ORIGINAL ARTICLE

Effectiveness of pneumococcal conjugate vaccine against presumed bacterial pneumonia hospitalisation in HIV-uninfected South African children: a case–control study

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ABSTRACT

Introduction We evaluated pneumococcal conjugate vaccine (PCV) effectiveness against hospitalisation for presumed bacterial pneumonia (PBP) in HIV-uninfected South African children. 7-valent PCV was introduced in April 2009 using a 2+1 schedule (doses at age 6, 14 and 39 weeks), superseded with 13-valent PCV in May 2011.

Methods A matched case–control study was conducted at three public hospitals (Soweto, Cape Town and KwaZulu-Natal) between April 2009 and August 2012. PBP cases had either WHO defined radiographically confirmed pneumonia or 'other infiltrate' on chest radiograph with C-reactive protein ≥40 mg/L. Hospitalised controls were children admitted with a disease unlikely to be pneumococcal and matched for case age, site and HIV infection status. Age-matched community controls were enrolled from Soweto. Adjusted vaccine effectiveness (aVE) was estimated using conditional logistic regression.

Results Of 1444 HIV-uninfected enrolled PBP cases, 1326 had ≥1 hospital controls (n=2075). Overall, aVE of an up-to-date PCV schedule was 20.1% (95% CI −9.3% to 41.6%) in children aged ≥8 weeks and 39.2% (95% CI 8.46% to 59.6%) among children 16–103 weeks of age. There were 889 PBP cases in Soweto with hospital controls and ≥1 community control (n=2628). The aVE using community controls was similar compared with hospital controls in Soweto, including 32.1% (95% CI 4.6% to 51.6%) and 38.4% (95% CI 7.7% to 58.8%), respectively, in age group ≥8 weeks and 52.7% (95% CI 25.7% to 69.9%) and 53.8% (95% CI 19.5% to 73.5%), respectively, in age group 16–103 weeks.

Conclusions PCV implemented using a 2+1 schedule in the routine infant immunisation programme was effective at preventing PBP in HIV-uninfected children. Effectiveness estimates were similar to efficacy measured by earlier randomised controlled trials using different vaccination schedules.

Key messages

What is the key question?

- This multicentred case–control study in South Africa evaluated the effectiveness of pneumococcal conjugate vaccine (PCV) in preventing pneumonia, following its introduction into the public immunisation programme.

What is the bottom line?

- This study provides the first data from Africa, showing the effectiveness of a 2+1 PCV dosage schedule, which may inform policy regarding other immunisation programmes in low-income and middle-income country settings.

Why read on?

- The study also provides insight into the effect which different sources of controls (ie, hospital controls vs community controls) have on the PCV vaccine effectiveness estimates against pneumonia.

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INTRODUCTION

Worldwide, pneumococcal disease is estimated to cause 450 000 deaths in children age less than 5 years annually, 90% of which are due to non-bacteraemic pneumonia and approximately 43% of which occur in Africa.[1] The WHO recommendation for immunisation of infants with pneumococcal conjugate vaccine (PCV) was based on efficacy trials undertaken in the USA and two African countries. In these randomised controlled trials, a 7-valent PCV (PCV7) in USA and 9-valent PCV in South Africa and The Gambia were efficacious in preventing vaccine-serotype invasive pneumococcal disease (75%–95%) and all-cause pneumonia associated with radiographically confirmed alveolar consolidation (CXR-AC; 25%–37%).[2–4]

Observational studies of the impact of PCV introduction on pneumonia from predominantly high-income countries have observed temporal declines in hospitalisation due to all-cause pneumonia ranging from 15% to 65%, and 47% to 78% for healthcare provider coded 'pneumococcal pneumonia' admissions among children <2 years of age.[5 6] However, ecological studies may fail to identify or inadequately adjust for other factors, which may affect incidence of pneumonia

hospitalisation. Case–control studies offer an alternate strategy for evaluating vaccine effectiveness (VE), and may also be the only method available in low-income countries where long-term administrative databases required for undertaking ecological studies are generally unavailable.

The aim of our study was to determine the effectiveness of PCV against hospitalisation for presumed bacterial pneumonia (PBP), which included CXR-AC, in HIV-uninfected South African children ≥8 weeks of age.

