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Immunologic non-inferiority and safety of the investigational pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) 4-dose vial presentation compared to the licensed PHiD-CV 1-dose vial presentation in infants: A phase III randomized study

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ABSTRACT

Background: To support vaccination programs in developing countries, a 4-dose vial presentation of pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) was developed. This study assessed immunologic non-inferiority and safety of the investigational PHiD-CV 4-dose versus licensed 1-dose vial presentation in infants.

Methods: In this phase III, mono-center, observer-blind study in Bangladesh, 6–10-week-old infants were randomized 1:1 to receive PHiD-CV primary vaccination (at ages 6, 10, 18 weeks) and a booster dose (at age 9 months) with a 4-dose vial (with preservative, 4DV group) or 1-dose vial (preservative-free, 1DV group). DTPw-HBV/Hib was (co)-administered per study protocol and polio, measles and rubella vaccines as part of the national immunization program. Non-inferiority of PHiD-CV 4-dose versus 1-dose vial for each vaccine pneumococcal serotype (VT) and vaccine-related serotype 19A in terms of antibody geometric mean concentration (GMC) was assessed (criterion: upper limit of 2-sided 95% confidence interval of antibody GMC ratios [1DV/4DV] <2-fold). Immune responses were measured. Solicited, unsolicited and serious adverse events (AEs) were evaluated.

Results: Of 320 infants (160 per group) vaccinated during the primary vaccination phase, 297 received a booster. Non-inferiority was demonstrated for each VT and 19A. One month post-primary vaccination, for most VT, ≥97.9% of infants in each group had antibody concentrations ≥0.2 μg/mL; for 19A ≥ 80.1% reached this threshold. Pneumococcal antibody responses and opsonophagocytic activity for each VT and 19A were within similar ranges between groups after primary and booster vaccination, as were anti-protein D responses. Booster immune responses were observed in both groups. Reported AEs were within similar ranges for both presentations.

Conclusion: Immunologic non-inferiority of PHiD-CV 4-dose vial (with preservative) versus PHiD-CV 1-dose vial (preservative-free) was demonstrated. Immune responses and reactogenicity following primary/booster vaccination were within similar ranges for both presentations. PHiD-CV 4-dose vial would help improve access and coverage in resource-limited countries.

Clinical Trial Registry: NCT02447432.

Abbreviations: AE, adverse event; ATP, according-to-protocol; CI, confidence interval; DTPw-HBV/Hib, diphtheria-tetanus-whole cell pertussis-hepatitis B and *H. influenzae* type b conjugate vaccine; EPI, Expanded Program on Immunization; GAVI, Global Alliance for Vaccines and Immunization; GMC, geometric mean concentration; GMTs, geometric mean titer; IgG, immunoglobulin G; IPD, invasive pneumococcal disease; LAR, legally acceptable representative; NIP, national immunization program; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine; SAE, serious AE; SBIR, central internet randomization system; TVC, total vaccinated cohort; UL, upper limit; VT, vaccine pneumococcal serotypes; WHO, World Health Organization; 1DV group, infants that received vaccination with PHiD-CV 1-dose vial; 4DV group, infants that received vaccination with PHiD-CV 4-dose vial; 22F-ELISA, enzyme linked immunosorbent assay with serotype 22F polysaccharide adsorption.

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1. Introduction

The invasive pneumococcal disease (IPD) burden has been substantially reduced worldwide since the introduction of pneumococcal conjugate vaccines (PCVs) in national immunization programs (NIPs) [1,2]. Currently, PCVs are supplied to developing countries via the Global Alliance for Vaccines and Immunization (GAVI) in high volume at affordable prices [3].

The efficacy and effectiveness/impact of pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV, GSK) against IPD have been demonstrated in clinical trials [4,5] and in post-marketing studies, including evidence for vaccine effectiveness against vaccine serotypes (VT) and vaccine-related serotype 19A IPD [6–13]. PHiD-CV, as preservative-free 1-dose or 2-dose vial presentations [13], is prequalified by the World Health Organization (WHO).

The previously licensed 2-dose vial improves logistics (delivery, storage and cold chain capacity) compared to the 1-dose vial. However, vaccine vials should be discarded within maximum 6 h after opening as this presentation is preservative-free.

GSK has developed a 4-dose vial presentation of PHiD-CV with addition of a preservative (2-phenoxyethanol) to control potential microbial contamination, allowing vaccine use up to 28 days after opening as per WHO multi-dose vial policy [14]. This would further enhance logistics and adherence to immunization programs in developing countries, as in place for other pediatric vaccines [15], including the recently WHO-qualified 13-valent pneumococcal conjugate vaccine (PCV13) 4-dose vial [16]. Here, we present the immunologic non-inferiority of the PHiD-CV 4-dose vial in infants compared to the PHiD-CV 1-dose vial after primary vaccination. The immunogenicity, reactogenicity and safety after primary and booster vaccination with PHiD-CV 4-dose and 1-dose vials were also assessed.

