Pneumococcal Conjugate Vaccine and Clinically Suspected Invasive Pneumococcal Disease

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abstract

OBJECTIVE: Ten-valent pneumococcal conjugate vaccine (PCV10) was earlier shown to reduce clinically suspected, non–laboratory-confirmed invasive pneumococcal disease (IPD) in a cluster-randomized trial (the Finnish Invasive Pneumococcal disease trial). PCV10 was introduced into the Finnish national vaccination program in September 2010 using a 3-dose schedule. We evaluated the impact of PCV10 on clinically suspected IPD among vaccine-eligible children in a population-based nationwide study.

METHODS: The target cohort eligible for vaccination program (children born June 2010–September 2013) was compared with 2 season- and age-matched (ages 3–42 months) reference cohorts before PCV10 introduction. The trial period (January 2009–August 2010) was excluded. Hospitals' inpatient and outpatient discharge notifications with *International Classification of Diseases, 10th Revision*, diagnoses compatible with IPD (A40.3/B95.3/G00.1/M00.1) and unspecified sepsis (A40.9/A41.9/A49.9/G00/G00.9/I30.1/M00/M00.9/B95.5) were collected from the national Care Register. Laboratory-confirmed IPD cases were excluded. Rates of register-based non–laboratory-confirmed IPD (or unspecified sepsis) before and after PCV10 implementation were calculated.

RESULTS: The rate of register-based non–laboratory-confirmed IPD episodes was 32 in 100 000 person-years in the vaccine-eligible target cohort and 94 in the combined reference cohorts. Relative rate reduction was 66% (95% confidence interval: 59–73) and absolute rate reduction 62 in 100 000 person-years. For the more sensitive case definition of register-based non–laboratory-confirmed IPD or unspecified sepsis, the relative rate reduction was 34% (95% confidence interval 29–39), but the absolute reduction was as high as 122 in 100 000 person-years.

CONCLUSIONS: This is the first report demonstrating nationwide PCV impact on clinically suspected IPD during routine vaccination program. The large absolute rate reductions observed have major implications for cost-effectiveness of PCVs.

WHAT'S KNOWN ON THIS SUBJECT: Conventional invasive pneumococcal disease (IPD) definition using laboratory confirmation lacks sensitivity. Using a vaccine-probe design, the FinIP trial showed that IPD disease burden and vaccine-preventable disease incidence were fourfold higher when a more sensitive outcome, clinically suspected IPD, was used.

WHAT THIS STUDY ADDS: Vaccine-preventable disease incidence (ie, absolute reduction due to PCV10 vaccination) during routine vaccination program was threefold with the more sensitive outcome of clinically suspected IPD compared with the conventional IPD definition. This has major implications for cost-effectiveness of PCVs.

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The reported rates of invasive pneumococcal disease (IPD) have conventionally been based on surveillance data of laboratory-confirmed disease, primarily isolation of *Streptococcus pneumoniae* from a normally sterile site by bacterial culture.[1–4] In Finland, the evaluation of the impact of the 10-valent pneumococcal conjugate vaccine (PCV10) in the national vaccination program showed that the relative rate reduction in culture-confirmed invasive disease among vaccine-eligible children was 80%, and the absolute reduction was 50 cases per 100 000 person-years.[5]

A cluster-randomized Finnish Invasive Pneumococcal disease (FinIP) trial was conducted in Finnish infants during 2009–2010.[6] The primary aim of the trial was to assess the effectiveness of PCV10 (Synflorix, GlaxoSmithKline Vaccines, Rixensart, Belgium) against laboratory-confirmed IPD using data collected through the National Infectious Diseases Register. The trial demonstrated excellent vaccine effectiveness against IPD of 94% (95% confidence interval [CI]: 77–99), with an absolute rate reduction of 75 per 100 000 person-years.[6] An additional analysis of the FinIP trial using administrative hospital discharge notification data[7] showed additional disease reduction of 207 of 100 000 person-years in hospital-diagnosed suspected IPD or unspecified sepsis for which no laboratory-confirmation was obtained. This novel case definition for IPD suggested that the additional disease burden was almost threefold compared with the specific case definition based on laboratory-confirmed IPD.

Here, we used a similar vaccine-probe design[8] to assess the population-based rates of suspected, non–laboratory-confirmed IPD preventable by PCV10 among all vaccine-eligible children during the first 3 years after national vaccination program introduction in Finland.

