Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Immunogenicity of 13-valent pneumococcal conjugate vaccine among children with underlying medical conditions

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ARTICLE INFO

Article history:
Received 24 March 2017
Received in revised form 30 May 2017
Accepted 25 June 2017
Available online xxxx

Keywords:
Pneumococcal conjugate vaccine
PCV13
Streptococcus pneumoniae
HIV
Kidney
Lung

ABSTRACT

Background: *Streptococcus pneumoniae* is a leading cause of vaccine-preventable disease in children under 5 years. Immunocompromised children and those with underlying diseases are at increased risk of severe complications from vaccine-preventable infections. We studied the humoral immune response to the 13-valent pneumococcal conjugate vaccine (PCV13) in children with HIV-infection, kidney or lung disease and compared this to the response in healthy control children.

Methods: Children aged 12–71 months with underlying conditions including HIV-infection and those with kidney and lung diseases (at-risk children), and a healthy control group were vaccinated with PCV13. The at-risk children received two doses of PCV13 and the controls received one dose. Serotype-specific antibodies for all PCV13 serotypes were measured by a luminex-based enzyme immunoassay at baseline and post-vaccination.

Results: After the first PCV13 dose, the fold-increase in serotype-specific antibody geometric mean concentrations (GMCs) from baseline and the percentage of participants with ≥4-fold-increase in antibody concentrations was similar between the control and at-risk children. GMCs were, however, lower for three of the 13 serotypes in HIV-infected children, higher for serotype 6B in children with kidney disease and higher for serotypes 6B and 14 in children with lung disease. After second vaccine dose HIV-infected children had an increase in GMCs from post-first dose for nine serotypes but the percentage of participants with ≥4-fold-increase from baseline was similar post-second dose compared to post-first dose except for serotypes 6A and 19F. In children with kidney or lung diseases the immune responses after second vaccine dose were similar to post-first dose. Attenuated responses were observed for serotypes 3 and 19A in all study-groups, which was especially pronounced in the at-risk groups.

Conclusion: All study-groups mounted an immune response to PCV13, with the at-risk groups having responses that were mostly similar to the control children.

1. Introduction

Streptococcus pneumoniae is a leading cause of vaccine-preventable disease in children under 5 years of age [1]. 7-valent pneumococcal conjugate vaccine (PCV7) and an investigational 9-valent PCV (PCV9) demonstrated efficacy and effectiveness against invasive pneumococcal disease (IPD), clinical pneumonia and death in children [1–8]; however, substantial IPD cases still occurred due to non-PCV7 serotypes, after global PCV7 rollout [9–12]. This led to the development of a 13-valent PCV (PCV13), containing the PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) and six additional serotypes (1, 3, 5, 6A, 7F and 19A) [13]. In 2010, 82% of IPD cases in South African children <5 years old were caused by the serotypes included in PCV13 [14,15].

In South Africa, PCV7 was first introduced in April 2009 as a 2 + 1 schedule for infants at 6 weeks, 14 weeks, and 9 months of age. PCV7 was replaced with PCV13 in April 2011, with gradual up-scaling of coverage by the end of 2011 [16]. PCV7 was introduced with no catch-up strategy implemented; however, a catch-up

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http://dx.doi.org/10.1016/j.vaccine.2017.06.081
0264-410X/

program was recommended following transition to PCV13, which included all children between 18 and 36 months of age; and children 36 and 71 months of age with underlying medical conditions, including immunocompromising conditions and chronic diseases [17].

Although PCVs have been established to be safe, immunogenic and efficacious in select groups of children with underlying medical conditions, including those with HIV/AIDS and malnutrition [14,18], further research is warranted to determine the optimal dosing schedule in these populations. The aim of this study was to determine the immunogenicity of one and two doses of PCV13 in pneumococcal vaccine-naive children aged 12–71 months with underlying medical conditions.

2. Materials and methods

An open-label study was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, South Africa, where children with chronic medical or immunocompromising conditions are followed-up at specialist clinics. With the transition from PCV7 to PCV13 a catch-up plan was developed in early 2012 and all parents/caregivers were encouraged to take their children to health facilities across South Africa to be vaccinated. Enrolment into the study targeted "at-risk" children aged 12–71 months old presenting at the HIV, Renal and Pulmonology clinics, and healthy control children in the same age group identified through the PCV13 catch-up program. Exclusion criteria for study enrolment included prior receipt of any pneumococcal vaccination. Enrolment took place from 30 July 2012 to 9 May 2013.