2. Methodology

2.1. Study design and population

This phase III, single-center, observer-blind, controlled study (ClinicalTrials.gov: NCT02447432) was conducted in Bangladesh between June 2015 and May 2016.

Infants aged 6–10 weeks were randomized 1:1 to receive either PHiD-CV 4-dose vial (4DV group) or PHiD-CV 1-dose vial (1DV group) administered in a 3 + 1 schedule at ages 6, 10 and 18 weeks (primary vaccination) and 9 months (booster vaccination) (Fig. S1). Children received diphtheria-tetanus-whole cell pertussis-hepatitis B and *H. influenzae* type b conjugate vaccine (DTPw-HBV/Hib, GSK) and polio, measles and rubella vaccines as described in Fig. S1.

Eligibility criteria for inclusion in the study, and reasons for exclusion of infants from the study are presented in supplementary text S1. A protocol summary is available at http://www.gsk-clinicalstudyregister.com (study ID 200799). Details regarding blinding and randomization are shown in supplementary text S2.

Overall, the study was conducted in accordance with the principles of Good Clinical Practice, Declaration of Helsinki and all applicable regulatory requirements.

Signed/thumb-printed and witnessed informed consent was obtained from the parent(s) or legally acceptable representative (s) (LAR[s]) of each infant before enrolment.

2.2. Study vaccines

The licensed PHiD-CV 1-dose vial (*Synflorix*, GSK) was a preservative-free suspension containing capsular polysaccharides of 10 pneumococcal serotypes: 1, 4, 5, 6B, 7F, 9V, 14 and 23F conjugated to non-typeable *H. influenzae* protein D, 18C to tetanus toxoid and 19F to diphtheria toxoid as described previously [17].

The investigational PHiD-CV 4-dose vial contained the same conjugated capsular polysaccharides as the PHiD-CV 1-dose vial but with the preservative 2-phenoxyethanol. Consecutive vial-doses from the PHiD-CV 4-dose presentation were used for vaccination of infants randomized to receive this vaccine (0.5 mL per dose).

Composition of the (co)-administered DTPw-HBV/Hib vaccine (*Tritanrix HB* and *Hiberix*, GSK) was previously published [18].

During primary vaccination, both PHiD-CV and DTPw-HBV/Hib were administered as intramuscular injections into the anterolateral thigh on the right and left sides, respectively.

2.3. Objectives

The confirmatory objectives were to demonstrate non-inferiority of the investigational PHiD-CV 4-dose vial versus licensed PHiD-CV 1-dose vial in terms of antibody geometric mean concentrations (GMCs) for each VT (primary objective) and vaccine-related serotype 19A (secondary objective) at 1 month post-primary vaccination.

Additional secondary objectives were to assess immune responses of PHiD-CV 4-dose vial against VT and vaccine-related serotypes 6A and 19A at 1 and 5 months post-primary vaccination and 1 month post-booster vaccination, and against protein D at 1 month post-primary and booster vaccinations. Reactogenicity and safety following PHiD-CV 4-dose vial vaccination were also assessed.

2.4. Immunogenicity assessment

Blood samples were collected 1 and 5 months post-primary vaccination, and 1 month post-booster vaccination (Fig. S1).

Serotype-specific pneumococcal immunoglobulin G (IgG) antibodies against VT and vaccine-related serotypes 6A and 19A were measured using the enzyme linked immunosorbent assay with serotype 22F polysaccharide adsorption (22F-ELISA) (at the laboratory Néomed-Labs Inc, Quebec, Canada), as previously described [19]. The percentage of children with antibody concentrations $\geq$0.2 μg/mL are presented here. This threshold is equivalent to an antibody concentration $\geq$0.35 μg/mL as measured by the non-22F-ELISA of the WHO reference laboratory [20].

Functional immune responses (opsonophagocytic activity, OPA) to each VT and vaccine-related serotypes 6A and 19A were measured in a selected subset (first 50% of infants recruited in each month of enrolment throughout the study) by a validated multiplex OPA assay (at the University College of London, Institute of Child Health, London, United Kingdom). The assay cut-off was an opsonic titer of 8 as previously described [21].

Antibodies against the protein D carrier were measured at 1 month post-primary and 1 month post-booster vaccination in the same selected subset as OPA using an in-house ELISA (GSK, Belgium). The assay cut-off was 153 ELISA units (EL.U)/mL.

2.5. Reactogenicity and safety assessment

Solicited adverse events (AEs) at the injection site (pain, redness and swelling) and general AEs (drowsiness, fever, irritability and loss of appetite) were reported on diary cards within 4 days post-vaccination. Unsolicited AEs were reported within 31 days post-vaccination, and serious AEs (SAEs) throughout the study. For the illiterate parents/LARs, fieldworkers visited each infant every day

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