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Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease in HIV-Infected and -Uninfected Children in South Africa: A Matched Case-Control Study

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Background. South Africa introduced 7-valent pneumococcal conjugate vaccine (PCV7) in April 2009 using a 2 + 1 schedule (6 and 14 weeks and 9 months). We estimated the effectiveness of ≥2 PCV7 doses against invasive pneumococcal disease (IPD) in human immunodeficiency virus (HIV)-infected and -uninfected children.

Methods. IPD (pneumococcus identified from a normally sterile site) cases were identified through national laboratory-based surveillance. Specimens were serotyped by Quellung or polymerase chain reaction. Four controls, matched for age, HIV status, and hospital were sought for each case. Using conditional logistic regression, we calculated vaccine effectiveness (VE) as 1 minus the adjusted odds ratio for vaccination.

Results. From March 2010 through November 2012, we enrolled 187 HIV-uninfected (48 [26%] vaccine serotype) and 109 HIV-infected (43 [39%] vaccine serotype) cases and 752 HIV-uninfected and 347 HIV-infected controls aged ≥16 weeks. Effectiveness of ≥2 PCV7 doses against vaccine-serotype IPD was 74% (95% confidence interval [CI], 25%–91%) among HIV-uninfected and −12% (95% CI, −449% to 77%) among HIV-infected children. Effectiveness of ≥3 doses against vaccine-serotype IPD was 90% (95% CI, 14%–99%) among HIV-uninfected and 57% (95% CI, −371% to 96%) among HIV-infected children. Among HIV-exposed but -uninfected children, effectiveness of ≥2 doses was 92% (95% CI, 47%–99%) against vaccine-serotype IPD. Effectiveness of ≥2 doses against all-serotype multidrug-resistant IPD was 96% (95% CI, 62%–100%) among HIV-uninfected children.

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METHODS

The pneumococcal polysaccharide-protein conjugate vaccine (PCV) is recommended for use globally, particularly in developing countries with a high childhood mortality [1]. A clinical trial in South Africa of a 9-valent PCV (PCV9) administered at 6, 10, and 14 weeks of age (ie, 3 + 0 schedule, 3-dose primary series and no booster dose) demonstrated efficacy of 83% (95% confidence interval [CI], 39%–97%) in HIV-uninfected children and 65% (95% CI, 24%–86%) in HIV-infected children against vaccine-serotype (VT) invasive pneumococcal disease (IPD) [2]. The 7-valent PCV (PCV7), administered in 3 + 1 or 2 + 1 schedules, has been shown to be highly effective against IPD in developed countries [3–10].

South Africa introduced PCV7 into the Expanded Program on Immunization (EPI) in April 2009 [11]. A novel, accelerated 2 + 1 schedule (6 weeks, 14 weeks, and early booster at 9 months), with no catch-up, was used [11]. This schedule was based on evidence of sufficient immunogenicity with 2 primary doses, cost savings afforded by a 2- rather than 3-dose primary series, data indicating waning efficacy without a booster dose in HIV-infected children (approximately 4% of South African children <5 years in 2009), and the need to deliver the primary and the booster doses at the youngest possible ages [12–14]. The 13-valent PCV (PCV13) replaced PCV7 in June 2011.

There are no published studies evaluating the effectiveness of routine PCV use on disease in Africa. Additionally, the effectiveness of the accelerated 2 + 1 schedule is unknown. Our primary objectives were to determine the effectiveness of ≥2 doses of routinely administered PCV7 against VT IPD and all-serotype IPD among HIV-uninfected and HIV-infected children. In addition, we evaluated whether HIV exposure altered vaccine effectiveness (VE), because the increasing availability of interventions for prevention of mother-to-child transmission (PMTCT) of HIV in high HIV-prevalence settings has led to increasing numbers of HIV-exposed but -uninfected children; however, there are no published data on PCV efficacy or effectiveness in this group [15, 16].