METHODS

We conducted a nationwide observational follow-up study in which study cohorts before and after national vaccination program introduction were compared. The annual birth cohort in Finland is ~60 000. Population data available through the Finnish Population Information System was used to estimate person-time denominator data.

National Vaccination Program

The national vaccination program vaccinations are administered in local municipal well-baby clinics free of charge. PCV10 was selected on the basis of a public tender and was introduced into the Finnish national vaccination program in September 2010. Children born on June 2010 or later were eligible for the national vaccination program to be immunized with a 3-dose schedule at 3, 5, and 12 months (2+1). No catch-up vaccinations were offered for older children. There was no previous use of PCV7 in the Finnish national vaccination program except for rare risk groups, and private use of PCV7 before the national vaccination program was estimated to be <2% on the basis of national sales data (http://raportit.nam.fi/raportit/kulutus/laakemyynti.htm). However, >30 000 children received PCV10 in the nationwide cluster-randomized PCV10 trial (FinIP) during 2009–2010,[6] which was ~20% of the corresponding birth cohort. After introduction to the national vaccination program, PCV10 uptake in the 2012 birth cohort was estimated to be 93% for the full 3-dose vaccination series (The data are available online [Finnish only]: https://www.thl.fi/fi/web/rokottaminen/kansallinen-rokotusohjelma/rokotuskattavuus/vuonna-2012-syntyneiden-lasten-rokotuskattavuus)

Study Cohorts

The target cohort eligible for PCV in the national vaccination program included all children born in Finland from June 1, 2010, through September 30, 2013, regardless of whether they had received the vaccine. We compared the target cohort to 2 season- and age-matched (ages 3–42 months) reference cohorts combined and selected a priori from calendar years 2003 to 2008 before the national vaccination program (Fig 1).[5]

The calendar period January 2009 to August 2010 was excluded from the cohort analysis because of the FinIP trial.[6]

Case Definitions and Data Collection

We used data from the national Care Register for Health Care, which is maintained at the National Institute for Health and Welfare (THL). The Care Register is a hospital discharge register that includes all inpatient and outpatient care notifications from hospitals with data on the patient, hospital, admission and discharge dates, *International Classification of Diseases, 10th Revision* (ICD-10) coded diagnoses at admission and at discharge, and various additional data (https://www.thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care).

We collected all care notifications with ICD-10 diagnoses (listed in the first 3 positions) compatible with IPD or unspecified sepsis as recorded by the hospital physicians (Table 1).

To identify the reported, culture-confirmed IPD cases, we used data from the National Infectious Diseases Register. We linked these culture-confirmed cases from national surveillance with cases identified in the Care Register by using the Finnish personal identity code and the dates of culture sampling and assigned diagnoses. Episodes of laboratory-confirmed IPD were excluded from the analyses unless stated otherwise. The national vaccination program impact on culture-confirmed IPD based on the National Infectious
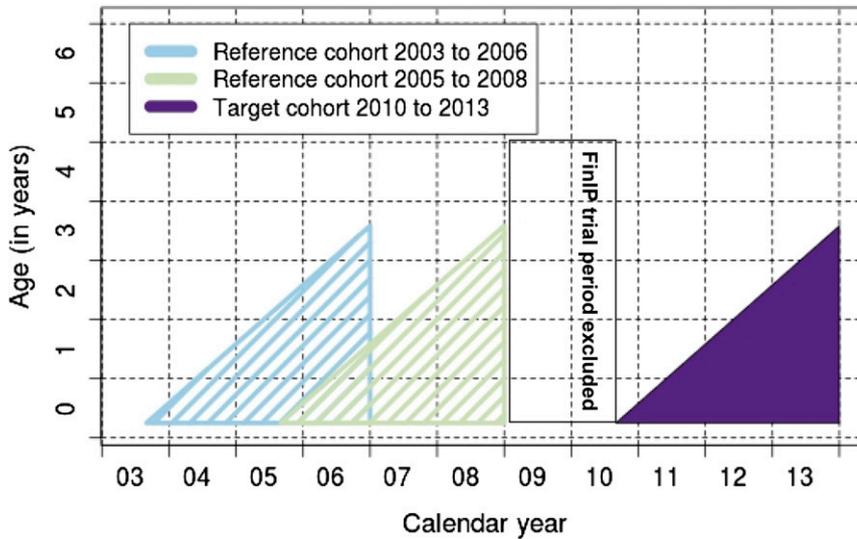
FIGURE 1
Cohorts for comparing PCV10 impact in vaccine-eligible children.

