Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of pneumococcal *Haemophilus influenzae* protein D conjugate vaccine against pneumonia in children: A cluster-randomised trial

T.M. Kilpi [a,*], J. Jokinen [a], T. Puumalainen [a], H. Nieminen [b], E. Ruokokoski [a], H. Rinta-Kokko [a], M. Traskine [c], P. Lommel [c], M. Moreira [c], J. Ruiz-Guinazu [c], D. Borys [c], L. Schuerman [c], A.A. Palmu [b]

[a] Department of Health Protection, National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland
[b] Department of Health Protection, National Institute for Health and Welfare, FinnMedi I, Biokatu 6, FI-33520 Tampere, Finland
[c] Vaccine Research and Development, GSK, Parc de la Noire Epine, 20, Avenue Fleming, 1300 Wavre, Belgium

ARTICLE INFO

Article history:
Received 21 November 2017
Received in revised form 30 July 2018
Accepted 8 August 2018
Available online xxxx

Keywords:
Vaccine effectiveness
Pneumococcus
Clinical trial
Pneumonia
Infant

ABSTRACT

Background: Pneumococcal conjugate vaccines have potential to prevent significant proportion of childhood pneumonia. Finnish Invasive Pneumococcal disease vaccine trial was designed to assess the vaccine effectiveness (VE) of the 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) against several outcomes. We now report results for pneumonia.

Methods: In this nationwide, cluster-randomised, double-blind trial, children younger than 19 months received PHiD-CV10 in 52 clusters or hepatitis vaccines as control in 26 clusters. Infants younger than 7 months at the first vaccination received either 3+1 or 2+1 vaccination schedule, children aged 7–11 months received 2+1, and those 12–18 months of age two-dose schedule. All hospitalizations and outpatient visits to hospital associated with ICD-10 codes compatible with pneumonia were identified through the National Care Register and 1–3 frontal chest X-ray images per event were collected. External readers who were unaware of the patients' vaccination status retrospectively interpreted the images. The evaluated outcomes were hospital-diagnosed, hospital-treated pneumonia as primary diagnosis, and radiologically confirmed pneumonia during the blinded, intention-to-treat follow-up period from the first vaccination to the end of 2011. Total VE was calculated as 1 minus rate ratio of all pneumonia episodes.

Results: 47 366 children were enrolled from February 2009, to October 2010. VE against all episodes of hospital-diagnosed pneumonia was 27% (95% confidence interval [CI]: 14%, 38%), 32% (95% CI: 3%, 52%), and 23% (95% CI: −5%, 44%) in subjects enrolled at age <7, 7–11, and 12–18 months, respectively. Corresponding rate reductions were 3.4, 4.7, and 2.5 per 1000 person-years. VE estimates against pneumonia with alveolar consolidation or pleural effusion (WHO criteria) in the three cohorts were 45% (95% CI: 26%, 60%), 56% (95% CI: 14%, 77%), and 48% (95% CI: 2%, 73%), respectively.

Conclusion: PHiD-CV10 vaccination remarkably reduced disease burden due to pneumonia in infants and young children.

Clinical trial registration: Main trial NCT00861380, nested carriage and otitis media trial NCT00839254 (ClinicalTrials.gov).

© 2018 Published by Elsevier Ltd.

1. Introduction

Pneumonia causes a considerable disease burden accounting for 15% of deaths in children under 5 years worldwide [1]. *Streptococcus pneumoniae* is regarded as the most common bacterial cause of childhood pneumonia [2,3]. Pneumococcal conjugate vaccines (PCVs) were introduced into infant immunisation programs throughout the world during the 2000s, which resulted in considerable decrease in vaccine-type invasive pneumococcal disease (IPD) in both vaccinated and unvaccinated populations [4–6]. However, IPD has been estimated to represent only 4% of the 14.5 million pneumococcal cases (excluding upper respiratory disease) occurring annually in children younger than 5 years worldwide, the remaining 96% being attributed to pneumonia [7]. Moreover, the total burden of IPD has not been reduced as much

* Corresponding author.
E-mail address: terhi.kilpi@thl.fi (T.M. Kilpi).

https://doi.org/10.1016/j.vaccine.2018.08.020
0264-410X/© 2018 Published by Elsevier Ltd.

Please cite this article in press as: Kilpi TM et al. Effectiveness of pneumococcal *Haemophilus influenzae* protein D conjugate vaccine against pneumonia in children: A cluster-randomised trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.08.020

as vaccine-type IPD, since non-vaccine serotypes have to a variable extent replaced vaccine types as causes of IPD [5,6,8,9]. These observations highlight the importance of paying attention to the total disease burden rather than its fractions (e.g. vaccine-type or invasive disease) when assessing the public health impact of vaccination programs. Recently, the 13-valent PCV was effective in preventing vaccine-type pneumonia in the elderly, but not in preventing community-acquired pneumonia from any cause [10,11]. Additionally, the value of vaccination should not be characterized solely by relative efficacy against a highly specific outcome, when public health decision makers also need reliable estimates of vaccine-preventable disease incidence (VPDI) of significant clinical syndromes [12].