Data Collection

Data were collected through standardized interviews of guardians and patient records review. Data from 1 month preceding the date of pneumococcal specimen collection (the reference period) were collected from each case and their matched controls. The cases were eligible if they had meningitis, bacteremic meningitis, or bacteremia. Controls were defined as having a fever at any time during the month preceding the date of pneumococcal specimen collection. Controls were excluded if they had meningitis, bacteremic meningitis, or bacteremia. The controls were matched to the cases on age, sex, and calendar period. The study protocol was approved by institutional review boards at the University of the Witwatersrand, the surveillance sites, and the venues where cases and controls were enrolled. Data were collected through standardized interviews of guardians and patient records review. Data from 1 month preceding the date of pneumococcal specimen collection (the reference period) were collected from each case and their matched controls. The cases were eligible if they had meningitis, bacteremic meningitis, or bacteremia. Controls were defined as having a fever at any time during the month preceding the date of pneumococcal specimen collection. Controls were excluded if they had meningitis, bacteremic meningitis, or bacteremia. The controls were matched to the cases on age, sex, and calendar period. The study protocol was approved by institutional review boards at the University of the Witwatersrand, the surveillance sites, and the venues where cases and controls were enrolled.
controls. Children with a history of being HIV infected were included as HIV infected. HIV testing is recommended for all hospitalized children with unknown HIV status in South Africa and was performed by enzyme-linked immunosorbent assay (ELISA) with confirmation by ELISA on a second specimen for children ≥18 months of age, and qualitative HIV DNA polymerase chain reaction testing for children <18 months of age. Documented maternal HIV status data was sought for all children from antenatal records or recent testing. CD4⁺ lymphocyte counts were determined at clinician discretion by flow cytometry [19]. Children were classified as having severe immunosuppression based on CD4⁺ percentage of total lymphocyte cell count [20]. Children were classified as HIV exposed but uninfected if they had a documented HIV-negative status but positive maternal HIV status. Children with weight-for-age z scores in the reference period <−2 using the 2009 World Health Organization (WHO) child growth standards (adjusting for prematurity for those born before 37 weeks’ gestation) and those with nutritional edema were classified as being malnourished [21]. Written documentation of immunization history was sought for all cases and controls, from patient-held immunization records and vaccination records at health facilities, as relevant. Patients giving a history of not receiving any vaccines were recorded as unvaccinated.

**Sample Size**

We assumed VE against all-serotype IPD of 40% in HIV-uninfected and 55% in HIV-infected children and against PCV7 serotypes of 85% in HIV-uninfected and 65% in HIV-infected children [2]. We assumed a case-control PCV7 vaccination correlation of 0.2 [22]. Assuming vaccine coverage of 60% with a 4:1 match of controls to cases at a significance level (α) of .05 and a power of 0.80, we needed to enroll 171 HIV-uninfected cases (13 vaccine serotype) and 70 HIV-infected cases (42 vaccine serotype).

**Statistical Analysis**

We used surveillance data to compare the characteristics of enrolled and non enrolled IPD case patients. PCV doses were counted only if received ≥14 days before the specimen collection date. The matched odds ratio of vaccination (vs no vaccination), controlling for confounders, was estimated using conditional logistic regression. We evaluated each individual potential confounder to identify those that altered the odds ratio of PCV vaccination by >10% irrespective of statistical significance; these were further evaluated in multivariable models [23]. We did not group related confounders. We included a single set of confounders for HIV-uninfected children and a second set for HIV-infected children for all adjusted VE analyses to ease comparisons of VE estimates within each group. VE was calculated as 1 minus the adjusted matched odds ratio ×100.

**RESULTS**

From March 2010 through November 2012, we identified 486 eligible children with IPD, of whom 126 were excluded (Figure 1A). We included 361 case patients aged ≥8 weeks; 237 (66%) were HIV uninfected. For the main analysis of the effectiveness of ≥2 doses, we included 296 children aged ≥16 weeks (187 [63%] HIV uninfected). The median age of all enrolled case patients was 43 weeks (interquartile range [IQR], 17–112), 51% (184/361) were male, 97% (351/361) were hospitalized, and the commonest clinical syndrome was bacteremic pneumonia (182/361 [50%]), followed by meningitis (121/361 [34%]), bacteremia without focus (44/361 [12%]), and other (14/361 [4%]). Cases included did not differ statistically from nonenrolled cases with regard to HIV infection status, sex, race, or case-fatality ratio (data not shown) but did differ with regard to specimen type and province (Supplementary Data).