METHODS

Study setting

We conducted a matched case–control study using two control groups from April 2010 to August 2012 in three South African public hospitals; hospital controls were enrolled at all three sites and community controls at one site. The hospitals included secondary–tertiary care-level hospital in Soweto, Johannesburg (Chris Hani-Baragwanath Academic Hospital, CHBAH) and a tertiary referral hospital in Cape Town (Red Cross War Memorial Children's Hospital) which serves an urban low-income population; and a secondary-level care hospital in Umfolozi, KwaZulu-Natal (Ngwelezane Hospital) which services a rural, low-income population. The under-5 mortality rates in the three study settings were 27, 54 and 68 per 1000 live births for Cape Town, Soweto and Umfolozi, respectively, in 2009.[7]

A 7-valent PCV (Prevnar-7, Wyeth Vaccines/Pfizer, Philadelphia, Pennsylvania, USA) was introduced into the South African national public immunisation programme in April 2009. From May 2011 onward, the programme transitioned to 13-valent PCV (Prevenar-13). The schedule includes two doses at ages 6 and 14 weeks and a third dose at 9 months.[8] There was no catch-up campaign of older children at PCV7 introduction, while a limited catch-up campaign targeted PCV-unvaccinated children age 18–36 months between May and September 2011 following transition to PCV13. All childhood vaccines in South Africa are provided at no cost to children in the public sector. The vaccine coverage for three doses of PCV in South Africa were estimated as 64%, 89% and 99% in 2010, 2011 and 2012, respectively.[9]

Maternal antenatal HIV prevalence in the study sites is high (Soweto 29%, Cape Town 18%, KwaZulu-Natal 38% in 2009).[10] Strengthening efforts to prevent mother-to-child HIV transmission from 2009 in South Africa resulted in a dramatic decline in vertical transmission of HIV infection to infants (<2% compared to 8%–12% in earlier years).[11]

Case and control enrolment

PBP cases

Sequential children hospitalised with attending physician diagnosed lower respiratory tract infection (LRTI) were screened for enrolment from 07:00 to 19:00, on 5–6 days of the week. Cases admitted overnight were enrolled the following morning. Study staff was trained to enrol cases based on the inclusion criteria for the study. Vaccination status was not ascertained until after the case had been enrolled, reducing the likelihood that receipt of PCV might have influenced whether or not a case was enrolled. Cases of PBP were defined by either (1) the presence of CXR-AC or (2) any other abnormal CXR infiltrate and a quantitative C-reactive protein (CRP) of at least 40 mg/L in a child hospitalised for LRTI.[12] CXRs were requested at the discretion of the attending physician and evaluated by two study physicians according to WHO guidelines for standardised interpretation of paediatric CXRs for vaccine studies.[13] The readers were calibrated against the WHO standard and they were required to achieve at least 70% concordance to the WHO standard prior to involvement in this study. The decision of the third reader for discordant readings was the final reading. For a CXR to be classified as CXR-AC, both readers had to agree; discordant findings were adjudicated independently by a third study physician. For a CXR to be categorised as having any abnormal infiltrate other than CXR-AC, only one of the two primary readers were required to interpret it as such. CRP on blood samples was analysed by immunoturbidometry (717 Automated Analyzer, Boehringer Mannheim/Hitachi, Mannheim, Germany).

Cases had to be age eligible to have received ≥1 PCV dose (ie, born on/after 15 February 2009). Exclusion criteria included: symptom onset ≥14 days prior to admission, inability to determine HIV status, previous enrolment as PBP case, having been discharged from hospital within the past 14 days, transfer from other hospital where the duration of stay was >1 day or lack of documented vaccination history. The primary source of vaccination history was the child's immunisation card. Children with no documented vaccination history were not eligible to participate; except for those in which a parent/guardian reported that the child had received no vaccines other than doses given at birth, in which case the child was considered to have received zero doses of PCV.

Hospital controls

Individually matched hospital controls were matched by site, HIV status and date of birth (±1 month from the case date of birth for cases ≤12 months old, ±2 months for cases >12 months old). Children eligible for ≥1 PCV dose (as for cases above) who were admitted for a non-LRTI illness that was unlikely to be due to pneumococcus (eg, exclusion of meningitis, sepsis and acute otitis media) were screened for possible participation as hospital controls. Exclusion criteria for hospital controls included: lack of documented vaccination history (as with cases, described above), hospitalisation in the past month for any suspected or proven pneumococcal disease including any LRTI, sepsis or meningitis and previous enrolment as a PBP case or hospital control. Hospital controls were targeted to be enrolled within 30 days following enrolment of the PBP cases. Hospital controls that were matched to cases that were subsequently determined to be ineligible (eg, did not meet case definition after final CXR interpretation or CRP results were available) were reallocated to other previously enrolled cases if all matching criteria were met.

