Vaccine 32 (2014) 2493–2500

Contents lists available at ScienceDirect

Vaccine

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

Efficacy of different pneumococcal conjugate vaccine schedules against pneumonia, hospitalisation, and mortality: Re-analysis of a randomised trial in The Gambia

Grant A. Mackenzie[a,*], Christian Bottomley[b], Albert J. van Hoek[c], David Jeffries[a], Martin Ota[a], Syed M.A. Zaman[c], Brian Greenwood[d], Felicity Cutts[d]

[a] Medical Research Council (UK), The Gambia Unit, Fajara, PO Box 273, Banjul, The Gambia
[b] MRC Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK
[c] Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK
[d] Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

ARTICLE INFO

Article history:
Received 5 November 2013
Received in revised form 12 February 2014
Accepted 25 February 2014
Available online 11 March 2014

Keywords:
Streptococcus pneumoniae
Vaccine
Schedule
Pneumonia
Mortality

ABSTRACT

Background: Pneumococcal conjugate vaccines (PCV) reduce disease due to *Streptococcus pneumoniae*. We aimed to determine the efficacy of different PCV schedules in Gambian children.
Methods: We reanalysed data from a randomised placebo-controlled trial. Infants aged 6–51 weeks were allocated to three doses of nine-valent PCV (n = 8718) or placebo (n = 8719) and followed until age 30 months. We categorised participants to compare: (a) a first dose at age 6 or 10 weeks, (b) intervals of 1 or 2 months between doses, and (c) different intervals between second and third doses. The primary endpoint was first episode of radiologic pneumonia; other endpoints were hospitalisation and mortality. Using the placebo group as the reference population, Poisson regression models were used with follow-up after the first dose to estimate the efficacy of each schedule and from age 6 weeks to estimate the incidence rate difference between schedules.
Results: Predicted efficacy in the groups aged 6 weeks (n = 2467, 154 events) or 10 weeks (n = 2420, 106 events) at first dose against radiologic pneumonia were 32% (95% CI 19–43%) and 33% (95% CI 21–44%), against hospitalisation 14% (95% CI 3–23%) and 17% (95% CI 7–26%), and against mortality 17% (95% CI −3 to 33%) and 16% (95% CI −3 to 32%) respectively. Predicted efficacy in the groups with intervals of 1 month (n = 2701, 133 events) or 2 months (n = 1351, 58 events) between doses against radiologic pneumonia were 33% (95% CI 20–44%) and 36% (95% CI 24–46%), against hospitalisation 15% (95% CI 5–24%) and 18% (95% CI 8–27%), and against mortality 17% (95% CI −2 to 33%) and 13% (95% CI −8 to 29%) respectively. Efficacy did not differ by interval between second and third doses, nor did the incidence rate difference between schedules.
Conclusions: We found no evidence that efficacy or effectiveness of PCV9 differed when doses were given with modest variability around the scheduled ages or intervals between doses.

1. Introduction

Streptococcus pneumoniae, estimated to cause 826,000 deaths and over 14 million serious infections in children globally each year, is responsible for more childhood deaths and morbidity than any other pathogen [1]. Two trials of a nine-valent pneumococcal conjugate vaccine (PCV9) demonstrated efficacy using three doses scheduled at 6, 10, and 14 weeks of age [2,3]. Other trials have tested the efficacy of PCV7 using three doses at age 2, 4, and 6 months with a 4th dose at 12–15 months of age [4,5]. A cohort study of PCV7 given at 3, 5, and 12 months showed reduced radiologic pneumonia, but the effects were not significant after 12 months of age [6].

