3-2019

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International Journal of Infectious Diseases 80 (2019) 28–33

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

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ARTICLE INFO

Article history:
Received 13 August 2018
Received in revised form 6 December 2018
Accepted 11 December 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Pneumococcal conjugate vaccine
Effectiveness
Invasive pneumococcal disease

ABSTRACT

Objective: To assess the effectiveness of 10-valent pneumococcal conjugate vaccine (PCV10) against invasive pneumococcal disease (IPD) due to vaccine serotypes of *Streptococcus pneumoniae* post introduction of the vaccine into the routine immunization program in Pakistan.
Methods: A matched case–control study was conducted at 16 hospitals in Sindh Province, Pakistan. Children aged <5 years (eligible to receive PCV10) who presented with radiographically confirmed pneumonia and/or meningitis were enrolled as cases. PCR for the *lytA* gene was conducted on blood (for radiographic pneumonia) and cerebrospinal fluid (for meningitis) samples to detect *S. pneumoniae*. The proportion of IPD due to vaccine serotypes (including vaccine-related serogroups) was determined through serial multiplex PCR. For each case, at least five controls were enrolled from children hospitalized at the same institution, matched for age, district, and season.
Results: Of 92 IPD patients enrolled during July 2013 to March 2017, 24 (26.0%) had disease caused by vaccine serotypes. Most case (87.5% of 24) and control (66.4% of 134) children had not received any PCV10 doses. The estimated effectiveness of PCV10 against vaccine-type IPD was 72.7% (95% confidence interval (CI) −7.2% to 92.6%) with at least one dose, 78.8% (95% CI −11.9% to 96.0%) for at least two doses, and 81.9% (95% CI −55.7% to 97.9%) for all three doses of vaccine.
Conclusions: The vaccine effectiveness point estimates for PCV10 were high and increased with increasing number of doses. However, vaccine effectiveness estimates did not reach statistical significance, possibly due to low power. The findings indicate the likely impact of vaccine in reducing the burden of vaccine-type IPD if vaccine uptake can be improved.

Introduction

Pneumococcal disease is a major cause of childhood morbidity and mortality worldwide (O'Brien et al., 2009). A significant proportion of pneumonia and meningitis in low and middle-income settings is attributed to *Streptococcus pneumoniae*, often presenting as invasive pneumococcal disease (IPD) (O'Brien et al., 2009; Zar et al., 2013). The pneumococcal conjugate vaccine (PCV) has contributed significantly in reducing vaccine-related childhood morbidity and mortality in the developed world (Hsu et al., 2009; Loo et al., 2014). Several middle- to low-income countries have introduced PCV into their routine immunization schedules with the assistance of Gavi—The Vaccine Alliance (IVAC, 2014).

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https://doi.org/10.1016/j.ijid.2018.12.007

There are, however, few reports on post-vaccine introduction assessment available from these countries, especially those in Asia. Pakistan was the first country in South Asia to introduce the 10-valent PCV (PCV10) into its national expanded program on immunization (EPI). A scientific assessment of vaccine effectiveness could help policymakers understand the performance of a routine vaccination program in Pakistan and provide information to guide decisions on introducing or sustaining PCV programs in other countries in the region. The primary objective of this study was to assess the effectiveness of PCV10 on IPD due to vaccine serotypes of *S. pneumoniae*. This appears to be the first such evaluation of any pneumococcal vaccine in the region.

Methods

Setting

Pakistan is a lower middle-income country with a population of more than 200 million (Pakistan Bureau of Statistics, 2017) and a gross domestic product (GDP) per capita of US$ 1468.20 (World Bank, 2019). Globally, Pakistan has the third highest burden of child mortality, and progress towards reducing child mortality has been slow (Bhutta et al., 2013). Infectious diseases, particularly vaccine-preventable illnesses, contribute a significant burden to childhood mortality, with Pakistan identified as one of the six countries globally with a high burden of *S. pneumoniae*-related mortality (WHO, 2000). Sentinel site surveillance has been established at several public and private secondary and tertiary care hospitals serving low and middle-income populations in eight districts of the province of Sindh. Sindh is the second most populous province in Pakistan, with a population of 48 million.