Among HIV-uninfected cases aged ≥16 weeks, 26% (48/187) had VT disease and 35% of these (17/48) had received ≥2 doses of PCV (Figure 2). An additional 12% (22/187) of disease was due to serotype 6A. Of available isolates from HIV-uninfected children ≥16 weeks, 49% (79/161) were nonsusceptible to penicillin and 16% (25/161) were multidrug resistant (MDR). Among HIV-infected cases aged ≥16 weeks, 39% (43/109) had VT disease and 63% (27/43) had received ≥2 doses of PCV7 (Figure 2). An additional 15% (16/109) of disease was due to serotype 6A. Among all isolates from HIV-infected children ≥16 weeks, 67% (68/101) were nonsusceptible to penicillin and 30% (32/101) were MDR. Among all cases, 67% (96/144) of penicillin-nonsusceptible and 85% (46/54) of MDR isolates with available serotyping data were VT or serotype 6A.

We identified 2037 eligible age-matched children as potential controls, of whom 715 were excluded (Figure 1B). The median number of controls per case was 4 for HIV-uninfected and 3 for HIV-infected children. The median interval between case specimen collection and control enrollment was 30 days (IQR, 4–144) for HIV-uninfected and 84 days (IQR, 9–276) for HIV-infected controls. Among HIV-uninfected controls aged ≥8
Figure 1. Flowchart of patients enrolled in the study. A, Cases. B, Controls. Abbreviations: HIV, human immunodeficiency virus; PCV13, 13-valent pneumococcal vaccine.
Figure 2. Number of cases included in the analysis (aged ≥16 weeks) by serotype and vaccination status. A. Human immunodeficiency virus (HIV)–uninfected patients (n = 187). B. HIV-infected patients (n = 109). *Confirmed to be a nonvaccine type on polymerase chain reaction (PCR). Unknown serotypes occurred either because an isolate was not available or because only serogroup(s) could be determined using PCR. Abbreviation: NVT, nonvaccine type.
| Characteristic                                               | HIV-Uninfected | HIV-Infected |  \( P \) Value<sup>a</sup> | HIV-Uninfected | HIV-Infected |  \( P \) Value<sup>a</sup> |
|--------------------------------------------------------------|----------------|--------------|-----------------------------|----------------|--------------|-----------------------------|
| **Demographics**                                             |                |              |                             |                |              |                             |
| Age, wk, median (IQR)                                        | 39 (18–107)    | 38 (16–106)  | .596                        | 52 (18–123)    | 54 (20–115) | .440                        |
| Male                                                         | 94/187 (50)    | 440/752 (59) | .070                        | 57/109 (52)    | 178/347 (51) | .739                        |
| Not black race                                               | 19/187 (10)    | 129/751 (17) | .018                        | 4/109 (4)      | 19/347 (5)  | .316                        |
| **Risk factors**                                             |                |              |                             |                |              |                             |
| Malnutrition<sup>b</sup>                                     | 71/184 (39)    | 207/669 (31) | .027                        | 70/105 (67)    | 107/288 (37) | <.001                       |
| Low birth weight<sup>c</sup>                                 | 40/180 (22)    | 149/738 (20) | .351                        | 19/107 (18)    | 71/340 (21)  | .493                        |
| Preterm<sup>d</sup>                                          | 36/173 (21)    | 98/707 (14)  | .074                        | 12/100 (12)    | 38/310 (12)  | .945                        |
| Underlying conditions (not HIV)<sup>e</sup>                 | 37/187 (20)    | 105/752 (14) | .136                        | 18/109 (17)    | 41/347 (12)  | .087                        |
| Smoking exposure                                             | 43/183 (24)    | 180/752 (24) | .838                        | 26/108 (24)    | 68/346 (20)  | .387                        |
| Day care attendance                                         | 44/183 (24)    | 129/751 (17) | .025                        | 14/108 (13)    | 37/347 (11)  | .490                        |
| No. of children aged <5 y in household                      |                |              |                             |                |              |                             |
| 0                                                            | 87/181 (48)    | 447/751 (60) | .018                        | 62/108 (57)    | 232/344 (67) | .396                        |
| 1–2                                                          | 84/181 (46)    | 580/751 (37) | .425                        | 42/108 (39)    | 101/344 (29) | .290                        |
| ≥3                                                           | 10/181 (6)     | 24/751 (3)   | .408                        | 4/108 (4)      | 11/344 (3)  | .833                        |
