode to which any ICD-10 code compatible with invasive pneumococcal disease or unspecified sepsis had been assigned in the Care Register without confirmation as invasive pneumococcal disease by laboratory assays (culture or DNA/RNA detection from a normally sterile site of the body). This is the most sensitive outcome, out of which the following two more specific subgroup definitions were formed.

Register-based non-laboratory-confirmed invasive pneumococcal disease

- Defined as an episode to which ICD-10 code compatible with invasive pneumococcal disease had been assigned in the Care Register as final discharge diagnosis without confirmation as invasive pneumococcal disease by laboratory assays.

Patient-file verified non-laboratory-confirmed invasive pneumococcal disease

- The first outcome also had to be classified as suspected invasive pneumococcal disease in the investigators' patient-file review.

ICD=International Classification of Diseases.

Panel 2: Research in context

Systematic review

We searched PubMed and Cochrane Library for reports published in English between Jan 1, 2000, and May 27, 2014, with the following search terms in any fields: "efficacy" or "effectiveness" and "clinical trial" or "controlled" and "conjugate vaccine" and "invasive pneumococcal disease* OR invasive pneumococcal*". We found no publications of clinical trials with a similar outcome of clinically suspected non-laboratory-confirmed invasive pneumococcal disease. Two observational studies11,12 with a register-based outcome of patients with a diagnosis of invasive pneumococcal disease admitted to hospital were found with documentation of both direct and indirect vaccine effect when comparing post-PCV era with the pre-introduction era. In these studies, the culture-confirmed cases were not excluded because no data for these were available. However, several clinical trials and observational studies have documented the substantial effect of the pneumococcal conjugate vaccines on laboratory-confirmed invasive pneumococcal disease and on clinical endpoints of pneumonia and acute otitis media.

Interpretation

Our study is the first to show the effect of a pneumococcal conjugate vaccine on clinically defined suspected non-laboratory-confirmed invasive pneumococcal disease. In the same study,4 the incidence of laboratory-confirmed invasive pneumococcal disease (80 per 100 000 person-years) was among the highest reported in Europe for infants. On top of this, the present vaccine-probe design in the randomised clinical trial setting detected nearly three times as high additional disease burden than that detected with laboratory- based outcomes. The result is that the invasive pneumococcal disease burden is grossly underestimated by the low sensitivity of the blood culture, probably to an even higher degree in countries with low reported incidences of laboratory-confirmed invasive pneumococcal disease.

Table 1. ICD-10 codes compatible with IPD or unspecified sepsis

ICD-10 code	Diagnosis in text	Distribution of episodes, N total 264*
A40.3†	**Sepsis due to *Streptococcus pneumoniae***	**86**
A40.9	Streptococcal sepsis, unspecified	13
A41.9	Sepsis, unspecified organism	92
A49.9	Bacterial infection, unspecified	68
G00	Bacterial meningitis, not elsewhere classified	0
G00.1†	**Pneumococcal meningitis**	**0**
G00.9	Bacterial meningitis, unspecified	1
I30.1	Infective pericarditis	0
M00	Pyogenic arthritis	0
M00.1†	**Pneumococcal arthritis and polyarthritis**	**0**
M00.9	Pyogenic arthritis, unspecified	3
B95.3†	***Streptococcus pneumoniae* as the cause of diseases classified elsewhere**	**1**
B95.5	Unspecified streptococcus as the cause of diseases classified elsewhere	0

* All cases included in the case definition of *register-based non-laboratory-confirmed IPD or unspecified sepsis*

† ICD-10 code for diseases caused by *Streptococcus pneumoniae*, these diagnoses when present as final discharge diagnoses included in the case definition of *register-based non-laboratory-confirmed IPD*

Table 2. Episodes of register-based non-laboratory-confirmed IPD or unspecified sepsis as classified in the patient file review

	Infants			Catch-up		
	PHID-CV10 3+1	PHID-CV10 2+1	Control 3+1/2+1	PHID-CV10 catch-up	Control catch-up	Total
Follow-up years	20 630	19 793	20 427	23 476	11 473	95 799
Category						
Patient-file verified non-laboratory-confirmed IPD						
Suspected IPD, urine antigen positive	-	-	2	-	1	3
Suspected IPD, without any laboratory indication of pneumococcal aetiology	16	8	41	13	21	99
Not verified as non-laboratory-confirmed IPD in patient file review						
Invasive non-pneumococcal disease (ID), culture-confirmed	1*	-	1†	1*	-	3
Invasive disease (ID), suspected, not specified	17	7	17	13	9	63
Urinary tract infection, culture-confirmed	8	3	2	1	3	17
Urinary tract infection, clinical diagnosis	-	1	1	-	-	2
Other bacterial infection, culture-confirmed	-	-	1	3	1	5
Other bacterial infection, clinical diagnosis	1	5	6	5	7	24
Viral infection, etiology demonstrated	-	2	-	-	-	2
Viral infection, clinical diagnosis	4	4	10	4	1	23
Respiratory infection, not specified	6	2	4	3	1	16
No acute infection	2	-	2	3	-	7
Total	55	32	87	46	44	264