PCV10 was introduced into the Sindh EPI on April 1, 2013, with a schedule of three doses given at 6, 10, and 14 weeks of age and no opportunity for catch-up vaccination (Ali et al., 2016). All vaccines are provided free of cost to children of eligible age through designated government EPI centers and outreach facilities. Twenty-nine percent of children in Sindh were reported to be fully vaccinated before the initiation of this study (Pakistan Demographic and Health Survey, 2013).

Sixteen healthcare facilities (nine public and seven private) were included in the study. These sites were established based on the availability of pediatric inpatient care, including the diagnosis, treatment, and management of childhood pneumonia and meningitis, the availability of chest radiography facilities, and the willingness of the hospital administration to participate in the study. A list of participating hospitals by district is provided in the Supplementary material (Appendix S1).

Study design and enrollment

A matched case–control study design was used. Case enrollment began in July 2013 and was concluded in March 2017. Children admitted to inpatient units at the sentinel hospitals were screened for eligibility prior to enrollment in the study. A research team (comprising a medical officer and/or nurse) at each sentinel site maintained inpatient lists and assessed each individual child's eligibility for enrollment.

Children born on or after February 15, 2013 (who would have been eligible to receive at least one dose of PCV10) and who were less than 5 years of age at the time of the study, who had a provisional diagnosis of pneumonia and/or meningitis, and who were residents of study catchment districts were screened for enrollment as a case patient. Children were considered to have suspected severe pneumonia if they presented with signs of fast respiratory rate (>60 breaths per minute for children younger than 2 months, >50 per minute for those aged 2–11 months, and >40 per minute for those aged 12–59 months), fever (>38.3 °C), and at least one of three danger signs, including lower chest wall indrawing, central cyanosis, and inability to drink (Scott et al., 2012). Similarly, children were considered to have suspected meningitis if they presented with fever (>38.3 °C) along with one of the following signs: neck stiffness, bulging fontanelle (in children aged <12 months), altered consciousness and irritability, or convulsions. Children eligible for recruitment into the study underwent chest radiography, blood specimen collection, and lumbar puncture, as determined by the treating physician.

All chest radiographs were screened for substantial alveolar consolidation by a physician at each sentinel site (reader 1) and scanned using a VIDAR high-resolution digitizer for further interpretation. The scanned radiographs were sent to two independent radiologists trained in World Health Organization (WHO) protocols (readers 2 and 3) (World Health Organization, 2001; O'Grady et al., 2010) for X-ray interpretation in a blinded fashion. Radiographs with discordant end-points between reader 2 and 3 were interpreted by an additional senior radiologist, with two out of three agreements considered the final diagnosis for radiographically proven pneumonia. For quality assurance, every fourth negative radiograph identified from each sentinel site was sent to readers 2 and 3 for verification.

Lumbar puncture specimens of cerebrospinal fluid (CSF) obtained from children with suspected meningitis were analyzed for cell count; visibly cloudy specimens or those with a white blood cell count $>10 \times 10^6$/l were considered diagnostic of bacterial meningitis.

All children with radiographically proven pneumonia or bacterial meningitis were considered eligible for study enrollment. Blood samples from children with radiographically proven pneumonia and CSF samples from bacterial meningitis case patients were sent to the Infectious Disease Research Laboratory at Aga Khan University (AKU-IDRL) in Karachi at a controlled temperature (2–8 °C) for the detection of *S. pneumoniae* by *lytA*-targeted real-time PCR (Maria da Gloria et al., 2007). A case met the criteria for IPD if *S. pneumoniae* was detected in either blood or CSF specimens on PCR. Serotype determination was done using serial multiplex PCR. Details of laboratory methods for blood PCR are provided elsewhere (Kabir et al., 2017). IPD cases were classified as vaccine-type (VT-IPD) if the serotype matched those present in the PCV10 composition (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) or if they were from the same serogroups (e.g. 6A/B/C/D, 7A/F, 18A/B/C/F).

