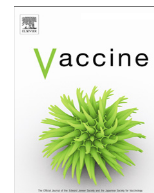
Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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



# Immunogenicity and safety of a booster dose of the 13-valent pneumococcal conjugate vaccine in children primed with the 10-valent or 13-valent pneumococcal conjugate vaccine in the Czech Republic and Slovakia ☆

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ARTICLE INFO

*Article history:*
Received 24 April 2017
Received in revised form 25 July 2017
Accepted 27 July 2017
Available online xxxx

*Keywords:*
Pneumococcal conjugate vaccine
Interchangeability
Immunisation schedule
Immunogenicity
Serotype 19A

ABSTRACT

*Background:* Although both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) are widely used, it is unclear how interchangeable they are in terms of immunogenicity.
*Methods:* Two phase 3, open-label, multicenter studies were conducted to assess the immunogenicity and safety of a booster dose of PCV13 in children primed with PHiD-CV or PCV13. In the Czech Republic, 12–15-month-old children received a PCV13 booster after 3-dose priming with either PHiD-CV or PCV13. In Slovakia, 11–12-month-old children received PCV13 following 2-dose priming with either PHiD-CV or PCV13. Serum IgG concentrations were assessed by enzyme-linked immunosorbent assay and functional antibodies were assessed by opsonophagocytic assay (OPA) before the booster and at 1 and 12 months afterward. The primary objective of these studies was to assess non-inferiority of OPA titers for serotype 19A in PHiD-CV-primed subjects compared to those in PCV13-primed children 1 month post-booster.
*Results:* A total of 98 subjects in the Czech Republic and 89 subjects in Slovakia were included. One month after the PCV13 booster dose, the IgG and OPA immune responses to serotype 19A in subjects primed with 2 or 3 doses of PHiD-CV were non-inferior to those in subjects primed with PCV13. Non-inferior and persistent immune responses to most other vaccine serotypes were also observed after the PCV13 booster in PHiD-CV-primed subjects. No safety issues were raised in either study.
*Conclusions:* Overall, robust IgG and OPA immunological responses were observed after booster vaccination with PCV13 in children primed with 2 or 3 doses of PHiD-CV or PCV13, including for serotypes not included in PHiD-CV. These results suggest that these vaccines are interchangeable in terms of safety and immunogenicity and that PCV13 can be used as a booster in the context of mixed schedules. (EudraCT numbers: 2012-005366-35 and 2012-005367-27).

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*Abbreviations:* AE, adverse event; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; GMT, geometric mean titer; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine; SAE, serious AE.

☆ Presented in part at the Annual Meetings of the European Society for Paediatric Infectious Diseases in Leipzig, Germany, in May 2015 and in Brighton, the United Kingdom, in May 2016; and at the International Symposium on Pneumococci and Pneumococcal Diseases in Glasgow, the United Kingdom, in June 2016.

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http://dx.doi.org/10.1016/j.vaccine.2017.07.103
0264-410X/© 2017 Published by Elsevier Ltd.

## 1. Introduction

Since the introduction of the first pneumococcal conjugate vaccine (PCV) in 2000, invasive and non-invasive diseases caused by *Streptococcus pneumoniae* vaccine serotypes have dramatically decreased worldwide [1,2]. This 7-valent vaccine (PCV7; Pfizer Inc.) included the capsular polysaccharides of the seven most frequent pneumococcal serotypes in the United States at the time of licensure (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) [3]. However, a small but significant rise in infections caused by non-PCV7 serotypes, notably serotype 19A, occurred in several countries, thereby eroding the impact of PCV7 [4–6]. The burden of disease caused by serotype 19A is of particular concern because of its invasive nature and antibiotic resistance profile [7]. To limit the rise of infections by non-vaccine serotypes and increase overall serotype coverage, second-generation PCVs with extended valencies became available in 2009 and have replaced PCV7. The 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV; GSK) includes the PCV7 serotypes plus serotypes 1, 5, and 7F, whereas the 13-valent PCV (PCV13; Pfizer Inc.) includes the PHiD-CV serotypes plus serotypes 3, 6A, and 19A. Both PHiD-CV and PCV13 have been licensed for protection against invasive pneumococcal disease on the basis of immunological non-inferiority compared to the licensed PCV7 [8].

Both vaccines were originally licensed in a 4-dose schedule consisting of 3 primary doses plus a booster dose administered at least 6 months after the third dose (3 + 1 schedule) [9]. Several alternative schedules are also used, without statistically significant differences in antibody concentrations after the booster dose for almost all serotypes [10,11]. One consists of 2 primary doses given 2 months apart, followed by a booster dose at least 6 months after the second dose (2 + 1 schedule) [9]. This schedule was first evaluated and implemented in the United Kingdom [12] and subsequently in several other countries [6]. In developing countries, a 3-dose primary schedule without a booster dose (3 + 0 schedule) is often used to match the schedules of the Expanded Programme on Immunisation [13].

