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Vaccine-preventable disease incidence of pneumococcal conjugate vaccine in the Finnish invasive pneumococcal disease vaccine trial

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ABSTRACT

Estimation of the full disease burden caused by *Streptococcus pneumoniae* is challenging due to the difficulties in assigning the aetiology especially in lower and upper respiratory infections. We estimated the pneumococcal disease burden by using the vaccine-preventable disease incidence (VPDI) of PHiD-CV10 vaccine (GSK) in our clinical trial setting.

Finnish Invasive Pneumococcal disease (FinIP) trial was a cluster-randomized, double-blind trial in children <19 months who received PHiD-CV10 in 52 clusters or hepatitis B/A vaccine as control in 26 clusters according to 3+1 or 2+1 schedules (infants < 7 months) or catch-up schedules (children 7–18 months). Outcome data were collected using Finnish routine health-care registers, consisting of THL National Infectious Diseases Register, THL Care register, and Benefits Register of Social Insurance Institution of Finland. Blinded follow-up lasted from the date of first vaccination (trial enrolment Feb-2009 through Aug-2010) to January 31, 2012 for Invasive Pneumococcal Disease (IPD) and to end of December 2011 for four other outcomes: non-laboratory-confirmed IPD, hospital-diagnosed pneumonia, tympanostomy tube placements, and antimicrobial purchases. VPDI was estimated as difference in disease incidences between PHiD-CV10 clusters and control clusters.

Altogether >47,000 children were enrolled. In 30,527 vaccinated infants <7 months at first dose, the VPDIs per 100,000 person-years were 75 for laboratory-confirmed IPD, 210 for non-laboratory-confirmed IPD, 271 for hospital-diagnosed pneumonia, 1143 for any tympanostomy tube placements and 11,381 for antimicrobial outpatient prescription, mainly due to otitis media.

In a European developed-country setting, over 95% of the disease episode reductions in vaccinated children were seen in mild upper respiratory infections. The VPDIs of severe diseases are underestimated, because the majority of invasive disease goes undetected with routine blood-culture-based definitions. Evaluation of the absolute reduction achievable with vaccinations using sensitive case detection is essential for understanding the full disease burden, for valid cost-effectiveness analyses and for appropriate vaccination policy decisions.

Registration: ClinicalTrials.gov, NCT00861380 and NCT00839254.

1. Introduction

Streptococcus pneumoniae, pneumococcus, causes a number of different clinical syndromes including invasive diseases like meningitis and sepsis/bacteraemia, pneumonia and upper respiratory infections like otitis media in children and sinusitis in adults. The disease burden is highest among infants and the elderly. Pneumococcus remains the number one killer in developing countries, especially due to the high disease burden of pneumonia, but mortality in highly developed countries has reduced to low levels although pneumonia remains the most common cause of infectious diseases death [1–3].

Pneumococcal vaccines have been developed to fight this disease burden. These vaccines are comprised of the polysaccharide antigens which coat the bacterial surfaces (capsules) and are important for the pathogenicity. Over 90 serologically different polysaccharide antigens have been identified so far. The polysaccharide vaccine (Pneumovax, Merck, USA) contains 23 different

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polysaccharide antigens. To overcome the poor immunogenicity of the polysaccharide vaccine in infants the polysaccharide antigens have been conjugated to protein carriers to elicit also a T-cell dependent immune reaction. Currently two conjugate vaccines are available, a 10-valent Pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10, Synflorix, GSK, Belgium) and a 13-valent vaccine conjugated to the nontoxic diphtheria-toxin analogue CRM197 (13-PnCRM197, Prevenar 13, Pfizer, USA). The latter is the successor of the 7-valent PnCRM197 (Prevenar, Pfizer), which has the most extensive documentation in pre- and post-marketing studies.

Evidence of the full impact of the vaccines on pneumococcal disease burden has remained scattered in the scientific literature. First, the estimation of the pneumococcal disease burden is challenging due to difficulties in assigning the aetiology especially in lower and upper respiratory infections [4]. Second, only a handful of high-quality randomised trials estimating clinical efficacy or effectiveness have been conducted with the pneumococcal vaccines either in the low-risk developed country settings [5–9] or in the high-risk settings [10–13]. Third, the outcomes used have been mostly selected on the basis of specificity to show the relative vaccine effectiveness (VE) in phase III efficacy trials; we recently showed for invasive pneumococcal disease that the routinely used culture-based detection is poorly sensitive, and thus severely underestimates the true disease burden and vaccine impact [14]. And finally, in most studies only part of the clinical syndromes associated with pneumococcus have been included.