Community controls

In Soweto, we also enrolled matched community controls. Approximately 23 000 of the 29 000 annual births in Soweto occur at CHBAH. Potential community controls were identified using a random sampling of live births recorded on the CHBAH labour ward admission log on the case's date of birth. If an insufficient number of children were born on the same date, potential controls with a date of birth ±1 day, ±2 days, etc., were sought, within the same age range for matching as detailed for hospital controls. Parents of potential controls were contacted via telephone call or home visit and invited to have their children enrolled. If three attempts to contact were unsuccessful or if the child did not fulfil eligibility criteria, the next child on the random list was sought until an appropriate control was identified. All potential controls in the community were assumed to be HIV-uninfected based on the low rate (<2%) of mother-to-child vertical transmission of HIV.[11] Children were

excluded as potential community controls if reported to be HIV-infected during the interview, or if born to a HIV-infected mother and reported to have had >2 hospitalisations since birth and in whom a confirmatory HIV test was unavailable or refused by the caregiver. Other exclusion criteria for community controls included those which were applied to the hospital controls. Enrolment of community controls was also targeted to occur within 30 days following case identification.

SAMPLE SIZE AND POWER

We assumed PCV effectiveness of 25% against PBP, with vaccine coverage of 85% over the course of the study and a correlation coefficient of 0.2.[14] The sample size was calculated using PASS 2008 (NCSS, Kaysville, Utah, USA). We aimed to enrol sufficient cases and controls so that the analysis using each set of controls would have ≥80% power using a 95% significance level to measure the effectiveness in children ≥16 weeks of age (eligible for ≥2 PCV doses). Thus, we targeted enrolling 1450 HIV-uninfected PBP cases overall, including an estimated 950 at CHBAH. We aimed for a 2:1 ratio for enrolling hospital controls when feasible in order to increase statistical power. Three community controls were enrolled for each case in Soweto.

Data collection

Once consented, the child's medical history, demographic and household characteristics were obtained by parent interview. Vaccination histories were abstracted from parent-held vaccine records at enrolment. In addition, starting in August 2010, we photocopied vaccine records and the vaccination history was reabstracted by an independent reviewer; discrepant vaccine histories were reviewed and resolved by a third study team member. For cases and hospital controls, the medical record was also reviewed to obtain information about the current illness and HIV status.

For cases and hospital controls with no documented HIV status, testing for HIV infection was based upon initial screening with a third-generation HIV-1 ELISA test, with positive results confirmed by a different HIV-1 ELISA assay in children ≥18 months of age. Qualitative HIV PCR assays were undertaken to determine HIV infection status in children <18 months of age who were known to have been born to an HIV-infected mother or in whom the screening HIV-ELISA test was reactive.

Statistical analysis

Only first episodes of PBP were included in this analysis. Control-children were assigned a reference date (date on which their corresponding case was hospitalised), which was used as the date for determining their vaccination status. Vaccine doses received at least 14 days before hospitalisation for cases and the reference date for controls were considered valid; all other doses were disregarded in the analysis. Children were considered to be up-to-date with PCV if they had received at least the recommended number of valid doses for their age: ≥1 dose among those aged 8–15 weeks, ≥2 doses among those aged 16–40 weeks and ≥3 doses among those aged ≥41 weeks.

Analyses were done using SAS software (V.9.3). We used conditional logistic regression to compare cases and controls. We estimated PCV effectiveness to be one minus the matched OR for PCV vaccination ×100%.To assess for confounding factors, other variables were added to the model individually; variables that changed the matched OR or the β parameter for PCV vaccination by ≥20% were evaluated for possible inclusion in multivariable models. For the two models using data from hospital controls (one for all sites and one for Soweto only) variables found to be confounders in either model were included in both final multivariable models. Multivariable models of adjusted vaccine effectiveness (aVE) were assessed for colinearity and two-way interactions. Crude and aVE were presented overall and by age strata based on eligibility for one, two and three doses (ie, 8–15, 16–40 and ≥41 weeks); we also examined effectiveness among the age group 16–103 weeks, which represented children eligible for at least two doses and was comparable to the age range of children included in the analysis of the PCV vaccine efficacy trials.[2–4] For all analyses, p values <0.05 were considered significant.

Ethics

Faculty of Health Sciences institutional review boards at the University of the Witwatersrand, University of KwaZulu-Natal, University of Cape Town and Johns Hopkins Bloomberg School of Public Health approved the study protocol. Parents/legal caregivers of all study participants provided written informed consent for their child's enrolment in the study. The trial was registered on the South African National Clinical Trial Register (DOH-27-0909-3030).