*both due to *Streptococcus viridans* species, the other in an immunocompromised host

† both *Haemophilus influenzae* and *Moraxella catarrhalis* detected in the one blood culture sample

Table 3. Baseline characteristics and clinical course of the episodes in all study cohorts

	Laboratory-confirmed IPD*	Register-based non-laboratory-confirmed IPD or unspecified sepsis	Register-based non-laboratory-confirmed IPD†	Patient-file verified non-laboratory-confirmed IPD†
Number of episodes	29	264	71	102
Age in months, mean (IQR)	19 (12-20)	19 (12-25)	20 (13-27)	20 (13-25)
Male	19 (66%)	148 (56%)	37 (52%)	62 (61%)
Underlying disease	2 (7%)	27 (10%)	4 (6%)	6 (6%)
Underlying immunosuppressive disease	0	7 (3%)	0	0
Antimicrobial exposure at admission	0	32 (12%)	6 (8%)	9 (9%)
CRP at admission, median (IQR)	50 (35-139)	92 (42-146)	104 (45-146)	103 (45-137)
CRP, highest during the hospitalization, median (IQR)	108 (57-234)	116 (59-174)	118 (64-181)	118 (54-172)
Blood leukocyte count at admission, median (IQR)	25.7 (20.3-32.5)	22.0 (15.4-27.2)	25.2 (20.5-29.0)	25.0 (20.5-29.0)
Blood leukocyte count, highest during the hospitalization, median (IQR)	29.6 (22.3-35.1)	22.3 (16.0-27.3)‡	25.2 (20.5-29.0)‡	25.0 (20.5-29.0)‡
Hospitalized	29 (100%)	251 (95%)	68 (96%)	101 (99%)
Duration of hospitalization in days, median (IQR)	2 (1-4)	2 (1-3)	2 (1-2)	2 (1-2)

* Published earlier[4]

† These episodes are a subgroup of the *register-based non-laboratory-confirmed IPD or unspecified sepsis*

‡ Statistically significant difference in comparison to laboratory-confirmed IPD (Kolmogorov-Smirnov test)

Table 4. Episodes of register-based non-laboratory-confirmed IPD or unspecified sepsis* and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up

	Number of episodes		Follow-up time, person-years		Episodes per 100 000 person-years, cluster-specific averages		Vaccine effectiveness (VE)		Incidence rate difference, cluster-specific averages	
Register-based non-laboratory-confirmed IPD or unspecified sepsis*, in the various study cohorts	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI	Reduction per 100 000 person-years	95% CI
3+1 and 2+1 schedule combined from dose 1	87	87	40423	20427	212•9	421•5	**50**	32-63	207	127-286
3+1 schedule from dose 1	55	87	20630	20427	274•7	421•5	**38**	13-56	153	62-245
2+1 schedule from dose 1	32	87	19793	20427	151•2	421•5	**62**	43-75	273	200-346
Catch-up 7-11 months	18	14	8672	4317	211•2	321•7	**37**	-43-71	112	-83-314
Catch-up 12-18 months	28	30	14804	7156	159•4	404•7	**56**	16-78	249	76-419

*Any of the following ICD-10 codes entered in any discharge notifications: A40.3, A40.9, A41.9, A49.9, G00, G00.1, G00.9, I30.1, M00, M00.1, M00.9, B95.3, or B95.5

Table 5. Episodes of register-based non-laboratory-confirmed IPD* and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up

	Number of episodes		Follow-up time, person-years		Episodes per 100 000 person-years, cluster-specific averages		Vaccine effectiveness (VE)		Incidence rate difference, cluster-specific averages	
Register-based non-laboratory-confirmed IPD* in the various study cohorts	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI	Reduction per 100 000 person-years	95% CI
3+1 and 2+1 schedule combined from dose 1	19	28	40423	20427	46•2	125•9	**65**	35-81	81	34-126
register-based, 3+1 schedule from dose 1	14	28	20630	20427	70•9	125•9	**50**	4-75	58	1-112
2+1 schedule from dose 1	5	28	19793	20427	21•5	125•9	**81**	54-94	104	64-143
Catch-up 7-11 months	4	3	8672	4317	39•1	77•9	**44**	-227-90	40	-41-120
Catch-up 12-18 months	7	10	14804	7156	43•6	112•3	**68**	-2-90	70	-14-165