| Wood fire in home                                            | 15/184 (8)     | 43/752 (6)   | .098                        | 7/108 (6)      | 18/347 (5)  | .688                        |
| Previous hospital admission (in past 12 mo)                  | 55/185 (30)    | 145/752 (19) | .001                        | 49/109 (45)    | 122/346 (35) | .026                        |
| Breastfed in reference period<sup>f</sup>                   | 73/185 (39)    | 255/751 (34) | .136                        | 30/108 (28)    | 45/346 (13)  | <.001                       |
| **Socioeconomic factors**                                    |                |              |                             |                |              |                             |
| Residence in an informal dwelling                           | 49/185 (26)    | 220/752 (29) | .845                        | 33/109 (30)    | 107/347 (31) | .973                        |
| Crowding <2 people/room                                      | 78/181 (43)    | 356/752 (47) | .186                        | 53/108 (49)    | 153/346 (44) | .595                        |
| 3–4 people/room                                              | 72/181 (40)    | 308/752 (41) | .421                        | 42/108 (39)    | 141/346 (41) | .45                             |
| 5–30 people/room                                             | 31/181 (17)    | 86/752 (11)  | .130                        | 13/108 (12)    | 52/346 (15)  | .222                        |
| Maternal education                                           |                |              |                             |                |              |                             |
| No secondary                                                 | 31/181 (17)    | 100/750 (13) | .013                        | 21/108 (19)    | 73/346 (21)  | .119                        |
| Some secondary                                               | 108/181 (60)   | 407/750 (54) | .565                        | 56/108 (52)    | 200/346 (58) | .584                        |
| Completed secondary                                          | 42/181 (23)    | 243/750 (33) | .310                        | 31/108 (29)    | 73/346 (21)  | .222                        |
| Has a car                                                    | 18/183 (10)    | 142/752 (19) | .004                        | 19/109 (17)    | 41/346 (12)  | .222                        |
| **HIV-related factors**                                      |                |              |                             |                |              |                             |
| HIV exposed                                                  | 10/182 (5)     | 25/661 (3)   | .214                        | 51/108 (47)    | 219/344 (64) | .025                        |
| HIV clinic attendance                                        | 1/183 (1)      | 9/661 (1)    | .469                        | 22/108 (20)    | 45/340 (13)  | .039                        |
| **Vaccines**                                                 |                |              |                             |                |              |                             |
| Hepatitis B at 16 wk                                         | 140/187 (75)   | 595/752 (79) | .322                        | 81/109 (74)    | 292/347 (84) | .071                        |
| DTP vaccine at 16 wk                                         | 106/187 (57)   | 504/752 (67) | .013                        | 67/109 (61)    | 264/347 (76) | .011                        |
| PCV7 ≥2 doses                                                | 110/187 (60)   | 509/752 (67) | .109                        | 68/109 (62)    | 246/347 (71) | .466                        |
| PCV7 ≥3 doses                                                | 30/187 (16)    | 165/752 (22) | .049                        | 26/109 (24)    | 85/347 (25)  | .438                        |
weeks (n = 928), 389 (42%) had a diagnosis of diarrhea, 133 (14%) had a surgical diagnosis (including burns), 87 (9%) had diarrhea and malnutrition, 74 (8%) had malnutrition alone, 68 (7%) had febrile seizures, and 177 (19%) had another diagnosis (Supplementary Data). Among HIV-infected controls aged ≥8 weeks (n = 394), 176 (45%) were enrolled during an

| Table 1 continued. | HIV-Uninfected | HIV-Infected |
|--------------------|----------------|--------------|
| **Characteristic** | **Cases (n = 187)** | **Controls (n = 752)** | **P Value**<sup>a</sup> | **Cases (n = 109)** | **Controls (n = 347)** | **P Value**<sup>a</sup> |
| Age of receipt of PCV7 doses, wk, median (IQR) | | | | | |
| Dose 1 | 6 (5–17) | 6 (5–17) | .265 | 6 (5–17) | 6 (5–22) | .321 |
| Dose 2 | 15 (13–39) | 15 (13–31) | .739 | 16 (13–43) | 16 (13–39) | 1.000 |
| Dose 3 | 40 (20–51) | 40 (25–48) | .785 | 40 (38–62) | 40 (38–52) | .597 |

Abbreviations: DTP, diphtheria, tetanus, pertussis; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; PCV7, 7-valent pneumococcal conjugate vaccine.

