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Immunogenicity following the first and second doses of 7-valent pneumococcal conjugate vaccine in HIV-infected and -uninfected infants☆,☆☆

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ABSTRACT

Background: The immunogenicity of pneumococcal conjugate vaccine (PCV) has not been evaluated in HIV-infected infants following the first and second PCV-doses. We studied antibody kinetics of serotypes included in 7-valent PCV in HIV-infected and HIV-uninfected infants prior to and following each of three PCV-doses.

Methods: HIV-uninfected infants born to HIV-uninfected (HUU) and HIV-infected mothers (HEU); and perinatal HIV-infected children with $CD^{4+} < 25\%$ randomized to initiate antiretroviral treatment (ART) when clinically and/or immunologically indicated (ART−) or immediately (ART+) were enrolled. Vaccination occurred at approximately 7.4, 11.5 and 15.5 weeks of age. Serotype-specific antibody was measured by ELISA following each PCV-dose and opsonophagocytic activity (OPA) to three serotypes following the second and third doses.

Results: Pre-vaccination, antibody geometric mean concentrations (GMCs) were higher in HUU compared to HIV-exposed groups for most serotypes. GMCs and proportion of infants with antibody ≥0.35 μg/ml were similar in HUU compared to other groups following the second PCV-dose. In all groups, GMCs were greater following the third compared to post-second dose; and a higher proportion within each group had antibody ≥0.35 μg/ml to 6B and 23F. OPA GMTs increased after the third compared to post-second dose for studied-serotypes; as did the proportion with OPA ≥8 to 23F.

Conclusion: A two-dose primary-series of PCV probably confers similar protection against invasive pneumococcal disease in HIV-infected compared to HUU children. The inferior response to serotypes 6B and 23F, and lower GMCs and OPA GMTs, following two compared to after three PCV-doses may have implications in the prevention of pneumococcal disease in high-burden countries.

1. Background

Pneumococcal conjugate vaccines (PCV) are licensed as a three-dose primary-series before seven months of age with a booster in the second year of life. Many infant immunization programs have, however, implemented alternate dosing schedules, including a two-dose primary-series with a booster dose later [1]. This is aimed at reducing the overall costs of PCV immunization and number of injectable vaccines during childhood. Recent WHO recommendations on infant PCV immunization recommend a three-dose primary-series or two doses followed by a booster dose at least 6 months later [1]. This decision was informed in-part by meta-analyses, without any study identified in HIV-infected children, of the immunogenicity and effectiveness of different PCV dosing schedules [2,3].

The potential effect of fewer doses of PCV in HIV-infected children, who contribute toward a high burden of invasive pneumococcal disease (IPD) in sub-Saharan African countries [4], requires

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study. A three-dose primary-series of 9-valent PCV without a booster dose was less efficacious against vaccine-serotype IPD in anti-retroviral treatment (ART) naïve HIV-infected (65%) compared to HIV-uninfected children (85%) after 2.3 years of follow-up [5]. Furthermore, there was waning of protection against IPD five years post-vaccination in the HIV-infected children [6]. The lower efficacy of PCV in HIV-infected children was corroborated by poorer qualitative antibody responses, measured by opsonophagocytic activity assay (OPA), following the three-dose primary-series compared to HIV-uninfected infants [7]. Also, greater decay of antibody was observed in HIV-infected compared to HIV-uninfected children five years post-vaccination [6]. Consequently, a three-dose primary-series coupled with a booster dose of PCV may be required in ART− naïve HIV-infected children.

There have, however, been recent changes in the management of HIV-infected infants, including early initiation of ART irrespective of their immunological status [8]. Similar quantitative and OPA responses following three doses of PCV during infancy were observed in HIV-infected infants initiated on ART immediately at 6–12 weeks of age as HIV-uninfected children [9]. This analysis of secondary-study objectives expand on our previous report on the quantitative and OPA responses following the third infant PCV-dose in HIV-infected and HIV-exposed- uninfected children; and infants born to HIV-uninfected mothers (HUU) [9].

The secondary-objectives analyzed in this report include: (i) comparison of pre-vaccination PCV-serotype antibody concentrations; (ii) comparison of antibody responses following the first and second-PCV-doses between HIV-infected and HEU children compared to HUU infants; (iii) comparison of the antibody responses and OPA responses after the second compared to post-third PCV-dose (which we previously reported [9]) within each group and relative to HUU infants.