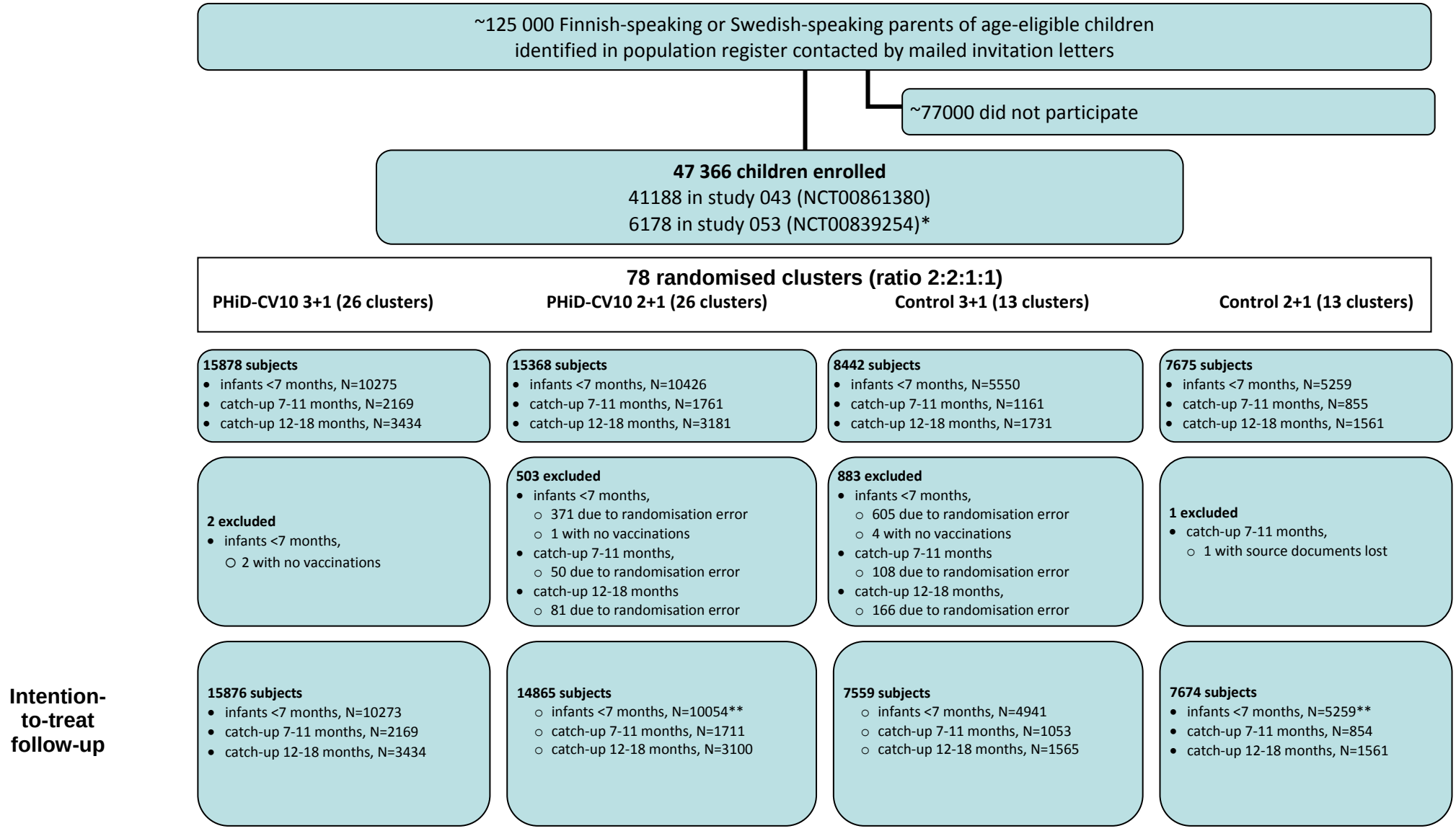
*Any of the following ICD-10 codes entered as final discharge diagnoses: A40.3, B95.3, G00.1 or M00.1

Table 6. Episodes of patient-file verified non-laboratory-confirmed IPD* and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up