Children were excluded if they had been enrolled previously, were not eligible to receive vaccines, resided outside the study catchment area, or if parental consent was not obtained.

Five controls were enrolled from the same hospital for each case of IPD, irrespective of serotype and vaccination status. Children were excluded from enrollment as controls if they had signs of suspected pneumonia, meningitis, or fever of unknown origin, if they lived outside the catchment area, or if their parents did not provide consent. Controls were matched to case patients by age, district, and season. Controls were age-matched within 8 weeks of case patient age for case patients aged <1 year and within 12 weeks for case patients aged ≥1 year. Controls were randomly identified from the inpatient wards and emergency rooms and enrollment was completed within 2 months of enrollment of the respective IPD case. In some instances, where an enrolled control was vaccinated but did not have a clear vaccination history (i.e., lacked a verifiable vaccination record), an additional control was enrolled. All additional controls were included in the calculation of vaccine effectiveness (VE).

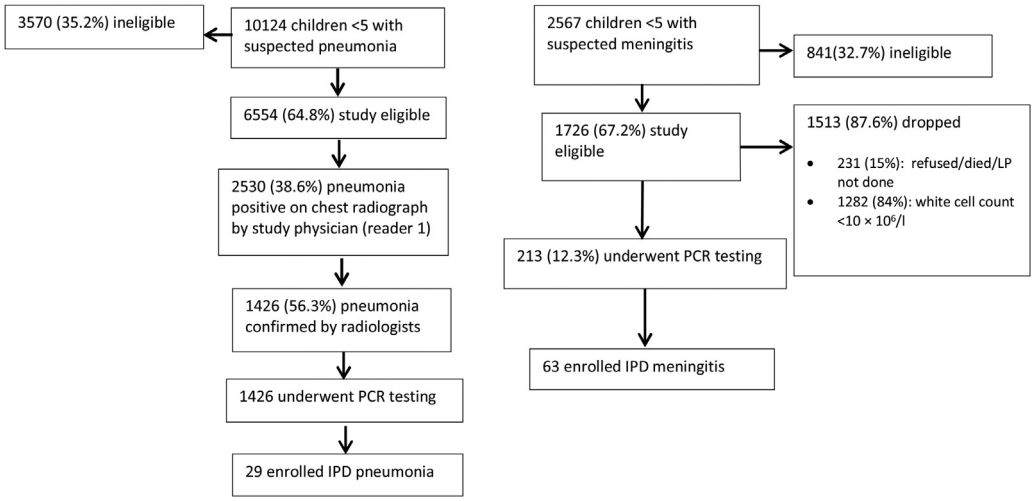

Figure 1. Study profile.

Data collection

Parents/caretakers of all enrolled children were interviewed in person by trained research staff using a standardized questionnaire. Data were collected on demographic characteristics and household information, including the number of people residing in the household, index child's exposure to smoke, treatment history and outcome of disease for the current illness, and vaccination history. Where available, vaccination cards were used to verify vaccination history. These cards were reviewed by two independent research staff in a blinded manner. In the case of discrepancy between the two readers, vaccination status was verified with the EPI center where the child was vaccinated, as identified by the parents. When parents indicated that the child had not received any vaccination, the oral history was used.

Sample size

The sample size was calculated using NCSS PASS v. 11 software (NCSS, 2019) for a matched case–control study design. Initially the sample size was calculated to assess VE against overall IPD. However, it was recalculated in 2014 to detect a VE of 73% for VT-IPD with at least three doses of PCV10 (Domingues et al., 2014). Using an alpha error of 0.05, 80% power, 50% vaccine coverage for PCV10, and a correlation coefficient for vaccination between matched cases and controls of 0.20, it was estimated that 28 VT-IPD cases with five matched controls for each case would be needed.

