Vaccine 35 (2017) 2531–2542

Contents lists available at ScienceDirect

Vaccine

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

Efficacy of a novel, protein-based pneumococcal vaccine against nasopharyngeal carriage of *Streptococcus pneumoniae* in infants: A phase 2, randomized, controlled, observer-blind study

Aderonke Odutola [a,*], Martin O.C. Ota [a], Martin Antonio [a], Ezra O. Ogundare [a], Yauba Saidu [a], Ebenezer Foster-Nyarko [a], Patrick K. Owiafe [a], Fatima Ceesay [a], Archibald Worwui [a], Olubukola T. Idoko [a], Olumuyiwa Owolabi [a], Abdoulie Bojang [a], Sheikh Jarju [a], Isatou Drammeh [a], Beate Kampmann [a], Brian M. Greenwood [b], Mark Alderson [c], Magali Traskine [d], Nathalie Devos [d], Sonia Schoonbroodt [d], Kristien Swinnen [d], Vincent Verlant [d], Kurt Dobbelaere [d], Dorota Borys [d]

[a] *Medical Research Council Unit, Vaccines & Immunity Theme, Banjul, Gambia*
[b] *Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK*
[c] *PATH, Seattle, WA, USA*
[d] *GSK, Wavre, Belgium*

ARTICLE INFO

Article history:
Received 7 December 2016
Received in revised form 21 March 2017
Accepted 22 March 2017
Available online 4 April 2017

Keywords:
Streptococcus pneumoniae
Nasopharyngeal carriage
Pneumolysin
Pneumococcal histidine triad protein D
Vaccine efficacy
Infant

ABSTRACT

Background: Conserved pneumococcal proteins are potential candidates for inclusion in vaccines against pneumococcal diseases. In the first part of a two-part study, an investigational vaccine (PHiD-CV/dPly/PhtD-30) containing 10 pneumococcal serotype-specific polysaccharide conjugates (10VT) combined with pneumolysin toxoid and pneumococcal histidine triad protein D (30 μg each) was well tolerated by Gambian children. Part two, presented here, assessed the efficacy of two PHiD-CV/dPly/PhtD formulations against pneumococcal nasopharyngeal carriage (NPC) prevalence in infants.

Methods: In this phase 2, randomized, controlled, observer-blind trial, healthy infants aged 8–10 weeks, recruited from a peri-urban health center, were randomized (1:1:1:1:1:1) into six groups. Four groups received PHiD-CV/dPly/PhtD (10 or 30 μg of each protein), PHiD-CV, or 13-valent pneumococcal conjugate vaccine at ages 2–3–4 months (3 + 0 infant schedule) and two groups PHiD-CV/dPly/PhtD-30 or PHiD-CV at 2–4–9 months (2 + 1 infant schedule). The primary objective was impact on non-10VT NPC at ages 5–9–12 months. Secondary objectives included confirmatory analysis of protein dose superiority and safety/reactogenicity. Impact on pneumococcal NPC acquisition, bacterial load, and *ply* and *phtD* gene sequencing were explored.

Results: 1200 infants were enrolled between June 2011 and May 2012. Prevalences of pneumococcal (60–67%) and non-10VT (55–61%) NPC were high at baseline. Across all post-vaccination time points, efficacy of PHiD-CV/dPly/PhtD-10 and PHiD-CV/dPly/PhtD-30 against non-10VT NPC (3 + 0 schedule) was 1.1% (95% CI −21.5, 19.5) and 2.1% (−20.3, 20.3), respectively; efficacy of PHiD-CV/dPly/PhtD-30 (2 + 1 schedule) was 0.5% (−22.1, 18.9) versus PHiD-CV. No differences were observed in pneumococcal NPC acquisition, clearance, or bacterial load. Both protein-based vaccines elicited immune responses to pneumococcal proteins.