	Number of episodes		Follow-up time, person-years		Episodes per 100 000 person-years, cluster-specific averages		Vaccine effectiveness (VE)		Incidence rate difference, cluster-specific averages	
patient-file verified non-laboratory-confirmed IPD* in the various study cohorts	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI	Reduction per 100 000 person-years	95% CI
3+1 and 2+1 schedule combined from dose 1	24	43	40423	20427	59•3	199•9	**71**	52-83	142	91-191
3+1 schedule from dose 1	16	43	20630	20427	82•3	199•9	**63**	34-80	121	58-182
2+1 schedule from dose 1	8	43	19793	20427	36•2	199•9	**80**	60-92	168	122-212
Catch-up 7-11 months	6	7	8672	4317	58•8	155•0	**63**	-39-91	98	-24-227
Catch-up 12-18 months	7	15	14804	7156	43•7	170•9	**78**	45-92	127	40-220

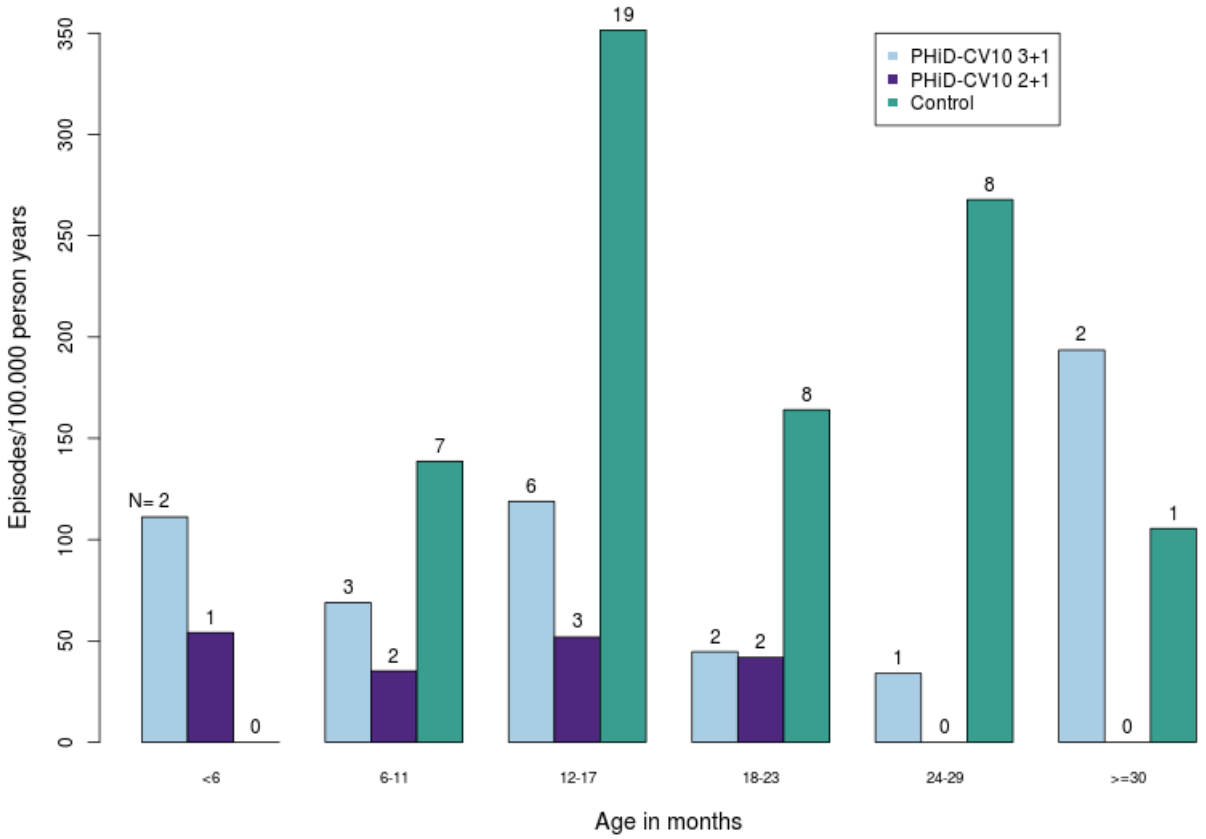
*Any of the following ICD-10 codes entered in any discharge notifications: A40.3, A40.9, A41.9, A49.9, G00, G00.1, G00.9, I30.1, M00, M00.1, M00.9, B95.3, or B95.5, patient-file verified as non-laboratory-confirmed IPD