Data quality and statistical analysis

All case registration forms were double-entered using Visual Foxpro v. 6.0 (Microsoft Corporation, USA). Enrollment logs (for cases and controls) were reviewed on a weekly basis by the primary investigator. Data were analyzed using Stata software version 12.0 (Hamilton, 2013). The Chi-square test and *t*-test were applied for the comparison of characteristics between case patients and controls. Standard analysis was conducted using logistic regression to calculate the odds ratio (OR) of PCV10 vaccination versus no vaccination in VT-IPD cases compared with controls (Pearce, 2016). VE was calculated with the formula, $VE = (1 - OR) \times 100\%$. For VE analysis, the vaccine dose was considered valid if received before hospitalization. Confounders and risk factors were assessed by including additional variables such as sex, age, wasting, stunting, underweight, paternal education, large family size ($\geq$5 family members), exposure to cigarette smoke in the house, exposure to cooking smoke, use of natural gas for cooking, at least one other child <5 years of age in the house, and crowding (>2 people sleeping in the same room as the child). Propensity scores for significant confounders and risk factors including sex, age, and paternal education, use of natural gas for cooking, crowding, cigarette smoking, and exposure to smoke (p-values $\leq$0.25) were used for the final adjusted multivariable model.

Results

A total 10 124 children with suspected pneumonia and 2567 children with suspected meningitis were screened at the sentinel sites using the eligibility criteria. Of 6554 eligible children, 2530 (38.6%) were identified as having suspected pneumonia by study physicians at the sentinel sites and underwent chest radiography. Of these, 1426 (56.3%) were diagnosed with radiographically confirmed pneumonia by radiologists at subsequent levels of X-ray interpretation.

Among 1726 eligible children with suspected meningitis, 213 (12.3%) were diagnosed with bacterial meningitis and their CSF samples were submitted for PCR testing.

A total of 92 case patients with IPD were enrolled, including 63 cases of pneumococcal meningitis and 29 cases of pneumococcal pneumonia (Figure 1). Among these, a serotype could be determined for 60 (65.2%). Twenty-four (26%) were identified as vaccine types (VT-IPD), as defined above. Thirty-six cases (39.1%) were non-vaccine types (NVT) and 32 (34.7%) could not be typed with the available panel of multiplex PCR reactions employed. Table 1 provides the general characteristics of the 24 VT-IPD case patients. The mean age of the VT-IPD case patients was 6.5 months;

Table 1
Characteristics of enrolled children with vaccine-serotype IPD.

Characteristics	Case patients (n = 24), n (%)
Age in months, mean ± SD	6.5 ± 4.1
Clinical syndrome	
Pneumococcal meningitis	17 (70.8)
Pneumococcal pneumonia	7 (29.2)
Medical care	
Admitted to hospital	24 (100)
Duration of hospitalization in days, mean ± SD	9.3 ± 6.7
Death (outcomes)	
Overall	5 (20.8)
In cases of pneumonia	2 (40)
In cases of meningitis	3 (60)

IPD, invasive pneumococcal disease; SD, standard deviation.

