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Long-term impact of 10-valent pneumococcal conjugate vaccination on invasive pneumococcal disease among children in Finland

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ABSTRACT

Background: The ten-valent pneumococcal conjugate vaccine (PCV10) was introduced into the Finnish National Vaccination Programme (NVP) in September 2010. The impact of PCV10 vaccination against invasive pneumococcal disease (IPD) in vaccine-eligible children has been high. We evaluated the long-term impact of PCV10 vaccination against IPD in vaccine-eligible and older, unvaccinated children six years after PCV10 introduction with a special focus on cross-protection against PCV10-related serotypes (serotypes in the same serogroups as the PCV10 types).

Methods: We used data on IPD from the national, population-based surveillance. A target cohort of vaccine-eligible children (born June 2010 or later) was followed from 3 months of age until the end of 2016. For the indirect effect, another cohort of older PCV10-ineligible children was followed from 2012 through 2016. IPD rates were compared with those of season- and age-matched reference cohorts before NVP introduction.

Results: Among vaccine-eligible children, the incidence of all IPD decreased by 79% (95% CI 74–83%). There was a statistically significant reduction in the incidence of 6A IPD, but for 19A, the reduction was non-significant and the incidence of 19A increased towards the end of the study period in the older vaccine-eligible children. The increase in non-PCV10 related serotypes was non-significant.

Results: In the unvaccinated older children, the incidence of all IPD decreased by 33% (95% CI 8–52%) compared to the reference cohort, and there was no impact on serotype 6A or 19A IPD.

Conclusion: Overall, the impact of PCV10 vaccination on IPD was high in vaccine-eligible children, with a major reduction in vaccine-type disease, and without notable replacement by other serotype groups. Our data suggest that PCV10 results in long-lasting direct cross-protection against 6A IPD. For 19A, no net reduction was observed six years after NVP introduction in the vaccine-eligible cohort. The indirect impact on IPD in unvaccinated children sustained.

1. Introduction

It has been estimated that *Streptococcus pneumoniae* (the pneumococcus) caused about 14.5 million episodes of serious pneumococcal disease, including pneumonia, meningitis and febrile bacteraemia, worldwide in 2000 [1]. The introduction of pneumococcal conjugate vaccines (PCVs) since 2000 has afforded excellent direct protection for vaccinated children against invasive pneumococcal disease (IPD) caused by serotypes included in the vaccines. At the same time, the impact has extended to unvaccinated populations through indirect protection due to reduced vaccine-type carriage in vaccinated children and the subsequently reduced transmission. However, replacement in carriage and subsequent disease by serotypes not included in the vaccines has partly eroded the direct and indirect benefits of vaccination across all age groups and is a growing concern [2–8].

In addition to protection against the vaccine serotypes, PCVs have been documented to provide cross-protection against some vaccine-related serotypes, i.e. serotypes that belong to the same serogroups as the vaccine serotypes. Previous studies have shown

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that the seven-valent vaccine (PCV7, Prevenar, Pfizer), which included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, reduced also IPD caused by 6A IPD, but not by 19A or 6C [3,9,10]. Serotype 19A IPD was among the most common causes of replacement disease after PCV7 introduction [3,4,11,12]. In 2010, PCV13 (Prevenar 13, Pfizer) with six additional serotypes (1, 3, 5, 6A, 7F, and 19A) replaced PCV7. Recently, cross-protection against 6C from the 6A component of PCV13 has been reported [13].

The 10-valent pneumococcal conjugate vaccine (PCV10, Synflorix, GSK Vaccines) including serotypes in the PCV7 + 1, 5 and 7F was introduced into the Finnish National Vaccination Programme (NVP) after a public tender in September 2010. In addition to providing protection against vaccine serotypes, PCV10 also had reduced incidence of 6A and 19A IPD among vaccine-eligible children in Finland three years after vaccine introduction into NVP [6]. Here we report updated data about the overall and indirect long-term impact of PCV10 vaccination against IPD among vaccine-eligible and unvaccinated older children, with a special focus on cross-protection against the vaccine-related serotypes.

2. Methods

2.1. The vaccination program

PCV10 was introduced into the NVP in September 2010. Children born on or after June 1, 2010, are eligible for vaccination with a 2 + 1 schedule (primary series at 3 and 5 months and a booster dose at 12 months of age). There was no catch-up vaccination at PCV10 introduction. In the birth cohort of 2012, the uptake of at least one dose of PCV10 was estimated at 94% based on data in the National Vaccination Register [14].