Figure 1. Trial profile



The three plus one and two plus one clusters differed only for the infant schedules. Catch-up schedules were identical for the three plus one and two plus one clusters and were always combined for the analyses * 3 subjects not randomised nor vaccinated, ** includes one subject withdrawn from the register follow-up during the blinded follow-up period

Figure 2. Incidence of patient-file verified non-laboratory-confirmed IPD by treatment and age group in children enrolled before 7 months of age



Supplement table 1. Episodes of register-based non-laboratory-confirmed IPD or unspecified sepsis with various CRP cut-off levels as additional criteria and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up, 3+1 and 2+1 schedule combined from dose 1

	Number of episodes		Episodes per 100 000 person-years, cluster-specific averages		Vaccine effectiveness (VE)		Incidence rate difference, cluster-specific averages	
Endpoint definition	PHiD-CV10 group N=20 327	Control group N=10 200	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI	Reduction per 100 000 person-years	95% CI
Non-laboratory-confirmed IPD or unspecified sepsis*	87	87	212•9	421•5	**50**	32-63	207	127-286
Non-laboratory-confirmed IPD or unspecified sepsis, CRP≥40 mg/l, first	60	69	148	342	**56**	38-69	192	131-251
Non-laboratory-confirmed IPD or unspecified sepsis, CRP≥40 mg/l, highest during hospitalization	70	76	171	374	**54**	36-67	201	126-275
Non-laboratory-confirmed IPD or unspecified sepsis, CRP≥80 mg/l, first	41	51	96	259	**59**	39-73	162	104-220
Non-laboratory-confirmed IPD or unspecified sepsis, CRP≥80 mg/l, highest during hospitalization	47	58	111	293	**59**	40-72	181	120-240
Non-laboratory-confirmed IPD or unspecified sepsis, CRP≥120 mg/l, first	22	31	51	158	**65**	40-80	105	61-151
Non-laboratory-confirmed IPD or unspecified sepsis, CRP≥120 mg/l, highest during hospitalization	28	46	64	238	**69**	51-81	173	115-233

*First row as in article table 4 for comparison.

Supplement table 2. Episodes of patient-file verified non-laboratory-confirmed IPD with various CRP cut-off levels as additional criteria and the vaccine effectiveness for the 10-valent PHiD-CV during intention-to-treat follow-up, 3+1 and 2+1 schedule combined from dose 1

	Number of episodes		Episodes per 100 000 person-years, cluster-specific averages		Vaccine effectiveness (VE)		Incidence rate difference, cluster-specific averages	
Endpoint definition	PHiD-CV10 group N=20 327	Control group N=10 200	PHiD-CV10 group	Control group	VE point estimate (%)	95% CI	Reduction per 100 000 person-years	95% CI
Non-laboratory-confirmed IPD*	24	43	59•3	199•9	**71**	52-83	142	91-191
Non-laboratory-confirmed IPD, CRP≥40 mg/l, first	16	38	41	180	**79**	63-88	139	95-182
Non-laboratory-confirmed IPD, CRP≥40 mg/l, highest during hospitalization	19	41	48	190	**77**	60-87	143	96-189
Non-laboratory-confirmed IPD, CRP≥80 mg/l, first	11	30	29	142	**81**	64-91	113	72-154
Non-laboratory-confirmed IPD, CRP≥80 mg/l, highest during hospitalization	11	32	29	150	**83**	67-92	121	79-161
Non-laboratory-confirmed IPD, CRP≥120 mg/l, first	5	18	13	85	**86**	65-95	72	44-98
Non-laboratory-confirmed IPD, CRP≥120 mg/l, highest during hospitalization	6	25	15	121	**88**	72-95	106	69-143

*First row as in article table 6 for comparison.

Supplement figure. Graphic presentation of the relative incidences and vaccine-preventable disease incidences (VPDI) for case definitions of confirmed and non-laboratory-confirmed IPD or unspecified sepsis in the FinIP trial infant cohorts

Graph area	Definition	Incidence per 100 000 person-years
Whole white circle	Care notifications with ICD-10 diagnoses listed in Table 1	
Whole white circle minus the yellow circle	Case definition 1 (excl. laboratory-confirmed IPD)	422
Lower half of the white circle minus the yellow circle	Case definition 3 (excl. laboratory-confirmed IPD)	200
Yellow circle	Laboratory-confirmed IPD	80
Light blue oval with fill	Total VPDI (1+2+3)	282
VPDI 1	Laboratory-confirmed IPD prevented by PHiD-CV10	75
VPDI 2	Case definition 3 disease prevented by PHiD-CV10	142
VPDI 2+VPDI 3	Case definition 1 disease prevented by PCV10	142 + 65 = 207