Diseases Register data has been published previously.[5]

On the basis of register records, we developed 2 case definitions with different sensitivity[7]:

1. Register-based non–laboratory-confirmed IPD or unspecified sepsis: admission or discharge notification with ICD-10 code compatible with invasive pneumococcal disease or unspecified sepsis (Table 1) assigned in the Care Register without confirmation as IPD by laboratory assays (isolation of *S pneumoniae* and/or detection of pneumococcal DNA/RNA from a normally sterile site).

2. Register-based non–laboratory-confirmed IPD: ICD-10 code compatible with IPD assigned in the Care Register as final discharge diagnosis (Table 1) without confirmation as IPD by laboratory assays. This is a subgroup of the more sensitive Case Definition 1.

We collected all notifications as defined earlier. Possible multiple notifications of the same child within 90 days since the first notification were combined into a single episode.

Episode rates in the study cohorts (vaccine-eligible vs noneligible before national vaccination program) were

compared using Poisson regression models. Relative rate reduction (expressed as percent) was calculated as (1 – relative risk) * 100%. Absolute rate reduction and the corresponding 95% CIs were estimated from the model parameters by using the delta method. For the primary analysis, reference cohorts were combined when comparing with the target cohort. Because of an increasing temporal trend of the register-based outcomes before 2009 (Fig 2), an additional analysis was conducted in

which only the most recent reference cohort was compared with the target cohort.

The study plan was approved by the THL institutional review board. Permissions to use the register data were obtained from the relevant register controllers at THL.

RESULTS

The annual incidence rates of register-based non–laboratory-confirmed and culture-confirmed IPD from 2004 through 2013 in children 3 to 42 months of age are shown in Fig 2. There was an increasing trend from 2004 through 2007, which then plateaued to turn into a sharp decline in 2012 and 2013.
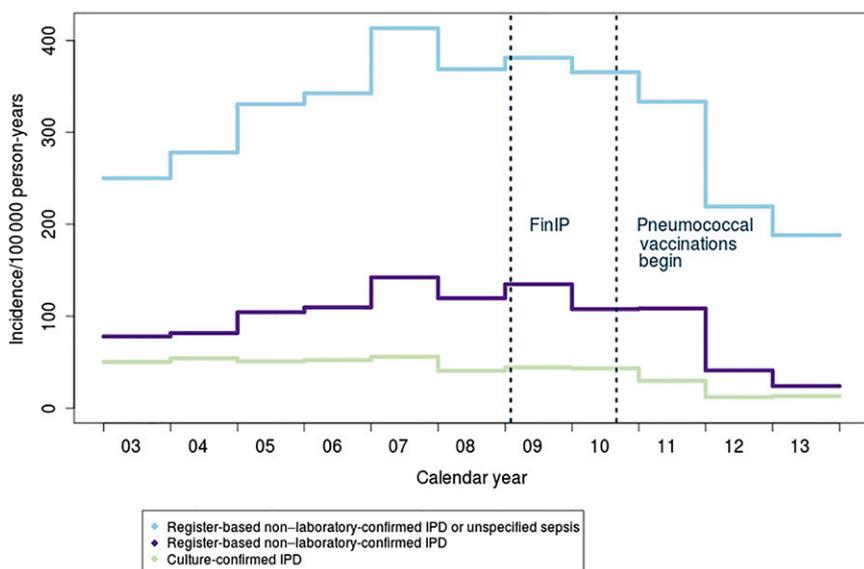
In the analyzed cohorts, there were a combined 3124 episodes of register-based non–laboratory-confirmed IPD or unspecified sepsis of which 714 (23%) were episodes of register-based non–laboratory-confirmed IPD. The results of the cohort analyses are shown in Table 2. For the register-based non–laboratory-confirmed IPD or unspecified sepsis, the absolute reduction due to PCV vaccinations in the national vaccination program was 122 per 100 000 person-years (95%

TABLE 1 ICD-10-Coded Diagnoses Compatible With IPD or Unspecified Sepsis Used in the Analysis