<sup>a</sup> Matched.
<sup>b</sup> Weight <80% of expected for age adjusted for prematurity or edema.
<sup>c</sup> <2500 g.
<sup>d</sup> Less than 37 completed weeks.
<sup>e</sup> Asplenia, including asplenia or sickle cell anemia; chronic illness, including chronic lung, renal, liver, cardiac disease, and diabetes; other immunocompromising conditions excluding HIV, including organ transplant, primary immunodeficiency, immunotherapy, and malignancy; and other risk factors, including head injury with possible cerebrospinal fluid leak, neurological disorders, burns, and chromosomal abnormalities.
<sup>f</sup> Reference period is the 1 month preceding the date of pneumococcal specimen collection.

Table 2. Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease in HIV-Infected and -Uninfected Children by Pneumococcal Serotype

| Outcome (No. of Cases/No. of Controls) | Unadjusted VE% (95% CI) | Adjusted VE% (95% CI)<sup>a</sup> |
|--------------------------------------|-------------------------|----------------------------------|
| HIV-uninfected, ≥16 wk, ≥2 doses vs 0 doses | | |
| PCV7 serotypes (48/194) | 77 (40–91) | 74 (25–91) |
| PCV7 serotypes plus 6A (71/289) | 71 (35–87) | 70 (28–88) |
| All serotypes (187/752) | 35 (–13 to 63) | 29 (–27 to 60) |
| Nonvaccine serotypes (101/403) | –56 (–315 to 41) | –76 (–384 to 36) |
| HIV-uninfected, ≥41 wk, ≥3 doses vs 0 doses | | |
| PCV7 serotypes (23/86) | 57 (–100 to 91) | 90 (14 to 99) |
| PCV7 serotypes plus 6A (31/122) | 47 (–109 to 87) | 78 (–15 to 96) |
| All serotypes (89/353) | 47 (–37 to 79) | 63 (–1 to 87) |
| Nonvaccine serotypes (48/195) | 2 (–433 to 82) | 21 (–390 to 87) |
| HIV-infected, ≥16 wk, ≥2 doses vs 0 doses | | |
| PCV7 serotypes (43/137) | 15 (–145 to 71) | –12 (–449 to 77) |
| PCV7 serotypes plus 6A (60/188) | 34 (–94 to 78) | 29 (–174 to 81) |
| All serotypes (109/347) | 31 (–42 to 67) | 6 (–194 to 70) |
| Nonvaccine serotypes (44/136) | 20 (–197 to 79) | –190 (–2997 to 73) |
| HIV-infected, ≥41 wk, ≥3 doses vs 0 doses | | |
| PCV7 serotypes (28/86) | 43 (–108 to 85) | 57 (–371 to 96) |
| PCV7 serotypes plus 6A (37/116) | 53 (–49 to 85) | 76 (–87 to 97) |
| All serotypes (68/223) | 26 (–84 to 70) | 46 (–122 to 87) |
| Nonvaccine serotypes (26/87) | –72 (–966 to 72) | 76 (–166 to 318) |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; PCV7, 7-valent pneumococcal conjugate vaccine; VE, vaccine effectiveness.