2. Methods

2.1. Study cohort

Detailed information of the study-cohort enrolled between April 2005 and June 2006 has been described. [9] Briefly, four groups of children aged 6 to 12 weeks were enrolled to address a co-primary study objective of quantitative antibody responses following the three-dose primary-series at 6, 10 and 14 weeks of 7-valent PCV (i.e. Prevnar®; Wyeth Vaccines, NJ, USA). Study-groups included HIV-infected infants, co-enrolled from the Children with HIV Early Antiretroviral (CHER) Study in South Africa [10], with CD^{4+} T-lymphocyte ≥25% randomized to either initiate ART immediately (ART+); or deferred (ART−) until clinically or immunologically indicated [10]. Also, a convenience sample of HIV-infected children with CD^{4+} < 25%, who were immediately initiated on ART, were enrolled (Group-5). The first-line ART regimen used in CHER included zidovudine, lamivudine and lopinavir/ritonavir. Methodology for HIV PCR, HIV ELISA and CD^{4+} count testing has been published [10].

In parallel to enrolment of HIV-infected children from CHER, two cohorts of HIV-uninfected children were also enrolled. This included infants born to HIV-infected mothers who were HIV PCR (Roche Amplicor Version 1.5 RNA PCR) negative at baseline and one month after the third PCV-dose (i.e. HEU); and children born to HIV-uninfected mothers who had a non-reactive HIV-ELISA at study-enrolment (HUU).

2.2. Study procedures

Venous blood samples were collected prior to the first PCV-dose, immediately prior to each of three subsequent PCV-doses and 3–6 weeks after the third dose and processed at Respiratory and Meningeal Pathogens Research Unit (RMPRU), Johannesburg, South Africa. Vaccine-serotype specific capsular IgG antibodies were measured using a standardized enzyme immunoassay (EIA) as described [9].

Antibody functionality post-second and third PCV-doses were determined by OPA for serotypes 9V, 19F and 23F as described. [9]. The coefficient of variation for the control sera, from a vaccinated-volunteer, which was included on each plate were 9.9%, 9.7% and 9.3% for serotypes 9V, 19F and 23F respectively post-second dose.

2.3. Statistical analysis

Data were analyzed using SAS® 9.1 (SAS Institute Inc., Cary, NC, USA). The geometric mean concentrations (GMC) or titers (GMT) and 95% confidence intervals (95% CI) of serotype-specific antibody concentrations and OPA titers were calculated following $\log_{10}$ data transformation. Comparisons of GMC or GMT were performed using analysis of covariance (ANCOVA) on $\log_{10}$ transformed data with study center, gender, race and baseline antibody concentration (for post-vaccination measures) as covariates. Samples with values below the assay detection limit were assigned half the detection limit when calculating GMC or GMTs. Logistic regression with study-center, gender and race as covariates were applied for comparisons of proportion of children in groups with serum antibody thresholds of ≥0.35 μg/ml; i.e. a putative measure of community-immunity against vaccine-serotype IPD [1].

If the maximum observed killing of pneumococci by HL-60 cells on OPA was less than 50%, at the lowest dilution, the serum was assigned an arbitrary titer of 4 [9]. Detectable killing activity on OPA was defined as a titer of ≥8. An α value of ≤0.05 was considered significant.

To minimize confounders between groups, only children in whom all previous study procedures were undertaken within protocol specified window-periods up to the analyzed time-point were evaluated. No statistical comparisons were undertaken for Group-5 because of its small sample size.

2.4. Ethics considerations

This study was approved by the Human Subjects Research Committees of the University of the Witwatersrand, Stellenbosch University, the Medicine Control Council of South Africa and Clinical Science Review Committee of the Division of AIDS. Signed informed consent was obtained from the parents of the children for participation in this study. The study was registered at ClinicalTrials.gov NCT00099658.

3. Results

Overall, 579 children were enrolled between the five groups. Further analysis was limited to 565 children in whom the immunogenicity evaluation following the first PCV-dose was undertaken within the protocol specified window-period. The mean age at vaccination and timing of antibody measures are detailed in Table 1. The median HIV-1 viral load was ≥750,000 copies/ml in HIV-infected children; and median CD4% were 35.5%, 36.6% and 21.8% among ART+, ART− and Group-5, respectively.

3.1. Geometric mean antibody concentrations

Pre-vaccination, HUU children had higher GMCs to all serotypes compared to HEU infants ($p \leq 0.006$ for all observations), as well for at least three serotypes (either 9V, 18C, 19F or 23F) compared to ART+ and ART− children; Table 2. Baseline GMCs were also higher for all serotypes, except 18C ($p = 0.24$), in HIV-infected children