Vaccine probe designs based on randomised clinical trial data can overcome some of these challenges [15,16]. Reduction of disease burden in vaccinated individuals and populations can be inferred to be due to the vaccine, i.e. the pathogens covered by the vaccine antigens, in case valid study designs, like randomised trials, are being meticulously followed. In the Finnish Invasive Pneumococcal disease Vaccine Trial (FinIP), we estimated the total PHiD-CV10 vaccine-preventable disease incidence (VPDI) using our cluster-randomised clinical trial setting.

2. Methods

The FinIP vaccine trial was a nation-wide phase III/IV cluster-randomised, double-blind field trial conducted in 2009–2012 by the National Institute for Health and Welfare (THL) in collaboration with municipal health care centres and their local well-baby clinics and GSK as trial sponsor. Children enrolled in the parallel acute otitis media (AOM) and carriage trial conducted by the Tampere University Vaccine Research Centre (TAUVRC) contributed to the follow-up [17]. The study design has been presented previously [8]. The full protocol is available at www.finip.fi. This trial and nested acute otitis media trial are registered at ClinicalTrials.gov, NCT00861380 and NCT00839254.

Briefly, children six weeks to 18 months of age were eligible for enrolment after written parental consent in case they had no specific or general contraindications to routine paediatric vaccinations. The 78 study clusters were constructed on geographical areas using health care centre, municipality and well-baby clinic boundaries. Two infant vaccination schedules for children enrolled before 7 months of age, either 3+1 or 2+1, were used in a non-blinded cluster-randomised fashion. Additionally, children 7–18 months of age received either 2+1 or 1+1 schedules, but these schedules are not evaluated in this report for sake of simplicity and since the routine vaccination programs include mainly young infants. A randomisation ratio of 2:2:1:1 was used to assign PHiD-CV10 3+1, PHiD-CV10 2+1, Control 3+1 and Control 2+1, respectively in double-blind manner. Thus, PHiD-CV10 was used in two thirds of clusters (N = 52) and one third of clusters served as controls (N = 26).

2.1. Vaccines and vaccinations

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 nontypeable *Haemophilus influenzae*, tetanus or diphtheria toxoids. In the control clusters, hepatitis B vaccine was used for children enrolled before 12 months of age and hepatitis A vaccine for children enrolled between 12 and 18 months of age. Vaccines were administered intramuscularly into the thigh.

Infants were vaccinated according to either 3+1 or 2+1 schedule if enrolled before seven months of age. Children enrolled in 3+1 schedule clusters received three doses (with intervals of at least 4 weeks) and children enrolled in 2+1 schedule clusters two doses (with intervals of at least 8 weeks) in primary vaccinations followed by a booster dose at least four months after the last primary dose, but not earlier than at 11 months of age.

2.2. Outcome data collection

Surveillance for effectiveness was based on the case definitions developed on data available in the established administrative national health registers as previously published (Table 1). In order to cover the whole spectrum of pneumococcal disease, the following outcomes related to pneumococcal infections were included: laboratory-confirmed IPD, non-laboratory-confirmed IPD, pneumonia, and two surrogate outcomes for otitis media: tympanostomy tube placement for recurrent, prolonged and complicated otitis and antimicrobial purchases for uncomplicated AOM. The definitions for the outcomes and duration of episodes are provided in Table 1. For capturing the VPDI as comprehensively as possible, the most sensitive of the case definitions used for each outcome disease in previous analyses was applied in the current analysis.

A composite outcome related to pneumococcal disease syndromes during the follow-up of interest was constructed out of five different outcomes. To avoid counting the same disease episode more than once, all pneumonia cases that concurred with either laboratory or non-laboratory-confirmed IPD were omitted. In addition, the first outpatient antimicrobial purchase that occurred during any IPD, pneumonia or tympanostomy surgery episode was excluded (assuming it was prescribed for the primary event and could therefore not be regarded as a surrogate for AOM).

The health-care related costs for each outcome were taken from a published economic evaluation of pneumococcal conjugate vaccination in Finland [18] updated to the current prices. The costs averted were calculated by multiplying the cost of a single disease episode with the VPDI of the disease to obtain the costs averted per 100,000 person-years. All outcome-specific costs were then summed up and the share of each specific outcome of the total costs averted was calculated.

2.3. Statistical analysis

Blinded intention-to-treat follow-up period of the FinIP trial started from the date of first vaccination (Feb 2009 through Oct 2010) and ended on January 31, 2012 for culture-confirmed IPD and on December 31, 2011 for all the other outcomes.

Since no major differences have been observed between the relative VE estimates of the 3+1 and 2+1 PHiD-CV10 schedules in the FinIP trial [8,14,19–21], the two schedules were combined to increase the power in the analysis and compared to the control group.

For the analysis of the VE negative binomial model was used to account for between-cluster variability in the incidence. Frequencies of episodes were grouped by cluster and the cluster-specific person-years were used as weights in the analysis. Factors used