<sup>a</sup> Adjusted for use of a wood fire in the home, number of children in the home aged <5 years, and maternal education level for HIV-uninfected children. Adjusted for receipt of trimethoprim-sulfamethoxazole prophylaxis, malnutrition, presence of severe immunosuppression on CD4<sup>+</sup> T-cell count, and whether the patient had received 3 doses of hepatitis B vaccine at 16 weeks of age for HIV-infected children.
Table 3. Effectiveness of ≥2 Doses of 7-Valent Pneumococcal Conjugate Vaccine Versus 0 Doses Against Invasive Pneumococcal Disease in HIV-Uninfected and -Infected Children Aged ≥16 Weeks by HIV Exposure, Malnutrition Status, and Type of Disease

| Risk Groupa | No. of Cases/No. of Controls | Outcome | Unadjusted VE% (95% CI) | Adjusted VE% (95% CI)b |
|-------------|------------------------------|---------|-------------------------|------------------------|
| HIV uninfected |                              |         |                         |                        |
| HIV exposed  | 21/57                        | PCV7 serotypes | 91 (54–98)            | 92 (47–99)          |
| HIV unexposed | 27/133                       | PCV7 serotypes | 72 (1–92)             | 58 (–73 to 90)      |
| HIV exposed  | 79/217                       | All serotypes | 12 (–87 to 58)        | 8 (–102 to 16)      |
| HIV unexposed | 102/508                      | All serotypes | 57 (–3 to 82)         | 51 (–25 to 86)      |
| Meningitis   | 13/55                        | PCV7 serotypes | 85 (–12 to 98)       | 93 (–6 to 100)      |
| Bacteremic pneumonia | 20/85   | PCV7 serotypes | 39 (–194 to 87)      | 78 (–60 to 97)      |
| Malnourishedc | 19/49                        | PCV7 serotypes | 57 (–79 to 90)       | 66 (–79 to 80)      |
| Not malnourished | 28/121                     | PCV7 serotypes | 84 (41–96)           | 81 (19–96)         |
| Multidrug-resistant IPD | 161/637         | All serotypes | 94 (55–99)           | 96 (62–100)         |
| Penicillin-nonsusceptible IPD | 161/637 | All serotypes | 54 (–2 to 79)        | 50 (–15 to 79)      |
| HIV infected |                              |         |                         |                        |
| Severe immunosuppressiond | 26/73                        | PCV7 serotypes | –146 (–2119 to 73)   | –202 (–3199 to 72) |
| No severe immunosuppression | 7/48                         | PCV7 serotypes | 81 (–32 to 97)      | 67 (–222 to 97)    |
| Malnourished  | 31/53                        | PCV7 serotypes | –53 (–547 to 64)     | –35 (–814 to 80)   |
| Not malnourished | 10/68                       | PCV7 serotypes | 36 (–790 to 95)     | 24 (–1358 to 96)   |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IPD, invasive pneumococcal disease; VE, vaccine effectiveness.

a VE in subgroups for which cases and controls were not matched (HIV exposure, malnutrition, severe immunosuppression) was evaluated by inclusion of an interaction term for the subgroup of interest in the multivariable model. P > .1 for all interactions evaluated except for HIV exposure where P = .081.

b Adjusted for use of a wood fire in the home, number of children in the home aged <5 years, and maternal education level for HIV-uninfected children. Adjusted for receipt of trimethoprim-sulfamethoxazole prophylaxis, malnutrition, presence of severe immunosuppression on CD4+ T-cell count, and whether the patient had received 3 doses of hepatitis B vaccine at 16 weeks of age for HIV-infected children.

c Only children with available data on malnutrition status in the reference period were included in this analysis.

d Based on CD4+ percentage of total lymphocyte cell count according to World Health Organization categories [20].

HIV-clinic visit, 66 (17%) had diarrhea and malnutrition, 64 (16%) had malnutrition alone, 60 (15%) had diarrhea alone, and 28 (7%) had another diagnosis. HIV-uninfected and -infected controls aged ≥16 weeks were similar to cases in age and sex distribution but differed for other characteristics (Table 1).