ICD-10 Code	Diagnosis in Text	Percentage of All Diagnoses in Reference Cohorts
A40.3[a]	Sepsis due to *S pneumoniae*	30
G00.1[a]	Pneumococcal meningitis	1
M00.1[a]	Pneumococcal arthritis and polyarthritis	<1
B95.3[a]	*S pneumoniae* as the cause of diseases classified elsewhere	1
A40.9	Streptococcal sepsis, unspecified	2
A41.9	Sepsis, unspecified organism	45
A49.9	Bacterial infection, unspecified	18
G00	Bacterial meningitis, not elsewhere classified	<1
G00.9	Bacterial meningitis, unspecified	2
I30.1	Infective pericarditis	<1
M00	Pyogenic arthritis, not elsewhere classified	<1
M00.9	Pyogenic arthritis, unspecified	2
B95.5	Unspecified *Streptococcus* as the cause of diseases classified elsewhere	<1

All codes in the table are compatible with register-based non–laboratory-confirmed IPD or unspecified sepsis (Case Definition 1).
[a] ICD-10 code specific for diseases caused by *S pneumoniae* (Case Definition 2, register-based non–laboratory-confirmed IPD).

FIGURE 2
Incidence of the IPD-related outcomes by calendar year in children 3 to 42 months of age. In this graph, the register-based outcomes also include the culture-confirmed cases.

CI: 100–144), which was more than twofold compared with laboratory-confirmed IPD (50 per 100 000 person-years).[5] We noted reductions for all the individual ICD-10 codes, except for A49.9 and the rarely used M00.9, and B95.5.

The incidences of register-based outcomes were higher in the second reference cohort (395 per 100 000 person-years for the register-based non-laboratory-confirmed IPD or unspecified sepsis) compared with the first reference cohort (322 per 100 000 person-years). This was due to the increasing temporal trend before 2009 (Fig 2). When using only the more recent second reference cohort in the analysis, both the relative and absolute rate reductions were higher: 71% (95% CI: 64%–77%) and 77 per 100 000 person-years for the register-based non–laboratory-confirmed IPD, respectively, and 40% (95% CI: 35%–45%) and 158 per 100 000 person-years for the register-based non–laboratory-confirmed IPD or unspecified sepsis. When using the most sensitive outcome and adding the rate reduction against laboratory-confirmed IPD (50 per 100 000),[5] the

estimated PCV10-preventable incidence of IPD-like illness was thus 208 per 100 000 person-years.

Ten children died during the hospitalization, 2 in the target cohort and 8 in the 2 reference cohorts combined. Of these, 2 in the target cohort and 6 in the reference cohorts combined had a primary diagnosis compatible with IPD or unspecified sepsis.

The relative mortality reduction for any death was 51% (95% CI: –94 to 93) and 35% (95% CI: –181 to 90) for cases with primary diagnosis compatible with IPD or unspecified sepsis.

DISCUSSION

This is the first report showing PCV impact on clinically suspected IPD during routine infant national vaccination program. The point estimates for relative rate reductions were lower compared with that reported for culture-confirmed IPD (80%),[5] but the absolute reduction was more than twofold for the most sensitive outcome of non–laboratory-confirmed IPD or unspecified sepsis (122 vs 50 per 100 000 person-

years). There was also a trend toward lower mortality in the cohort eligible for the national vaccination program, but the finding was not statistically significant.

The current results are compatible with the vaccine effectiveness estimates for the identical case definitions reported from the FinIP trial.[7] However, both the relative and absolute reduction estimates for the more sensitive case definition of register-based non–laboratory-confirmed IPD or unspecified sepsis were somewhat lower in the current study. This may be partly due to the inclusion of unvaccinated children in the vaccine-eligible cohort (vaccination coverage estimated at 93%) and the inclusion of vaccinated children in the reference cohorts (estimated <2%) and the higher incidence of this outcome in the FinIP control group, which in turn may be explained by the increasing trend in register-based outcomes before 2009 (Fig 2). Statistical adjustment to account for similar increasing trends as observed in this study have been used (eg, Miller et al),[9] in which the observed increasing trend before the vaccine introduction was extrapolated to the period during the national vaccination program. Although useful additions to a conventional before-and-after comparison, such adjustments necessitate rather strong model assumptions. Instead of adjustment, we performed a more simple additional analysis by constraining the comparison with the most recent reference cohort, which produced estimates closer to those reported from the FinIP trial. The observed increase in incidence from 2003 through 2008 may have been associated with increased awareness of the clinical IPD syndrome among pediatricians in Finland.

