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Immunogenicity, safety and reactogenicity of the pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in 2–17-year-old children with asplenia or splenic dysfunction: A phase 3 study

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ABSTRACT

Background: Immunization with pneumococcal vaccines is an important prophylactic strategy for children with asplenia or splenic dysfunction, who are at high risk of bacterial infections (including *S. pneumoniae*). This study aimed to assess immunogenicity and safety of pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, GSK) in this at-risk population.

Methods: This phase III, multi-centre, open-label, controlled study, in which at-risk children with asplenia or splenic dysfunction were enrolled (age strata: 2–4, 5–10 and 11–17 years), was conducted in Poland and the Russian Federation. For the 2–4 years at-risk group, healthy age-matched children were enrolled as control. Unprimed children (not previously vaccinated with any pneumococcal vaccine) received 2 PHiD-CV doses (≥2 months apart) and pneumococcal vaccine-primed children received 1 dose. Immune responses were assessed pre-vaccination and one month post-each dose. Solicited and unsolicited adverse events (AEs) were recorded for 4 and 31 days post-vaccination, respectively, and serious AEs (SAEs) throughout the study.

Results: Of 52 vaccinated children (18 at-risk primed, 28 at-risk unprimed and 6 control unprimed), 45 (18, 23 and 4, respectively) were included in the according-to-protocol cohort for immunogenicity. Post-vaccination (post-dose 1 in primed and post-dose 2 in unprimed children), for each vaccine pneumococcal serotype and vaccine-related serotype 6A all at-risk children had antibody concentrations ≥0.2 μg/mL, and for vaccine-related serotype 19A at least 94.4%. Increases in antibody geometric mean concentrations were observed. For most serotypes, all at-risk children had post-vaccination opsonophagocytic activity (OPA) titers ≥8 and increases in OPA geometric mean titers were observed. No safety concerns were raised. One non-fatal SAE (respiratory tract infection, considered not vaccine-related) was reported by one at-risk unprimed child.

Conclusion: PHiD-CV was immunogenic and well tolerated in 2–17-year-old children with asplenia or splenic dysfunction.

Clinical Trial Registry: www.clinicaltrials.gov, NCT01746108.

Abbreviations: AE, adverse event; ATP, according-to-protocol; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; 22F-ELISA, enzyme-linked immunosorbent assay with serotype 22F polysaccharide adsorption; GMC, geometric mean concentration; GMT, geometric mean titer; IgG, immunoglobulin G; EL.U, ELISA units; LARs, legally acceptable representatives; NIP, national immunization program; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine; PPSV23, 23-valent pneumococcal plain polysaccharide vaccine; SCD, sickle cell disease; SAE, serious adverse event; TVC, total vaccinated cohort; ST, serotype; SD, standard deviation.

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1. Introduction

1.1. Background

Individuals with asplenia (anatomical or functional) or splenic dysfunction (e.g., sickle cell disease [SCD]), or with complement deficiencies are at increased risk of infection caused by encapsulated bacteria such as *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* type b [1]. The risk of life-threatening infections is particularly high in young children with asplenia or splenic dysfunction, as compared with older children and adults [2].

Antibiotic prophylaxis is recommended, but not always efficient due to antibiotic-resistant strains [3]. Immunization is an important strategy for preventing infections in this high-risk group [4].

The use of the 23-valent pneumococcal plain polysaccharide vaccine (PPSV23) has been recommended for many years in asplenic or immunocompromised children aged ≥2 years [5], but not in younger children, for whom this vaccine is ineffective [6,7]. With the advent of pneumococcal conjugate vaccines (PCVs), protection of younger children <2 years became possible. Many countries have now implemented routine pediatric vaccination with PCVs in their national immunization program (NIP), and also recommend PCVs for children at high risk for pneumococcal disease [5]. The use of PPSV23 in addition to PCVs is still recommended in children ≥2 years to protect this high-risk group against pneumococcal infection due to serotypes not included in PCVs [5].

A number of clinical studies have been conducted with PCV13 and its predecessor PCV7 in children with asplenia or splenic dysfunction [8–12], suggesting that these vaccines were immunogenic in this at-risk population.