* Corresponding author at: MRC Basse Field Station, Upper River Region, PO Box 273, Banjul, The Gambia, Tel.: +220 5669255; fax: +220 5668626.
E-mail addresses: gmackenzie@mrc.gm (G.A. Mackenzie), Christian.bottomley@lshtm.ac.uk (C. Bottomley), albertjan.vanhoek@hpa.org.uk (A.J. van Hoek), djeffries@mrc.gm (D. Jeffries), otama@afro.who.int (M. Ota), azaman@mrc.gm (S.M.A. Zaman), Brian.Greenwood@lshtm.ac.uk (B. Greenwood), Felicity.Cutts@lshtm.ac.uk (F. Cutts).

http://dx.doi.org/10.1016/j.vaccine.2014.02.081
0264-410X/

Three primary doses

Group	Age at dose 1	Age at dose 2	Age at dose 3
3p	40–77 days	>25 and <77 days after dose 1	>25 and <77 days after dose 2

Age at first dose, 6 weeks compared to 10 weeks

	Age at dose 1	Age at dose 2	Age at dose 3
1st dose 6 wk	40–63 days	>25 and <77 days after dose 1	>dose 2
1st dose 10 wk	70–105 days	>25 and <77 days after dose 1	>dose 2

Interval between doses, 1 month compared to 2 months

	Age at dose 1	Age at dose 2	Age at dose 3
Int. 1 mo after dose 2	Any age	>25 and <42 days after dose 1	>25 and <42 days
Int. 2 mo after dose 2	Any age	>56 and <91 days after dose 1	>56 and <91 days

Variable intervals between second and third dose

	Age at dose 1	Age at dose 2	Interval between dose 2 and 3
Int. dose 2–3	40–112 days	>25 and <70 days after dose 1	<30 days
			30–59 days
			60–89 days
			≥90 days

Panel 1. Criteria for inclusion in different vaccination schedules.

One cluster-randomised trial in Finland has compared the efficacy of two or three primary doses with a booster dose against invasive pneumococcal disease (IPD). Only 1 episode of vaccine-type IPD was detected limiting the power of the trial to detect differences between the schedules [7]. Otherwise, RCTs comparing schedules have been limited to immunogenicity and colonisation endpoints [8–12].

Systematic reviews of RCTs with immunologic outcomes suggest that schedules with three (3p) rather than two (2p) primary doses may provide improved responses [8–11]. However, observational studies indicate similar short-term effectiveness of 2p or 3p schedules against IPD and likewise for schedules which include booster doses (2p1 or 3p1) [8–14]. Scheduling factors that may influence the efficacy of PCV include the number of doses, the age at which the first dose is given, and the interval between doses. Affluent countries currently choose 3p, 2p1, or 3p1 schedules with similar frequency, with the age at first dose varying between 6 weeks and 3 months and intervals of 1 or 2 months between the primary doses [11,15]. Given the limited evidence on the efficacy of different schedules against disease, we re-analysed data from a randomised trial of PCV9 in The Gambia, estimating the efficacy of different schedules.

2. Methods

We used data from a randomised, placebo-controlled, double-blind trial of PCV9 conducted in eastern Gambia between August 2000 and April 2004. The methods and results of this trial have been reported previously [3]. We present these methods in brief but focus on the methods of our re-analysis in which participants in the trial have been stratified by vaccination schedule.

2.1. Participants

All participants in the trial were potentially eligible for analysis. Participants were excluded if the age at administration of vaccine doses was outside the specified ranges which determined inclusion in different study groups (Panel 1).

2.2. Study design

The trial was originally designed to determine vaccine efficacy against all-cause mortality but, in 2002, radiologic pneumonia became the primary outcome. Hospitalisation was a secondary endpoint. Our study compared different schedules, using the endpoints of radiologic pneumonia, hospitalisation, and mortality.

The 3p group included children who received three doses of PCV9 before 6 months of age (Panel 1); other groups had no restriction on age at third dose. Infants were categorised as to whether they received their first dose within ranges corresponding to a scheduled age of 6 or 10 weeks, the former being standard in high burden countries, the latter being more frequent in affluent countries. Categorisation into groups with 1 or 2 month intervals between doses was used as these intervals are widely used around the world. To explore a potential optimal interval between doses 2 and 3, the duration between these doses was categorised in intervals of 30 days up to 90 days or more.

2.3. Procedures

Enrolment in the trial began in August 2000 and ended in February 2003. The protocol stipulated that doses be given at a minimum age of 6, 10, and 14 weeks. Enrolment at the beginning