Abbreviations: AE, adverse event; ATP, according-to-protocol; CI, confidence interval; dPly, pneumolysin toxoid; ELISA, enzyme-linked immunosorbent assay; EPI, Expanded Program on Immunization; GMC, geometric mean concentration; IPD, invasive pneumococcal disease; non-10VT, non-PHiD-CV pneumococcal serotypes or serogroups; NPC, nasopharyngeal carriage; PCV, pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; PhtD, pneumococcal histidine triad protein D; Ply, pneumolysin; qPCR, quantitative polymerase chain reaction; SAE, serious adverse event.

* Corresponding author at: Medical Research Council Unit, Vaccines & Immunity Theme, P.O. Box 273, Banjul, Gambia.
E-mail addresses: aaodutola@mrc.gm (A. Odutola), otama@who.int (M.O.C. Ota), mantonio@mrc.gm (M. Antonio), tundeyogundare@yahoo.com (E.O. Ogundare), ysaidu@clintonhealthaccess.org (Y. Saidu), efosternyarko@mrc.gm (E. Foster-Nyarko), pkowiafe@uhas.edu.gh (P.K. Owiafe), faceesay@mrc.gm (F. Ceesay), aworwui@mrc.gm (A. Worwui), oidoko@mrc.gm (O.T. Idoko), oowolabi@mrc.gm (O. Owolabi), ambojang@mrc.gm (A. Bojang), shjarju@mrc.gm (S. Jarju), idrammeh@mrc.gm (I. Drammeh), bkampmann@mrc.gm (B. Kampmann), Brian.Greenwood@lshtm.ac.uk (B.M. Greenwood), malderson@path.org (M. Alderson), magali.x.traskine@gsk.com (M. Traskine), nathalie.i.devos@gsk.com (N. Devos), sonia.j.schoonbroodt@gsk.com (S. Schoonbroodt), kristien.m.swinnen@gsk.com (K. Swinnen), vincent.verlant@gsk.com (V. Verlant), dobbelaerekurt@gmail.com (K. Dobbelaere), dorota.d.borys@gsk.com (D. Borys).

http://dx.doi.org/10.1016/j.vaccine.2017.03.071
0264-410X/

Conclusions: In this high carriage prevalence setting, inclusion of pneumococcal proteins in the PHiD-CV/dPly/PhtD investigational vaccine had no impact on pneumococcal NPC in infants, regardless of protein dose or schedule. Future evaluations will assess its impact against pneumococcal disease endpoints.
Funding: PATH, GlaxoSmithKline Biologicals SA. ClinicalTrials.gov identifier NCT01262872.

1. Introduction

Remarkable reductions in the incidence of vaccine serotype invasive pneumococcal disease (IPD) and nasopharyngeal carriage (NPC) prevalence have been recorded in countries that have included a pneumococcal conjugate vaccine (PCV) in their infant immunization program [1–3]. This was observed in The Gambia following the introduction of the seven-valent PCV (PCV7) into its immunization program in August 2009 followed by replacement with the 13-valent vaccine (PCV13) in May 2011 [4,5]. Immunization with PCVs also has indirect effects, leading to decreases in the incidence of vaccine serotype carriage and disease in non-vaccinated populations [6]. However, use of PCVs is limited by the potential for serotype replacement and high manufacturing costs [3,7]. Protein antigens that are conserved across all pneumococcal serotypes have therefore been explored as an alternative and a number, used either alone or in combination with other proteins or polysaccharide conjugates, are being evaluated in clinical trials after demonstration of protection against pneumococcal disease or carriage in animal models [3,8–14].

Two protein candidates, pneumolysin (Ply) [15] and pneumococcal histidine triad protein D (PhtD) [16] (alone or in combination), have shown protection against lethal challenge, septicemia, pneumonia, and NPC prevalence in animal models [17–23] and have been selected for clinical development by GSK (Belgium). Investigational vaccines containing dPly (a pneumolysin toxoid) and PhtD (two formulations with either 10 or 30 μg of each protein) plus 10 serotype-specific polysaccharide conjugates of the pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV/dPly/PhtD-10 or PHiD-CV/dPly/PhtD-30) were well tolerated and immunogenic in healthy European adults [11] and toddlers [12]. The PHiD-CV/dPly/PhtD-30 formulation was also well tolerated and immunogenic in children aged 2–4 years in the first part of this study conducted in The Gambia [13]. In the second part, we evaluated the impact of the two protein-based pneumococcal vaccine formulations on NPC prevalence of pneumococci, and their reactogenicity, safety, and immunogenicity in infants when given in a three-dose schedule together with routine Expanded Program on Immunization (EPI) vaccines.