Among HIV-uninfected children aged ≥16 weeks (ie, post-primary series), the adjusted effectiveness of ≥2 doses of PCV7 was 74% (95% CI, 25%–91%) against VT disease, 70% (28%–88%) against VTs plus serotype 6A, and 29% (95% CI –27% to 60%) against all-serotype IPD (Table 2). Among HIV-uninfected children aged ≥41 weeks, the adjusted effectiveness of ≥3 doses of PCV7 was 90% (95% CI, 14%–99%) against VT IPD and 63% (95% CI, –1% to 87%) against all-serotype IPD. There was no significant VE against non-VT disease. Among HIV-infected children aged ≥16 weeks, the adjusted effectiveness of ≥2 doses of PCV7 was –12% (95% CI, –449% to 77%) against VT disease and 6% (95% CI, –194% to 70%) for all-serotype IPD, and confidence intervals were wide. VE confidence intervals for VT and all-serotype IPD following ≥3 doses at ≥41 weeks were also wide (Table 2).

The adjusted VE for ≥2 doses among HIV-exposed but -uninfected children aged ≥16 weeks was 92% (95% CI, 47%–99%) against VT IPD (Table 3). The adjusted VE of ≥2 doses for HIV-uninfected children aged ≥16 weeks against all IPD due to penicillin-nonsusceptible disease was 50% (95% CI, –15% to 79%) and against MDR IPD was 96% (95% CI, 62%–100%). Point estimates of VE were lower for malnourished children than for nonmalnourished children and for HIV-infected children with severe immunosuppression.

Table 4. Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease Caused by Vaccine Serotypes in HIV-Uninfected Children by Number and Timing of Doses

| Schedule (No. of Cases/No. of Controls) | Age Group | Unadjusted VE% (95% CI) | Adjusted VE% (95% CI)a |
|----------------------------------------|-----------|-------------------------|------------------------|
| 1 + 0 vs 0 (64/255)                    | ≥8 wk     | 13 (–90 to 60)          | –11 (–167 to 54)      |
| 2 + 0 vs 0 (48/194)                    | ≥16 wk    | 82 (48–97)              | 76 (27–92)            |
| 2 + 0 vs 0 (25/108)                    | 16–40 wk  | 83 (36–96)              | 73 (–18 to 94)        |
| 2 + 1 vs 0 (23/86)                     | ≥41 wk    | 55 (–117 to 91)         | 88 (–3 to 99)         |

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

a Adjusted for use of a wood fire in the home, number of children in the home <5 years, and maternal education level.
compared to others, but numbers in each subgroup for these analyses were small and differences were not statistically significant. Among HIV-uninfected children, receipt of 2 primary doses alone or 2 primary doses plus a booster dose had similar effectiveness against VT disease (Table 4). A single dose of PCV7 given at about 6 weeks provided no protection against VT IPD.

DISCUSSION

We have demonstrated effectiveness of 2 doses of PCV7 administered at 6 and 14 weeks of age with a booster dose at 9 months in a low- to middle-income country. A 2 + 1 schedule has been demonstrated to be effective in Europe and North America administered at 2 and 4 or 3 and 5 months of age with a booster dose in the second year of life [7, 10, 24, 25]. Although we were unable to demonstrate effectiveness of this schedule in HIV-infected children, VE in HIV-exposed but -uninfected children was high [16, 26]. The effectiveness against penicillin-nonsusceptible and MDR IPD caused by any serotype was high, indicating that PCV may have a substantial impact in reducing the prevalence of MDR pneumococcal disease, as has been demonstrated in other settings [27].

Effectiveness of ≥2 doses in HIV-uninfected children was 74% (95% CI, 25%–91%) against VT disease, similar to estimates of PCV9 efficacy in HIV-uninfected children administered a 3-dose primary schedule at 6, 10, and 14 weeks of age in South Africa (83%; 95% CI, 39%–97%) and The Gambia (77%; 95% CI, 51%–90%) [2, 28]. This is also similar to the approximately 85% reduction in VT IPD observed in HIV-uninfected children aged <2 years from surveillance data in South Africa (A. von Gottberg, unpublished data). Two primary doses are not as immunogenic as 3 primary doses during infancy, but the differences overall are small [29]. A 2 + 1 schedule is feasible for implementation in low- to middle-income countries with high measles vaccine coverage at 9 months and provides cost savings and reduced number of injections compared with a 4-dose schedule, but still includes a booster dose [11].