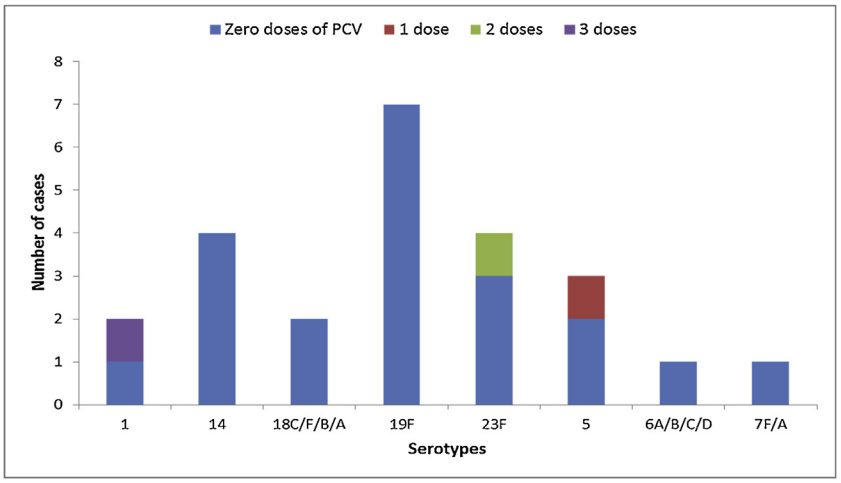

Figure 2. Vaccination status by serotype for vaccine serotype cases ($n = 24$).

Table 2
Comparison of characteristics of case patients and controls.[a]

	Case patients ($n = 24$), n (%)	Controls ($n = 134$), n (%)
Sex, male	7 (29.2)	81 (60.5)
Age (months), mean ± SD	6.5 ± 4.1	7.1 ± 4
Wasting (weight-to-height *Z*-score <2)	9 (39.1)	31 (26.7)
Stunting (height-to-age *Z*-score <2)	12 (52.2)	64 (58.2)
Underweight (weight-to-age *Z*-score <2)	14 (66.7)	72 (60)
Illiterate (paternal education)	18 (75)	55 (41)
Large family size (≥5 family members)	14 (58.3)	91 (67.9)
Person smoking cigarettes in the house	7 (29.2)	38 (28.4)
Exposure to cooking smoke (2 meters or closer to cooking smoke)	2 (8.3)	4 (3.0)
Use of natural gas for cooking	15 (62.5)	116 (86.6)
At least 1 other child <5 years old in the house	15 (62.5)	98 (73.1)
Crowding (>2 people sleeping in the same room as the child)	22 (91.7)	130 (97)
At least one dose of pentavalent vaccine[b]	7 (29.2)	59 (44)
Number of doses of PCV10		
Zero doses	21 (87.5)	89 (66.4)
1 dose	1 (4.2)	12 (9.0)
2 doses	1 (4.2)	9 (6.7)
3 doses	1 (4.2)	24 (17.9)
≥1 dose	3 (12.5)	45 (33.6)
≥2 doses	2 (8.7)	33 (27.1)

SD, standard deviation; PCV10, 10-valent pneumococcal conjugate vaccine.
[a] *p*-Values for the comparison of proportions between the study groups were calculated using the Chi-square test; *p*-values to compare means across the study groups were calculated using the unpaired *t*-test.
[b] Comprising five vaccine antigens: diphtheria, pertussis, tetanus, hepatitis B, and *Haemophilus influenzae* type B.

six of 24 were <14 weeks of age, too young to have been eligible for three PCV10 doses. Seventeen (71%) had meningitis and seven (29%) had pneumonia. The average duration of hospitalization for these case patients was 9.3 days. Of the 24 VT-IPD case patients, five died during their hospital stay.

Among the 24 cases of VT-IPD, seven (29%) were serotype 19F, with 14 and 23F as other predominant serotypes. Furthermore, 21 out of 24 cases occurred in children who had not received even a single dose of PCV10. Only one case each of serotypes 23F and 5 were identified: one in a child who had received two doses of PCV10 and one in a child who had received a single dose; only one child with serotype 1 disease had received all three doses of PCV10 (Figure 2).