2.1. Study procedures

At-risk children were administered two doses of PCV13, two months apart, while control children received only one PCV13 dose at enrolment. Venous blood samples were collected on four occasions from the at-risk children and on three occasions from controls: just prior to each PCV13 dose and one month after each PCV13 dose in the at-risk children; and just prior PCV13 vaccination, at one month post-PCV13 and at three months post-PCV13 in control children. Samples were processed at the Respiratory and Meningeal Pathogens Research Unit in Johannesburg, South Africa. Vaccine serotype-specific capsular IgG antibodies were measured using a luminex-based enzyme immunoassay as described previously [19].

2.2. Statistical analysis

The number of children targeted for enrolment was based on a convenience sample of children with the at-risk conditions presenting at the outpatient clinics at CHBAH, who were willing to participate in the study. Continuous variables were summarized as means or medians and compared by Student *t*-test or Wilcoxon rank-sum test between the study-groups; categorical variables were described as proportions and compared by Chi-squared test or Fisher's exact test, as appropriate. Geometric mean concentrations (GMCs) of serotype-specific antibodies with 95% confidence intervals (95%CI) were generated and p-values between groups were computed on log10 transformed data using an unpaired *t*-test. Comparisons of GMCs and fold-increase in concentration between the study-groups were performed using analysis of covariance on log10 transformed data with age and baseline GMCs as covariates, where necessary. The percentage of children with GMC $\geq$0.35 μg/mL (threshold measure of protective immunity against vaccine serotype IPD following the primary series in young infants) [1] and the percentage of children with $\geq$4-fold-increase in antibody concentration were calculated and multivariable logistic regression was used to compare proportions between study-groups, adjusting for confounders where necessary. Data were analysed using GraphPad prism 6 (GraphPad Software, Inc. La Jolla, CA, USA) and Stata14 (StataCorp LP, Texas, USA).

2.3. Ethical considerations

Study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M120366) and conducted in accordance with Good Clinical Practice guidelines. Signed informed consent was obtained from the parents or legal guardians of the children for participation in this study.

3. Results

Overall 112 children were enrolled in the study, 45 HIV-uninfected controls with no chronic illness, 50 HIV-infected, 8 children with kidney disease and 9 with lung disease; Table 1. The median age at enrolment was 61.5 months, with controls having a median age of 62.3 months, which was similar to those with HIV infection (61.4 months), but higher than in children with kidney (51.6 months, p = 0.007) or lung diseases (54.1 months, p < 0.001). Overall 53.2% of participants were female and 95.5%

Table 1
Demographic characteristics of the study participants.

	Overall	Control participants	HIV-infected participants	Kidney disease participants	Lung disease participants
Number of participants (%)	112	45 (40.2)	50 (45.1)	8 (7.2)	9 (8.1)
Female (%)	59 (53.2)	21 (47.7)	30 (60.0)	3 (37.5)	5 (55.6)
Black African descent ethnicity (%)	106 (95.5)	42 (93.3)	50 (100.0)	6 (75.0)	8 (88.9)
Visit 1: Median age - months (IQR)	61.5 (55.5–63.7)	62.3 (58.5–63.2)	61.4 (58.0–66.8)	51.6 (47.0–58.7)	54.1 (48.0–58.3)
Visit 2: Median age - months (IQR)	62.6 (56.7–64.9)	63.3 (58.8–64.3)	62.5 (59.1–67.8)	52.6 (48.1–59.7)	54.2 (48.5–61.2)
Visit 3: Median age - months (IQR)	62.0 (54.9–67.5)	–	63.6 (61.0–68.9)	52.2 (48.9–58.6)	55.2 (50.0–60.2)
Last visit: Median age - months (IQR)	64.5 (58.8–66.4)	65.2 (63.3–66.1)	64.4 (61.2–69.1)	53.2 (49.8–59.5)	56.1 (51.2–61.3)
Median CD4 + cell count at enrolment - cells/mL (IQR)		–	1139 (814–1465)	–	–
Mean CD4 + cell% at enrolment (SD)		–	32 (7.8)	–	–
Antiretroviral therapy (%)		–	49 (98)	–	–
Immunosuppressive drugs (%)		–	–	2 (22.2)	7 (77.8)

The age differences between the control versus kidney and lung disease participants were statistically significant at all visits.
Visit-1 occurred at study enrolment, at which time children were consented into the study, baseline blood samples were taken and the first PCV13 dose was given.
Visit-2 occurred one month after enrolment, at which time blood was drawn from the children.
Visit-3 (for at-risk participants only) occurred two months after enrolment, at which time a third blood specimen was taken and the second PCV13 dose of was given.
Last visit occurred one month after the second PCV13 dose in at-risk children, and three months after the single PCV13 dose in controls.
Abbreviations: IQR: interquartile range; SD: standard deviation.

Please cite this article in press as: Jallow S et al. Immunogenicity of 13-valent pneumococcal conjugate vaccine among children with underlying medical conditions. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.06.081