In 2009–2011, the effectiveness of PCV10 against vaccine-type IPD was investigated in a nation-wide FinIP vaccine trial, in which over 30,000 children born 2008 through May 2010 were vaccinated with PCV10 [15]. During the FinIP trial, the PCV10 vaccine coverage varied regionally from 0 to 60%. Prior to the FinIP trial and the introduction of PCV10 into the NVP, no pneumococcal conjugate or polysaccharide vaccines were routinely used for healthy children and adults, and the vaccine uptake was estimated to be less than 2%.

Influenza vaccine was introduced into the NVP in the beginning of the influenza season 2007/2008 for children aged 6–36 months. The uptake of this age group has been estimated to vary between 15 and 40% [14].

2.2. Data sources and case definition

IPD cases were identified from the National Infectious Diseases Register (NIDR), a population-based electronic laboratory surveillance system maintained by the National Institute for Health and Welfare (THL). It is mandatory for all clinical microbiology laboratories to notify all isolations of *Streptococcus pneumoniae* from blood or cerebrospinal fluid to NIDR and the process has been automated to send electronic reports to the database. Furthermore, the corresponding case isolates are sent to the national reference laboratory at THL for confirming the species and serotyping. Currently, more than 97% of the case isolates are received [16]. IPD case was defined as isolation of *S. pneumoniae* from blood or cerebrospinal fluid. The IPD surveillance in Finland and the THL laboratory methods have been described earlier [6,17].

Vaccination status of each IPD case was verified from the National Vaccination Register and local electronic vaccination cards. Data on comorbidities were obtained from the national hospital discharge register (the Care Register for Health Care at THL). The study population was determined by using data from the Finnish Population Information System. All register-based information was linked by using the unique national personal identity code which is assigned to all permanent residents in Finland.

IPD cases were categorized according to the causative serotype into three mutually exclusive groups: PCV10 serotypes, PCV10-related serotypes (i.e. serotypes belonging to the same serogroups as vaccine types; in the data: 6A, 6C, 7C, 9N, 18B, 19A, 23A, 23B), or non-PCV10 serotypes. The impact of PCV10 vaccination on each of the three serotype groups was evaluated. In addition, the impact was assessed separately for serotypes 6A and 19A.

2.3. Overall impact of PCV10 vaccination in vaccine-eligible children

To estimate the overall impact of PCV10 vaccination on IPD, the relative reduction in the incidence of IPD for each serotype group was estimated by comparing a target cohort, comprising all vaccine-eligible children irrespective of vaccination status and born between June 2010 and September 2016, to a season- and age-matched reference cohort in years 2002–2008 (Fig. 1, panel A). The children who were enrolled in the FinIP trial in years 2009–2010 were excluded from the analysis. The follow-up period started at 3 months of age (the first scheduled vaccination dose) and lasted until the end of December 2016 for the target cohort and December 2008 for the reference cohort. The follow-up thus included children from 3 to 78 months of age.

To assess time trends in the age-specific risk of 19A IPD, age-specific cumulative hazards were calculated for the target and reference cohorts.

2.4. Indirect impact of PCV10 vaccination in unvaccinated children

To estimate the indirect impact of PCV10 vaccination against IPD, the relative reduction in the incidence of IPD for each serotype group was estimated by comparison of unvaccinated cohorts of older children after and before PCV10 introduction (Fig. 1, panel B). The unvaccinated target cohort was chosen to comprise children born between January 2006 and May 2010. Children vaccinated in the FinIP trial with PCV10 were excluded. The age- and season-matched reference cohort comprised all children born between January 2000 and May 2004. The follow-up period started in January 2012 (2006) and lasted until the end of December 2016 (2010) for the target (reference) cohort. The follow-up included children from 19 to 131 months of age.

2.5. Statistical methods

Comparison of IPD incidence rates was performed by using Poisson regression. Vaccine impact was defined as $(1 - \text{incidence rate ratio}) * 100\%$, comparing the target and reference cohorts. Absolute rate reductions and the corresponding confidence intervals were calculated from the parameter estimates with the delta method. No adjustments were made for comorbidities or influenza vaccinations in the NVP because of the small number of cases, evenly distributed comorbidities in the study cohorts and the low coverage of the influenza vaccinations. Statistical significance was deemed at the 5% level. Statistical software R version 3.4.2 [18] was used for all analyses.

2.6. Ethical considerations

As part of its statutory tasks, the National Institute for Health and Welfare (THL) is obliged to monitor the effectiveness and safety of the vaccines used in NVP. The study plan was approved by the THL institutional review board (May 23, 2013). Permissions to use the register data for research were obtained from the relevant register controllers at THL (THL/1090/6.02.00/2013).

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