VE for PCV10 was calculated for the 24 VT-IPD cases along with 134 age-matched controls. Table 2 presents a comparison of the demographic characteristics of enrolled case patients and controls. There was no difference in mean age, nutritional status, family size, or crowded living conditions between case patients and controls. Statistically significant differences between case patients and controls were found in sex, parental education, exposure to cigarette smoke in the home, use of natural gas for cooking, and vaccination status. While 44% of controls compared to 29% of case patients had received at least a single dose of pentavalent vaccine (comprising five vaccine antigens: diphtheria, pertussis, tetanus, hepatitis B, and *Haemophilus influenzae* type B), this difference was not statistically significant. The majority of both case patients (87.5%) and controls (66.4%) had not received any doses of PCV10.

Table 3 provides unadjusted and adjusted VE against VT-IPD with 95% confidence intervals (CI). Estimated VE against VT-IPD was 72.7% (95% CI −7.2% to 92.6%) for at least one dose of PCV10 and 78.8% (95% CI −11.9% to 96.0%) for at least two doses. Only 4.2% of case patients had received all three doses of PCV10, compared to 17.9% of controls, resulting in VE of 81.9% (95% CI −55.7% to 97.9%). Point estimates of VE were lower for those receiving exactly two doses of PCV10 (71.4%) and one dose of PCV10 (51.5%), compared to no vaccination. Effectiveness against non-PCV10 serotypes was not significantly different from zero for different vaccination statuses (Table 3).

Table 3
Unadjusted and adjusted PCV10 effectiveness against vaccine-type and non-vaccine type invasive pneumococcal disease outcomes in case patients and controls.

Vaccination status	Cases (n = 24), n (%)	Controls (n = 134), n (%)	Unadjusted VE (%) (95% CI)	Adjusted VE (%)[a] (95% CI)
VE for PCV10 serotypes				
Zero PCV doses	21 (87.5)	89 (66.4)	Reference	Reference
1 dose	1 (4.2)	12 (9)	64.7 (−186.9 to 95.7)	51.5 (−343.7 to 94.7)
2 doses	1 (4.2)	9 (6.7)	52.9 (−292.3 to 94.3)	71.4 (−227.6 to 97.5)
3 doses	1 (4.2)	24 (17.9)	82.3 (−38.0 to 97.7)	81.9 (−55.7 to 97.9)
≥1 dose	3 (12.5)	45 (33.6)	71.7 (−0.2 to 92.0)	72.7 (−7.2 to 93.1)
≥2 doses	2 (8.7)	33 (27.1)	74.3 (−15.6 to 94.3)	78.8 (−11.9 to 96.0)
Vaccination status	Cases (n = 67), n (%)	Controls (n = 345), n (%)	Unadjusted VE (%) (95% CI)	Adjusted VE (%)[a] (95% CI)
VE for non-PCV10 serotypes				
Zero PCV doses	38 (56.7)	203 (58.8)	Reference	Reference
≥1 dose	29 (43.3)	142 (41.2)	−9.1 (−85.1 to 35.7)	−44.9 (−154.6 to 17.6)
≥2 doses	23 (37.7)	115 (36.2)	−6.8 (−88.2 to 39.3)	−54.1 (−183.7 to 16.3)

PCV10, 10-valent pneumococcal conjugate vaccine; VE, vaccine effectiveness; CI, confidence interval.
[a] Adjusted for sex, age, paternal education, use of natural gas for cooking, crowding and exposure to smoke based on propensity scores, VE = (1 − OR) × 100%.

Discussion

The study findings suggest that PCV10 is protective against IPD (mainly pneumococcal meningitis) in the study population, for disease caused by vaccine types among children in South Asia. The study also showed that VE was associated with the number of doses received, as the point estimate for VE increased with each subsequent dose, from 51.5% among those receiving a single dose to 81.9% among those receiving all three doses, a trend that has also been identified in other studies (Domingues et al., 2014; Palmu et al., 2013; Conklin et al., 2014). The study provides a useful insight into VE and the distribution of vaccine serotypes in South Asia. The estimated results of VE are encouraging and data from this study could be helpful in studies performing a pooled analysis of PCV effectiveness.