RESULTS

We enrolled 3508 children with LRTI, of whom 1705 (48.6%) were categorised as PBP; of these, 78.0% had CXR-AC and 22.0% had other infiltrate with CRP ≥40 mg/L (figure 1). There were 1444 HIV-uninfected children with a first episode of PBP and adequately documented vaccination records, including 1326 (91.8%) for whom at least one matched hospital control was enrolled (total 2075 hospital controls). Furthermore, we enrolled 2628 community controls that were matched to 889 PBP cases enrolled in Soweto (figure 1). For community controls, 74% of attempts to contact a randomly selected potential control were successful; among those contacted, 71% were found to be eligible of whom 85% were enrolled. Case-patient characteristics varied between sites in age, proportion of PBP cases with lower chest wall indrawing, proportion of cases that were mechanically ventilated, proportion of PBP cases with CXR-AC and case fatality rate (table 1).

Most cases (>95%) were Black African and 58% were males (table 2). Case and hospital controls had relatively similar characteristics, although prior hospitalisations, low birth weight and having a flush toilet were more commonly reported for cases; day care attendance and maternal education <11 years were more frequent among controls. Conversely, cases in Soweto differed from community controls in nearly all demographic and household characteristics examined. More than 94% of all cases and controls (hospital and community) had received their first dose of diphtheria–tetanus–pertussis *Haemophilus influenzae* type B vaccine. Among hospital controls, the most common discharge diagnoses were gastroenteritis (n=1015, 48.9%), febrile convulsions (n=358, 17.2%), underweight/malnutrition, (n=261, 12.6%) and poisoning/ingestions (n=116, 5.6%).

Using hospital controls, the aVE of an up-to-date PCV schedule was 20.1% (95% CI −9.3% to 41.6%) in children ≥8 weeks of age. The point estimate of effectiveness was slightly higher in the 16–40-week age group (ie, eligible to have received at least two doses of PCV; 36.9%) and the ≥41-week group (ie, eligible to have received the complete three-dose schedule; 15.7%) compared to the 8–15-week age group (ie, eligible for only one dose; 8.5%), although the CIs overlapped (table 3). Among children age 16–103 weeks, the aVE of an up-to-date schedule was 39.2% (95% CI 8.4% to 59.6%).