The magnitude of the all-serotype IPD VE estimate (29%; 95% CI, −27% to 60%) should not be misinterpreted to mean that PCV confers limited overall impact. The vaccine is effective against VT, but not against non-VT, and the measured all-serotype IPD vaccine effectiveness is a combination of effectiveness against VT and non-VT together. When PCV is highly effective, the majority of remaining cases available to be included in a case-control study are non-VT, therefore resulting in a lower measured VE estimate for all-IPD than efficacy against all-IPD as measured in a randomized clinical trial.

We were unable to demonstrate statistically significant effectiveness of ≥2 PCV7 doses in HIV-infected children. This could reflect a lack of statistical power to detect a lower VE than anticipated. Surveillance data from South Africa have shown a 55% relative reduction in VT compared with non-VT among HIV-infected children aged <2 years following PCV7 introduction (A. von Gottberg, unpublished data). At least some of this reduction likely results from indirect protection [30, 31]. HIV-infected children with CD4+ T-cell percentage ≥25% and delayed highly active antiretroviral therapy (HAART) initiation had similar immunoglobulin G (IgG) antibody responses to HIV-uninfected children for PCV administered at 6 and 10 weeks of age; however, this subgroup had functionally impaired antibody responses as measured by opsonophagocytic activity (OPA) compared to children with early HAART initiation [15, 32]. In the latter study, IgG and OPA (serotype 23F) responses were substantially improved in HIV-infected and -uninfected children following a third PCV7 dose at 14 weeks of age, particularly for serotypes 6B and 23F, for which responses were generally lowest. HIV-infected children may benefit from a full 3-dose infant primary series, as was demonstrated to be effective in the South African clinical trial [2]. Practical implementation of a different vaccination schedule by HIV status may, however, not be feasible in settings where HIV status is not known at 10 weeks of age.

Numbers of HIV-exposed but -uninfected children in South Africa remain high (30% of pregnant women in 2011 were HIV infected) following widespread PMTCT implementation, and this group has an increased risk of severe infections [14, 16, 33, 34]. Importantly, the VE in HIV-exposed but -uninfected children was similar to HIV-unexposed children. Antibody responses have been found to be slightly higher in HIV-exposed but -uninfected children compared with HIV-unexposed children after 2 and 3 doses of PCV, possibly related to less interference from maternal antibodies [15, 32].

Our study has limitations. Controls were enrolled from hospitals and clinics rather than the community and thus may differ in their vaccination and disease risk factor status in unmeasured ways from the general population. In our setting, where barriers may exist to access hospital care, hospital controls may, however, be more similar to cases than community controls with respect to unmeasured factors associated with access to care. Low numbers of HIV-infected hospitalized children led to delays in identification of suitable controls and the potential for poor information recall; vaccination histories were gathered from written records and thus would not have been affected, but this might have been a concern for potential confounder variables. HIV-infected controls enrolled from HIV clinics may have had better access to care, which would have biased toward an overestimate of VE. In addition, this group of controls were less immunosuppressed and more likely to receive HAART than cases. Because controls are more likely to be vaccinated than cases, proportionately more vaccinated controls than cases who had received PCV13 were excluded. This should not have substantially affected our estimate of VE but may have
reduced our power to detect an effect. Boys were more common among controls, likely because of high numbers of surgical controls [35]. Although we evaluated a large number of potential confounders in the analysis, residual confounding is possible. Unadjusted and adjusted VE estimates were similar in children aged <41 weeks but differed in older children. This is likely because hospitalization is relatively common in younger children; thus, hospitalized children in this group are probably representative of the general population. Older hospitalized children, however, may have specific risk factors for hospitalization, leading to them being less representative of the source population and therefore more confounding in this age group. For some subanalyses, few cases were observed, limiting our ability to evaluate VE and precluding estimation of effectiveness against individual serotypes.

We were not able to definitively assess the effectiveness of a 2 + 1 schedule in HIV-infected children, but based on existing clinical trial data [2], 3 primary doses should be considered. As coverage with PCV increases among South African children, indirect effects may enhance protection of HIV-infected children [31]. Our study demonstrates that a 2 + 1 schedule of PCV7 aligned with the EPI schedule is effective against VT IPD and MDR IPD in HIV-uninfected and HIV-exposed, -uninfected children, supporting the recent WHO statement indicating use of this alternative schedule in some settings [1].

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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