Although immunogenicity of both PHiD-CV and PCV13 has been compared to that of PCV7 [14,15], only a few studies have directly compared PHiD-CV and PCV13 [16–18]. In this study, we compared the immunogenicity and safety of PCV13 when administered as a booster in children primed with PHiD-CV or PCV13, either as a 2- or 3-dose schedule.

## 2. Materials and methods

### 2.1. Study design and subjects

These were two phase 3, multicenter, open-label studies conducted in 10 centers in the Czech Republic (EudraCT, 2012-005366-35) and in 8 centers in Slovakia (EudraCT, 2012-005367-27) to assess immunogenicity and safety of alternative vaccination schedules with pneumococcal conjugate vaccines. Both study protocols were approved by the relevant independent ethics committees and the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from parents or legal representatives of all children before enrolment.

In the Czech Republic (3 + 1 schedule), healthy children were eligible if they were 12–15 months of age and had completed a 3-dose vaccination course before 7 months of age with either the 10-valent PCV (PHiD-CV; *Synflorix*™, GSK, Rixensart, Belgium) or the 13-valent PCV (PCV13; *Prevenar*/*Prevnar* 13™, Pfizer, New York, NY). In Slovakia (2 + 1 schedule), healthy children were eligible if they were 11–12 months of age and had completed a 2-dose vaccination course before 6 months of age with either PHiD-CV or PCV13.

Children were excluded if they had received a previous booster dose against *S. pneumoniae*, any investigational product (drug or vaccine) within 30 days preceding the study vaccination, immunoglobulins or any blood product within 3 months preceding the study vaccination (or were to receive these during the study period), a vaccine (except licensed influenza or diphtheria-tetanus-acellular pertussis vaccines) within 30 days before or after the study vaccination, immunosuppressants or other immune-modifying drugs for >14 days since birth; had any confirmed or suspected immunodeficient condition or family history of immunodeficiency, serious chronic disease, history of neurological disorders or seizures; had any contraindications to vaccination such as allergies; had acute infection or fever (oral, axillary, or tympanic temperature > 37.5 °C or rectal temperature > 38.0 °C) at enrollment.

### 2.2. Study vaccines

All children received one booster dose of PCV13 by intramuscular injection (0.5 mL) in the anterolateral region of the thigh or the deltoid region. This vaccine contains capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23 F, all conjugated to the diphtheria $CRM_{197}$ carrier protein. Co-administration of the routine diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-*H. influenzae* type b vaccine (DTaP-HBV-IPV/Hib; *Infanrix hexa*™; GSK) was allowed in the Czech Republic and was mandatory in Slovakia.

### 2.3. Assessment of immunogenicity

Blood samples were taken for immunogenicity analyses before the booster dose (study month 0) and 1 and 12 months after the booster dose. Sera were stored at −20 °C until analysis. Analyses were performed at the World Health Organization pneumococcal serology reference laboratory (University College London, United Kingdom). Immunoglobulin G (IgG) serum concentrations specific for the 13 vaccine serotypes were measured using an enzyme-linked immunosorbent assay (ELISA) after adsorption with cell-wall and 22F polysaccharides to increase the assay specificity [19]. A standardized opsonophagocytic assay (OPA) was used to measure functional antibodies against the same serotypes [20]. The OPA titer was defined as the reciprocal of the lowest serum dilution that induces ≥50% bacterial cell death compared to the assay control. The OPA response to vaccine-related serotype 6C [21] was also measured, although not planned in the protocol.

### 2.4. Assessment of safety and reactogenicity

Solicited local reactions (pain, redness, and swelling at the injection site) and solicited systemic reactions (drowsiness, fever, irritability/fussiness, and loss of appetite) were recorded by parents on diary cards for 4 days after vaccination (days 0–3). Unsolicited adverse events (AEs) were recorded for 31 days (days 0–30) after vaccination and serious adverse events (SAEs) were recorded over the entire study period. The intensity of solicited reactions, and AEs was scored on a scale from 1 (mild) to 3 (severe). Redness and swelling at the injection site were scored as 1 for >0 to ≤20 mm diameter, 2 for >20 to ≤30 mm, and 3 for >30 mm. Fever was defined as rectal temperature ≥38.0 °C or oral, axillary, or tympanic temperature ≥37.5 °C. Grade 3 fever was defined as rectal temperature >40 °C or axillary, oral, or tympanic temperature >39.5 °C. Pain was scored as 1 for minor reaction to touch, 2 for crying on touch, and 3 for crying when limb is moved or spontaneously painful. The other solicited reactions were scored as 1 if

Please cite this article in press as: Urbancikova I et al. Immunogenicity and safety of a booster dose of the 13-valent pneumococcal conjugate vaccine in children primed with the 10-valent or 13-valent pneumococcal conjugate vaccine in the Czech Republic and Slovakia. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.07.103

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