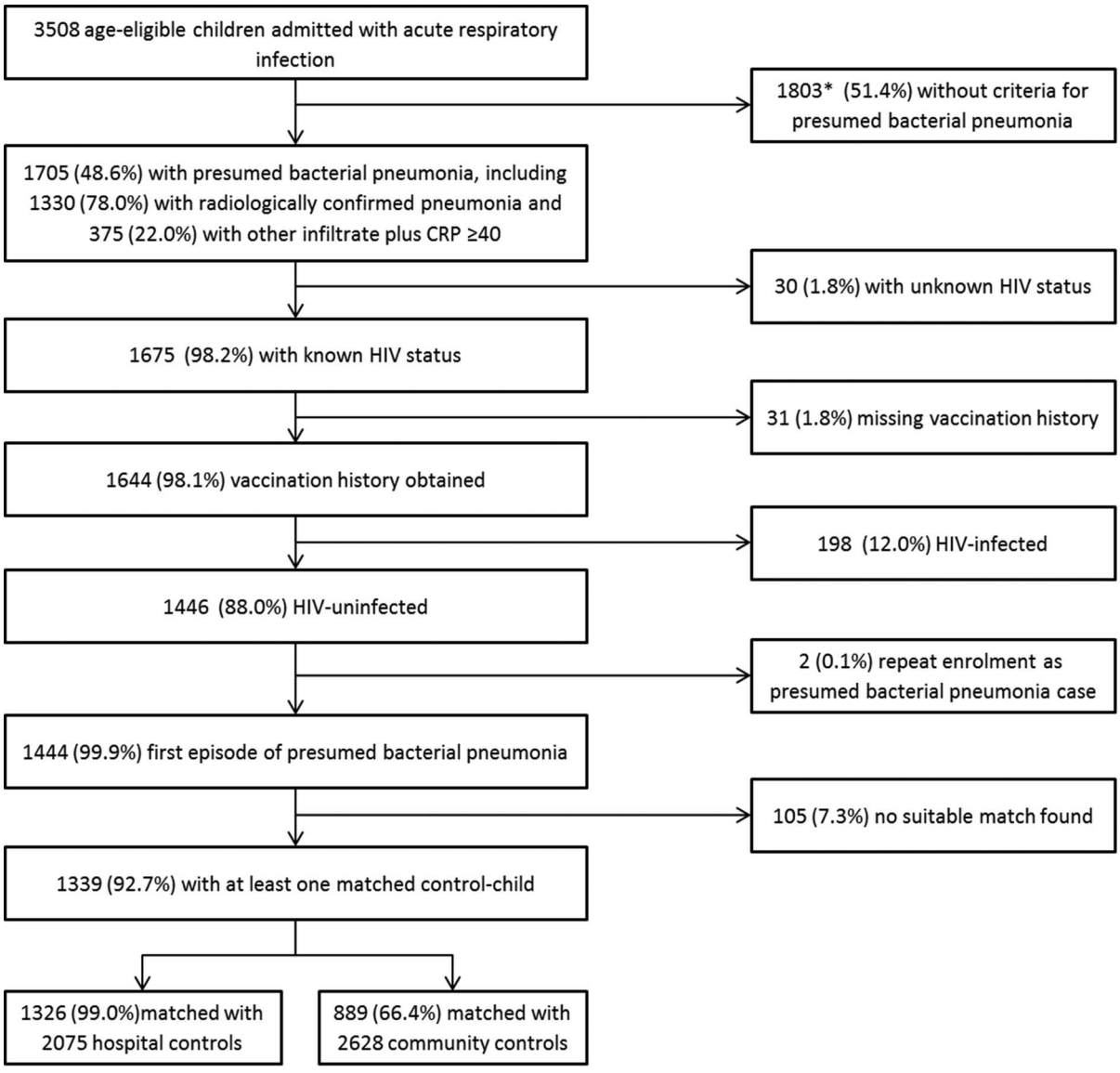

Figure 1 Overview of enrolment of eligible cases and controls. CRP, C-reactive protein; CXR, chest radiograph; PBP, presumed bacterial pneumonia.

An exploratory analysis comparing children born before March 2011, who were mainly likely to have been vaccinated with PCV7, compared to those born thereafter and who would most likely received PCV13, did not show much difference in the aVE (see online supplementary tables 1A, B). However, the study was not powered to address the effectiveness of the specific vaccine formulations.

Using hospital controls from the Soweto site only, the aVE of an up-to-date schedule was 38.4% (95% CI 7.7% to 58.8%) overall (ie, ≥8 weeks of age) and 53.8% (95% CI 19.5% to 73.5%) in the 16–103-week age group (table 3). Similar estimates were observed overall (32.1%; 95% CI 4.6% to 51.6%) and among the 16–103-week age group (52.7%; 95% CI 25.7% to 69.9%) when comparing cases from Soweto with matched community controls.

For analyses using hospital controls overall and from Soweto, adjusted point estimates of effectiveness were higher than the crude estimates. However, when using community controls, adjusted models generally yielded lower or similar estimates to the unadjusted models. There was no significant change in VE when analyses were restricted to cases with CXR-AC; among ≥8 weeks of age, the aVE using hospital controls was 12.2% (95% CI −25.7% to 38.7%), hospital controls from Soweto only was 36.5% (95% CI 0% to 59.7%) and community controls was 30.6% (95% CI −0.7% to 52.1%). When restricting to cases with CXR-AC among children aged 16–103 weeks, the aVE using hospital controls was 26.0% (95% CI −21.7% to 55.0%), hospital controls from Soweto only was 41.3% (95% CI −12.3% to 69.3%) and community controls was 50.3% (95% CI 18.1% to 69.8%). Similarly, excluding hospital controls that tested positive for rotavirus did not significantly alter VE estimates (data not shown). Among all cases and controls included in the analysis that had received at least one dose of PCV, the median age at receipt was 6 weeks (IQR 6–7 weeks); for the second PCV dose, the median age was 15 weeks (IQR 14–17 weeks); and for the third dose, the median age was

Table 1 Demographic and clinical characteristics of presumed bacterial pneumonia cases*

Case characteristics	Cases with hospital controls				Cases with community controls
	All sites n=1326 n (%)	Soweto n=893 n (%)	Cape Town n=274 n (%)	KwaZulu-Natal n=159 n (%)	Soweto n=889 n (%)
Age of admission (weeks)					
Median	35.0	38.0	30.0	25.0	38.0
Mean	43.1	46.4	36.0	36.3	46.0
Range	8–167	8–167	8–119	8–154	8–167
CXR-AC	1040 (78.4)	742 (83.1)	168 (61.3)	130 (81.8)	741 (83.4)
CRP≥40 +CXR-OI	286 (21.6)	151 (16.9)	106 (38.7)	26 (17.2)	148 (16.6)
Lower chest indrawing	666 (52.9)	274 (32.6)	235 (89.5)	157 (100.0)	273 (32.6)
Wheezing	603 (47.6)	387 (45.3)	153 (59.8)	63 (40.1)	381 (44.8)
Mechanical ventilation	34 (2.7)	6 (0.7)	6 (2.2)	22 (14.3)	6 (0.7)
Death	13 (1.0)	2 (0.2)	1 (0.4)	10 (6.3)	2 (0.2)