2. Methods

2.1. Study design and participants

A phase 2 randomized, controlled, observer-blind study was conducted at the Fajikunda Health Center situated in a peri-urban area of The Gambia. The prevalence of pneumococcal NPC in infants in Fajikunda was known to be high (76% in children aged 15–53 weeks) [24]. The study area and population have been described previously [24]. The study was conducted in accordance with Good Clinical Practice guidelines and principles of the Declaration of Helsinki. Written informed consent was obtained from a parent or legally-acceptable representative of each infant before any study procedure was performed except when deviations from the informed consent process occurred (Supplementary Text 1).

Interest in participating in the trial was determined from mothers at the time of delivery in the health center or when the infant was brought for first immunizations shortly after birth. Healthy infants aged 8–10 weeks were recruited at the health center when brought for immunizations scheduled at two months of age. Inclusion and exclusion criteria are listed in Supplementary Text 2.

Eligible participants were randomized (1:1:1:1:1:1) into one of six groups using a computer-generated, block randomization program (block size of six). The methods for pneumococcal vaccine allocation and blinding are described in Supplementary Text 2. Infants in four groups were vaccinated at 2, 3, and 4 months of age with PHiD-CV/dPly/PhtD-30, PHiD-CV/dPly/PhtD-10, PHiD-CV (*Synflorix*; GSK, Belgium), or PCV13 (*Prevenar 13*; Pfizer, USA) (3 + 0 infant schedule) (Fig. 1). Infants in the remaining two groups received either PHiD-CV/dPly/PhtD-30 or PHiD-CV at 2, 4, and 9 months of age (2 + 1 infant schedule).

Administration of other vaccines (Supplementary Text 2) was in accordance with the routine Gambian EPI schedule.

2.2. Study endpoints

The primary trial endpoint was the detection of non-10VT serotypes/groups in the nasopharynx at post-immunization visits at ages 5, 9, and 12 months, which was one, five, and eight months after the third vaccine dose in the 3 + 0 groups, and one and five months after the second dose and three months after the booster dose in the 2 + 1 groups. Non-10VT serotypes/groups included any pneumococcal isolates with unknown or determined serotype or serogroup other than those included in the 10-valent PHiD-CV (serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F). The first secondary endpoint was the immune response to Ply and PhtD given at a dose of 10 or 30 μg. A list of primary and secondary endpoints is provided in Supplementary Text 2.

2.3. Study vaccines

The investigational pneumococcal vaccines (PHiD-CV/dPly/PhtD-10 or PHiD-CV/dPly/PhtD-30) contained dPly and PhtD at 10 or 30 μg each, combined with the 10 serotype-specific PHiD-CV polysaccharide conjugates, as described previously [13]. The antigens were adsorbed on aluminum phosphate (vaccine adjuvant; aluminum content 500 μg). The control vaccines were PHiD-CV and PCV13. All pneumococcal vaccines were provided by GSK as mono-dose vials (PHiD-CV and PHiD-CV/dPly/PhtD vaccines) or pre-filled syringes (PCV13) and administered intramuscularly into the right thigh. All other co-administered injectable vaccines were administered intramuscularly into the left thigh.

2.4. Study procedures

Nasopharyngeal swabs were obtained (as described previously [24], apart from the use of flocked nylon-tipped swabs in this study) from all participants at recruitment (age 8–10 weeks), and at ages 5, 9, and 12 months. A study-specific microbiological laboratory standard operating procedure was followed at the Medical