It is particularly challenging to assess the impact of any vaccination on pneumonia, because its clinical diagnosis is far from unambiguous, the clinical syndrome of pneumonia can be caused by multiple pathogens and the microbial cause of an individual case of pneumonia cannot usually be confirmed in clinical practice. When a pneumococcal vaccine is introduced into the national immunisation program, it may be very difficult to say, whether or not the vaccination program induces significant reduction in the incidence of pneumonia, which tends to fluctuate by season and epidemics caused by other pathogens. Because of these etiological and epidemiological characteristics, randomised controlled trials are particularly valuable for defining the vaccine-preventable burden of pneumonia and also for estimating which proportion of pneumonia can be attributed to a specific pathogen, in this case *Streptococcus pneumoniae*. Five randomised controlled trials have previously published results on the effectiveness of PCVs for pneumonia in children [13–17]. These studies were conducted in Africa, Asia, North and South America. They investigated 7-, 9-, 10- or 11-valent vaccines with three different carrier proteins or protein combinations and produced variable estimates for both vaccine effectiveness (VE) and vaccine-preventable disease incidence.

The Finnish Invasive Pneumococcal disease (FinIP) vaccine trial is the first European randomised controlled trial to investigate PCV effectiveness in children. The vaccine evaluated in this trial was the 10-valent pneumococcal non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine (PHiD-CV10, *Synflorix*, GSK, Belgium) [18]. We have previously reported VE of PHiD-CV10 for vaccine-type IPD (primary outcome) [18], overall and clinically suspected IPD [19] and some otitis media related outcomes [20,21]. We here report the results for one of the secondary objectives of assessing total VE for hospital diagnosed all-cause pneumonia with or without radiologic findings.

2. Methods

2.1. Trial design

FinIP vaccine trial was a nation-wide cluster-randomised, double-blind trial designed to assess the effectiveness of PHiD-CV10 against diseases caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Detailed design has been previously presented [18]. The pneumonia outcomes are listed as secondary endpoints in the main protocol (available at https://thl.fi/en/web/thlfi-en/research-and-expertwork/projects-and-programmes/finip-trial) and the protocol of the nested trial (available at https://www.gsk-clinicalstudyregister.com/study/112595?study_ids=112595#ps).

2.2. Participants

All children 6 weeks to 18 months of age living in the study area were eligible for enrolment. Enrolment and vaccinations took place in the well-baby clinics of the participating public health care centres serving altogether nearly 80% of the Finnish population and in the study clinics of the nested carriage and acute otitis trial run by the Tampere University Vaccine Research Centre (TAUVRC) [22].

The enrolment started in February 2009 and ended, as planned, when PHiD-CV10 was introduced into the Finnish National Vaccination Program (NVP) in September 2010 after public tender. Since September 1, 2010, PHiD-CV10 was offered to all infants born June 1, 2010 or thereafter (vaccinations given at 3, 5 and 12 months).

2.3. Study vaccines and vaccinations

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

Hepatitis B (*Engerix-B* 10 μg/0.5 ml, GSK) and hepatitis A virus vaccines (*Havrix* Junior 720, GSK) were used as control vaccines for children enrolled under 12 months of age and at 12 months or older, respectively.

2.4. Vaccinations, cohorts and follow-up definitions

Enrolled children were vaccinated according to either 3+1 or 2+1 schedule if enrolled before 7 months of age (infant cohorts), 2+1 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 cohorts) as described previously [18]. Concomitant vaccination details are provided in Table S1 in the Supplementary Appendix.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.08.020.

All results presented here were analysed by intention-to-treat, the follow-up period for every subject starting at the date of the first vaccination. Pneumonia events that were recorded in the register data by December 31, 2011 were included in the primary analysis and chest X-rays related to these events were retrospectively collected. In addition, the results for the register-based outcomes for 2012 through 2014 were collected; however, with no chest X-ray review performed for the latter period.

2.5. Cluster randomisation and masking

The study areas were divided geographically into 72 clusters taking into account public health care provision regions and birth cohort size [18]. Eleven municipalities covered exclusively by TAUVRC were divided into 6 additional clusters. The treatments were allocated to the 78 clusters using two infant schedules and a randomisation ratio of 2:2:1:1 (PHiD-CV10-3+1:PHiD-CV10-2+1:Control-3+1:Control-2+1). Treatment allocation was stratified according to the following factors: size of the birth cohort (below/above average), TAUVRC trial enrolment (50 of 78 clusters), and urbanity (24 urban, 54 rural clusters). Treatment allocations were unblinded on April 5, 2012. The children in the control group were not offered PHiD-CV10 vaccination after unblinding, as no children born before June 1, 2010 were offered PCV vaccinations in NVP in Finland.

2.6. Outcomes

Pneumonia outcome data were collected through the National Care Register, which covers by law all in- and outpatient care provided in the Finnish hospitals. We identified all hospitalizations and outpatient visits to hospitals associated with the ICD-10 codes

Please cite this article in press as: Kilpi TM et al. Effectiveness of pneumococcal *Haemophilus influenzae* protein D conjugate vaccine against pneumonia in children: A cluster-randomised trial. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.08.020

Download English Version:

https://daneshyari.com/en/article/8962293

Download Persian Version:

https://daneshyari.com/article/8962293

Daneshyari.com