*Missing values excluded from denominators; missing data ranged from 0% to 5%.
CRP, C-reactive protein; CXR-AC, confirmed alveolar consolidation; CXR-OI, chest radiograph with infiltrate other than alveolar consolidation.

Table 2 Characteristics of all PBP cases with hospital controls, cases with hospital controls from Soweto only and cases with community controls

Characteristic	Cases with hospital controls			Cases with hospital controls, Soweto only			Cases with community controls		
	Cases n=1326 n (%)	Controls n=2075 n (%)	Matched p value	Cases n=893 n (%)	Controls n=1453 n (%)	Matched p value	Cases n=889 n (%)	Controls n=2628 n (%)	Matched p value
Black race	1266 (95.5)	1979 (95.4)	0.062	883 (98.9)	1426 (98.1)	0.149	879 (98.9)	2564 (97.6)	0.028
Male sex	765 (57.7)	1191 (57.4)	0.824	525 (58.8)	832 (57.3)	0.604	521 (58.6)	1343 (51.2)	<0.001
Weight-for-age Z score <2	332 (25.1)	558 (26.9)	0.524	225 (25.2)	419 (28.9)	0.096	224 (25.2)	145 (5.5)	<0.001
Any chronic condition*	41 (3.1)	85 (4.1)	0.277	17 (1.9)	44 (3.0)	0.147	17 (1.9)	17 (0.6)	0.002
Prior hospitalisation	265 (20.0)	295 (14.2)	<0.001	155 (17.4)	185 (12.8)	0.003	151 (17.0)	228 (8.7)	<0.001
Prior pneumonia hospitalisation	144 (11.1)	100 (4.8)	<0.001	86 (9.9)	65 (4.5)	<0.001	83 (9.6)	99 (3.8)	<0.001
Low birth weight†	296 (22.7)	326 (15.8)	<0.001	191 (21.8)	223 (15.4)	<0.001	187 (21.5)	386 (14.7)	<0.001
Mother HIV-infected	432 (33.3)	620 (30.4)	0.094	288 (32.8)	428 (30.1)	0.303	286 (32.6)	601 (22.9)	<0.001
TB contact	112 (8.5)	165 (8.0)	0.524	53 (6.0)	75 (5.2)	0.353	53 (6.0)	143 (5.5)	0.632
Exclusive breast fed <4 months	698 (52.8)	1102 (53.2)	0.939	464 (52.2)	770 (53.1)	0.721	464 (52.4)	1635 (62.2)	<0.001
Brick house	870 (66.1)	1355 (65.5)	0.198	615 (69.6)	973 (67.2)	0.244	612 (69.6)	2064 (78.5)	<0.001
Indoor water supply	474 (35.8)	699 (33.8)	0.664	309 (34.6)	517 (35.7)	0.688	302 (34.0)	1234 (47.0)	<0.001
Flush toilet	1020 (77.0)	1479 (71.4)	0.012	770 (86.3)	1194 (82.3)	0.010	763 (85.9)	2339 (89.0)	0.011
Coal/wood primary fuel	47 (3.6)	103 (5.0)	0.797	0 (0)	2 (0.1)	0.973	0 (0)	6 (0.2)	0.973
Primary care giver smokes	86 (6.5)	117 (5.6)	0.615	48 (5.4)	89 (6.1)	0.447	47 (5.3)	29 (1.1)	<0.001
Day care	216 (16.4)	436 (21.0)	<0.001	165 (18.5)	330 (22.8)	0.024	156 (17.6)	515 (19.6)	0.091
Mother education <11	386 (30.0)	686 (33.2)	0.021	214 (24.8)	433 (29.9)	0.005	211 (24.5)	543 (20.7)	0.016
Crowding‡	685 (51.8)	1092 (52.7)	0.654	443 (49.8)	794 (54.8)	0.013	443 (50.0)	814 (31.0)	<0.001
At least one dose of DTP	1258 (94.9)	1954 (94.1)	0.231	855 (95.7)	1371 (94.4)	0.111	851 (95.7)	2527 (96.2)	0.494
PCV doses§									
0	144 (10.9)	234 (11.3)	–	75 (8.4)	133 (9.2)	–	76 (8.6)	157 (6.0)	–
1	394 (29.7)	579 (27.9)	0.318	229 (25.6)	368 (25.3)	0.674	234 (26.3)	614 (23.4)	0.191
2	476 (35.9)	729 (35.1)	0.961	340 (38.1)	519 (35.7)	0.978	338 (38.0)	1066 (40.6)	<0.001
3	296 (22.3)	498 (24.0)	0.325	237 (26.5)	401 (27.6)	0.371	232 (26.1)	755 (28.7)	<0.001
4	16 (1.2)	35 (1.7)	0.173	12 (1.3)	32 (2.2)	0.052	9 (1.0)	36 (1.4)	0.004