Safety and immunogenicity of the pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, GSK) in young children has been demonstrated [13] as well as its efficacy and effectiveness/impact against invasive pneumococcal disease in large double-blind, randomized, controlled trials in Latin America [14] and Finland [15], and post-marketing studies in Brazil [16,17], Finland [18] and Quebec [19,20]. Since its licensure in 2008, it has been implemented in many NIPs, including for high-risk groups. Previous clinical studies assessed PHiD-CV use in high-risk children, such as premature infants [21], infants infected with or exposed to human immunodeficiency virus [22], and infants and toddlers with SCD [23].

Here, we studied the safety and immunogenicity of PHiD-CV in high-risk children 2–17 years of age with asplenia or splenic dysfunction.

2. Methodology

2.1. Study design and population

This phase III, open-label, controlled, multi-center study (ClinicalTrials.gov: NCT01746108) was conducted between June 2013 and June 2015 in Poland and the Russian Federation in 3 centers in each country.

Study participants were planned to be enrolled based on their age and health status (2–17-year-old children at increased risk of pneumococcal infection or healthy children) and on their priming status (primed children, i.e. previously vaccinated with a pneumococcal vaccine [at least one dose of a PCV more than 2 months before enrolment, or PPSV23 more than 2 years and less than 5 years before enrolment], and unprimed children, i.e. not previously vaccinated with any pneumococcal vaccine). At-risk children aged 2–17 years were divided into 2–4 (24–59 months), 5–10 and 11–17 years age strata. For the 2–4 years at-risk group, healthy age-matched children were enrolled as control group.

Detailed inclusion and exclusion criteria are described in supplementary text S1.

Eligible study participants in the at-risk groups were children with asplenia, splenic dysfunction or complement deficiencies (Table S1).

Inclusion of the participants in each age strata (or to study group for 2–4-year-old children) was performed based on age and medical condition. The list of treatment numbers was generated at GSK, using SAS (Statistical Analysis System) software. The treatment numbers were allocated at the investigator site by a central randomization system to control the number of children enrolled in each age strata and group, and to limit the allowed number of children with SCD. The treatment numbers were allocated by dose (1 dose for primed children and 2 doses for unprimed children).

The study was conducted in accordance with the principles of Good Clinical Practice, Declaration of Helsinki and all applicable regulatory requirements. The study protocol was approved by local ethics committees and regulatory authorities. Informed consent was obtained from the parents or legally acceptable representatives (LARs) of each child before enrolment. In addition, written informed assent was obtained from each study participant at or above the age of assent. A protocol summary is available at www.gsk-clinicalstudyregister.com (study ID: 115884).

2.2. Vaccination schedule and vaccines

In both at-risk and control groups, unprimed children received a 2-dose catch-up vaccination with PHiD-CV (*Synflorix*, GSK), with an interval of at least 2 months between doses, and primed children received 1 dose of PHiD-CV (Fig. S1). Vaccine composition is described in the supplementary text S2.

The vaccine was administered as intramuscular injection into the deltoid (non-dominant side) or thigh (if deltoid size was not adequate).

2.3. Objectives

The primary objective was to assess the immunogenicity of PHiD-CV when administered to at-risk children aged 2–17 years, either as a 2-dose catch-up vaccination in unprimed children, or as a single dose in primed children.

The secondary objectives were to assess PHiD-CV immunogenicity when administered to healthy primed or unprimed children aged 2–4 years, and its reactogenicity and safety in children aged 2–17 years in both at-risk and control groups, regardless of the priming status.

2.4. Immunogenicity assessment

Blood samples were collected before dose 1 and 1 month after each dose, regardless of vaccination schedule (Fig. S1).

Immunoglobulin G (IgG) antibodies against vaccine pneumococcal serotypes and vaccine-related serotypes (6A and 19A) were measured by enzyme-linked immunosorbent assay with serotype 22F polysaccharide adsorption (22F-ELISA) (at Néomed-Labs Inc, Quebec, Canada), as described previously [24]. The 0.2 μg/mL threshold is equivalent to antibody concentrations ≥0.35 μg/mL measured by the non-22F-ELISA of the reference laboratory of the World Health Organization [25].

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