Simonsen and coworkers have also reported PCV impact results from the United States based on hospital discharge register data.[10,11] They

TABLE 2 Numbers and Rates of Register-Based IPD and Laboratory-Confirmed Episodes and the Associated Vaccine-Prevented Disease Burden by the National PCV10 Vaccine Program

Case Definition	No. of Episodes		Episodes/100 000 PY		Relative Rate Reduction		Absolute Rate Reduction
	NVP-Eligible Cohort[a]	Before NVP[b]	NVP Eligible	Before NVP	Point Estimate (%)	95% CI	Episodes/100 000 PY (95% CI)
Register-based non–laboratory-confirmed IPD or unspecified sepsis[c]	791	2333	237	359	34	29–39	122 (100–144)
Register-based non–laboratory-confirmed IPD[d]	106	608	32	94	66	59–73	62 (52–71)
Laboratory-confirmed IPD[5]	43	409	13	63	80	72–85	50 (43–57)

NVP, national vaccination program; PY, person-years.

[a] Born in 2010–2013, follow-up 334 088 y.

[b] Cohort born in 2003–2008 follow-up 649 877 y.

[c] Any of the following ICD-10 codes 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. Culture-confirmed IPD cases were excluded.

[d] Any of the following ICD-10 codes entered as final discharge diagnosis: A40.3, G00.1, M00.1, or B95.3. Culture-confirmed IPD cases were excluded.

only included inpatient hospital discharge data and were not able to differentiate between the culture-confirmed and nonconfirmed IPD cases. They reported relative rate reduction, which was similar to our more specific case definition, but the absolute rate reduction was negligible, mainly because of extremely low incidence, even manyfold lower than reported for culture-confirmed IPD.[4]

The register-based outcome definitions are unspecific compared with 100% specific case definition of culture-confirmed IPD. However, the major pitfall of culture-confirmed IPD is poor sensitivity of blood culture, the recent estimate being 31%.[7] Thus, a considerable proportion of true cases remain undetected. The purpose of these less specific and more sensitive register-based outcome definitions is to tease out the total disease burden caused by the pneumococcus and the vaccine preventable disease due to vaccine antigens in the PCV by using the vaccine-probe approach.[8]

We performed no patient-file review for the cases of non–laboratory-confirmed IPD because of the high number of episodes collected from all pediatric hospitals around the country. However, the outcomes have been validated previously against patient-file-verified outcomes. The results for the different case definitions were comparable, and the clinical features of nonconfirmed cases were indistinguishable from culture-confirmed IPD cases.[7] Although the case definitions of clinically suspected IPD may include disease caused by other pathogens besides *S pneumoniae*, this misclassification is unlikely to bias the evaluation of the absolute disease burden prevented by the use of the vaccine.

The before-and-after design used in this analysis is prone to many sources of bias. However, our results are consistent with the findings reported earlier from the FinIP trial setting. Naturally, the trial design with parallel randomized controls is less prone to bias, and its results should be considered more valid in quantitative terms. Nevertheless, the current evaluation was more powered, resulting in narrower CIs and therefore more precise estimates.

Our results are relevant to both high-income and less developed countries. Although considerable differences in clinical diagnosis (including coding practices) and treatment exist, it is clear that the sensitivity of detection of pneumococcal invasive disease

using confirmation by culture is low. Furthermore, in countries with limited access to hospitals with adequate diagnostic evaluation, the disease burden estimates based on culture-confirmed disease are probably an even more severe underestimation of the true invasive pneumococcal disease.

CONCLUSIONS

Use of sensitive case definitions, such as clinically suspected IPD, in the evaluation of the total disease burden prevented by the vaccination program is important for understanding the total burden of pneumococcal disease and the cost-effectiveness of public health interventions.

ABBREVIATIONS

CI: confidence interval
FinIP: Finnish Invasive Pneumococcal disease trial
ICD-10: *International Classification of Diseases, 10th Revision*
IPD: invasive pneumococcal disease
PCV: pneumococcal conjugate vaccine
THL: National Institute for Health and Welfare of Finland

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