*Includes parental report of malnutrition, asthma, heart disease, cerebral palsy, sickle cell, kidney disease.
†Birth weight <2500 g.
‡More than two people sleep in the room with the child.
§Using zero doses as referent group.
PBP, presumed bacterial pneumonia; PCV, pneumococcal conjugate vaccine.

Table 3 Effectiveness of up-to-date pneumococcal conjugate vaccine schedule against presumed bacterial pneumonia in HIV-uninfected children

		Cases with hospital controls Cases=1326, controls=2075			Cases with hospital controls, Soweto only Cases=893, controls=1453			Cases with community controls Cases=889, controls=2628		
	Age group (weeks)	Strata in model	Crude VE (95% CI)	Adjusted† VE (95% CI)	Strata in model*	Crude VE (95% CI)	Adjusted† VE (95% CI)	Strata in model*	Crude VE (95% CI)	Adjusted¶ VE (95% CI)
By age group	8–15	93/229	−38.4 (−113.0 to 10.1)	8.5 (−68.0 to 50.2)	62/135	−26.5 (−114.2 to 25.2)	51.0 (−10.9 to 78.4)	68/142	14.6 (−42.6 to 48.8)	−9.4 (−91.2 to 37.4)
	16–40	45/538	32.4 (−7.5 to 57.5)	36.9 (−10.6 to 64.0)	20/338	41.2 (−14.7 to 69.9)	60.9 (9.7 to 83.1)	44/335	49.8 (13.5 to 70.8)	52.2 (15.4 to 73.0)
	≥41	40/559	−4.8 (−67.6 to 34.5)	15.7 (−48.2 to 52.1)	33/420	−4.5 (−81.4 to 39.9)	24.5 (−45.6 to 60.9)	25/412	58.6 (24.0 to 77.4)	49.6 (2.5 to 73.9)
	16–103	81/1017	27.5 (−1.6 to 48.3)	39.2 (8.4 to 59.6)	46/688	34.5 (−2.7 to 58.2)	53.8 (19.5 to 73.5)	67/680	55.5 (32.3 to 70.7)	52.7 (25.7 to 69.9)
Overall	>=8	187/1326	1.0 (−27.4 to 23.1)	20.1 (−9.3 to 41.6)	117/893	5.7 (−30.2 to 31.7)	38.4 (7.7 to 58.8)	138/889	40.9 (18.9 to 56.9)	32.1 (4.6 to 51.6)

*The denominator indicates the number of strata (case–control sets) in that subgroup, and the numerator indicates the number of strata contributing to the model. When using conditional logistic regression, only discordant strata (ie, sets with vaccinated case and at least one non-vaccinated control or with non-vaccinated case and at least one vaccinated control) contribute to the model.
†Adjusted for race, sex, discharge diagnosis of malnutrition, low birth weight, exclusive breast feeding up to the age of 4 months, prior hospitalisation for pneumonia, day care attendance, mother self-reported HIV-infected, maternal education level <11th grade, contact with an adult with TB, more than two people sleeping in room with child, flush toilet in the home and receipt of ≥1 dose of diphtheria–tetanus–pertussis vaccine.
¶Adjusted for weight, for age Z score <2.
VE, vaccine effectiveness.

39 weeks (IQR 39–41 weeks). Although we intended to evaluate PCV effectiveness in both HIV-infected and -uninfected children, we were unable to enrol sufficient numbers of cases to evaluate VE among HIV-infected children.