The confidence intervals for the VE estimates crossed the null for all vaccination statuses examined, i.e., ≥1 dose, ≥2 doses, and three doses PCV10. The wide confidence intervals can be attributed to the small sample size and poor coverage of PCV10 within the catchment population, where only 4.2% of case patients and 17.9% of controls had received all three doses of PCV10. At the outset of vaccine rollout, the EPI had planned to achieve 72% coverage of PCV10 within 6 years of vaccine introduction (EPI, 2014). An independent survey conducted during 2016 in three rural districts of Sindh indicated the highest coverage for all three doses of PCV10 to be 38.5% (Anon, 2017). The sample size calculation for this study employed an assumption of at least 50% coverage of PCV10 within 3 years of vaccine rollout. However, the required coverage levels were not achieved within the study duration. This may have affected the power of the study. In order to achieve the optimal impact of PCV10 at the population level, vaccine coverage needs to increase significantly through investments in vaccine promotion, addressing vaccine hesitancy among the local population and enhancing coverage.

An interesting feature of this study was the relatively small proportion of VT-IPD out of the total IPD detected. Prior to the introduction of the vaccine into the routine immunization program in Pakistan, a hospital-based surveillance study from Sindh indicated that 66.7% of all IPD cases among children aged less than 5 years were PCV10 type serotypes (Shakoor et al., 2014). The proportion of VT-IPD cases in this study was only 26%. This is likely an indication of the altering bacteriological milieu with the introduction of PCV10. With the level of coverage measured among the controls in this study and in the independent surveys, the proportion of IPD caused by vaccine serotypes would be expected to drop, both because of direct protection among children who have received PCV10 doses and the decreased transmission of vaccine serotype strains from vaccinated children to unvaccinated children (indirect or herd effects). At these coverage levels, however, indirect protection will probably not be as good as expected with higher coverage (Loughlin et al., 2014). The most common PCV10 serotype found in this study was 19F, which accounted for a higher proportion of the isolates than was found in a previous study in the same setting (Shakoor et al., 2014). Whether this represents a relative shift because other vaccines serotypes are less common after vaccine introduction is unknown.

In addition to the lack of coverage with PCV10, other factors found to be associated with IPD included parental illiteracy and natural gas used for cooking. The odds of having an illiterate parent were significantly higher among case patients than among controls, suggesting that parental education may play a role in knowledge about vaccines and other health services or in the family's economic status and overall well-being. The use of natural gas for cooking was more prevalent for control patients than for case patients; while the findings suggest that there may be a direct linkage between exposure to indoor smoke and the subsequent development of IPD, data to control for confounding factors are insufficient.

In conclusion, the VE point estimates for PCV10 were high and increased progressively with increasing doses of PCV10. The VE estimates did not reach statistical significance in this study, but this may be due to the low power, as explained above. The study results suggest that the introduction of PCV10 with adequate coverage is likely to decrease the IPD burden among children less than 5 years of age in Pakistan.

Ethical approval

The study received approval from the Ethics Review Committee (ERC) of Aga Khan University, Karachi, Pakistan. Written informed consent was obtained from the parents of all study participants.

Funding source

The study was funded by Gavi—The Vaccine Alliance (grant number PP33961213A1).

Conflict of interest

All authors declare no conflict of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agency or the Centers for Disease Control and Prevention.

Contributions

AA supervised all aspects of the study including manuscript preparation. AKMZ designed the study and contributed to manuscript revision. AR, SM, and SH participated in study oversight, data review, and manuscript writing. MTY, NR, and SM contributed to the data analysis and manuscript revision. FK supervised the laboratory testing and contributed to manuscript revision. WM, BS, and NM interpreted the radiographs and contributed to manuscript revision. CGW and SBO contributed to the data interpretation and manuscript revision. KP, KMAK, SJR, FA, KI, and HKZ participated in the data collection and manuscript revision.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.12.007.

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