DISCUSSION

This is the first African study to demonstrate effectiveness of PCV in prevention of PBP hospitalisation, when used as part of routine childhood immunisation with a novel vaccination schedule at 6, 14 and 40 weeks of age. The data corroborate those of earlier randomised controlled phase III trials of 7–11 valent PCVs.[2–4 12 15] The observed protection among children age 16–103 weeks (39.2%) is similar to the 33% efficacy against CXR-AC observed in a meta-analysis of PCV in the randomised, placebo-controlled trials in which follow-up time was largely limited to children <2 years of age.[5] Also, the overall adjusted VE of 20.1% for children who were up to date for vaccination and ≥8 weeks of age was similar to the vaccine efficacy of 25% (95% CI 4% to 41%) observed in a randomised, placebo-controlled trial of a 9-valent PCV against CXR-AC previously undertaken in Soweto, South Africa.[16] Notably, the national PCV schedule implemented in South Africa and evaluated in this study differed from those in the randomised controlled trials where children received three doses within 4–6 months of age with or without a booster in the second year of life. As such, the observation of similar VE among children age 16–40 weeks, a group eligible to have received only two doses of PCV in the current study, is important, particularly since young infants are at greatest risk of pneumonia-associated morbidity and mortality.[1]

Additional factors must be considered in comparing our results to those of PCV clinical trials. First, the results although heavily weighted in regard to evaluating PCV7 effectiveness, are a composite for VE following the transition from PCV7 to PCV13 during the course of the study. That some children received PCV13, which includes serotypes 1 and 5, may explain in part why our results were similar to those seen in the clinical trials that used the 9-valent PCV.[16] In addition, our case definition (PBP) was broader than that proposed by WHO (ie, CXR-AC) for measuring PCV VE against pneumonia, although VE estimates in our study remained similar when analysis was restricted to only cases with CXR-AC. The decision to use an expanded case definition of PBP was based on a previous post-hoc analysis that this composite endpoint provided greater sensitivity for detecting the burden of pneumonia prevented by PCV,[17 18] without affecting the specificity of the pneumonia endpoint for establishing vaccine efficacy. One randomised controlled trial of a 10-valent PCV that used the same case definition as ours reported an efficacy of 26% (95% CI 8% to 40%) against radiologic pneumonia.[12]

Conducting case–control studies in a way that minimises bias, and therefore provides accurate results, can be challenging. This includes selection of appropriate controls that represent the same source population of cases and adjustment for important confounders is crucial. In this study, we used two different control groups. The hospital controls had similar characteristics as the case-patients, yet the analysis using that control group was heavily affected by confounding. Community controls, not unexpectedly, differed in many characteristics from cases, particularly in relation to known risk factors for pneumonia such as male gender, malnutrition, chronic underlying conditions, low birth weight, absence of exclusive breast feeding at age <4 months, overcrowding and maternal HIV status. Nevertheless, VE estimates using this control group were less

affected by other variables and results of adjusted analyses using each control group were remarkably consistent. Of note, in Soweto, there is readily available access to healthcare at little direct cost to families. Hospital controls in other settings with barriers to accessing healthcare may be more problematic. Our results highlight the importance of adjusting for confounding in the analysis. However not all confounders can be easily or accurately measured, and it is possible that key factors were not adjusted for in the analysis. A further limitation of our study related to the reliability of verbally reporting vaccination status, in which accepted parental declaration of non-vaccination (beyond birth doses) was viewed as evidence of zero PCV doses. This was done, as children who have not received any vaccines beyond birth doses are unlikely to have a card documenting their lack of vaccination, however excluding this group of children could lead to important bias. Therefore we chose to include children whose parents reported no vaccines received beyond those given at birth.

Other limitations of our study include having restricted community control enrolment to only one of the three sites. We observed important differences in the severity of illness among cases across sites, with a case fatality proportion of 6.3% in KwaZulu-Natal and <1% in Cape Town and Soweto; such variability may reflect differences in access to care, which can influence the optimal control group. However, due to logistical and financial challenges of undertaking enrolment of community controls at the other sites, we were only able to enrol community controls in Soweto. Although we included children from three diverse settings, the findings may not be generalisable to all contexts in South Africa or to other African countries. Furthermore, although we aimed at limiting hospital controls to illnesses in which pneumococcus was unlikely to have been the aetiological agents, the inclusion of children with febrile convulsions and other non-specified febrile illness as hospital controls, could inadvertently have included children with pneumococcal illness as hospital controls, potentially biasing towards the null.

In conclusion, our study corroborates the findings from randomised controlled trials and ecological studies from high-income countries, which establish a major role of PCV in protecting young children against pneumonia. We present the first estimates of PCV protection against a pneumonia endpoint using a case–control methodology. Our data support the use of a two-dose primary schedule plus a booster dose and provide evidence of PCV effectiveness against pneumonia in the context of a routine immunisation programme in an African country.

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