Effectiveness of pneumococcal conjugate vaccines against invasive pneumococcal disease in Vietnamese children prior to national introduction: A matched case-control study

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Abstract

Background: Evidence on the effectiveness of pneumococcal conjugate vaccines (PCVs) in Vietnam remains limited, despite the availability of 10-valent (PCV10) and 13-valent (PCV13) conjugate vaccines in the private sector since 2014 and 2019. We evaluated the effectiveness of PCVs against invasive pneumococcal disease (IPD) among Vietnamese children prior to national introduction.

Methods: We conducted a matched case-control study between February 2022 and January 2025 in southern Vietnam. Cases were children aged 2-59 months hospitalized with culture-confirmed IPD from normally sterile sites at three tertiary pediatric hospitals. Four age- and neighborhood-matched community controls were enrolled per case. Vaccine effectiveness (VE) was estimated using conditional logistic regression as (1 - adjusted odds ratio) × 100%.

Results: We enrolled 72 IPD cases and 288 matched controls; 37.5% of cases had received ≥1 PCV dose. The most frequent clinical syndromes were

meningitis (36.1%) and pneumonia-associated sepsis (30.6%). Serotype 19A predominated (26.4%), followed by 6A (13.9%) and 19F (11.1%); 77.8% of cases were caused by serotypes included in PCV13. For vaccine-type IPD (VT-IPD), adjusted VE of PCV10 against PCV10-type IPD was 86.3% (95% CI: 13.3-97.9) for ≥1 dose and 89.5% (95% CI: 16.1-98.7) for ≥2 doses; VE of PCV13 against PCV13-type IPD was similarly high. Against all-serotype IPD, adjusted VE was 65.1% (95% CI: 21.8-84.4) for ≥1 PCV10 dose and 84.4% (95% CI: 20.0-97.0) for ≥1 PCV13 dose. No significant effectiveness was observed against non-PCV10-type IPD. VE was highest against serotype 6A and declined with increasing time since vaccination.

Conclusions: This first Vietnamese evidence demonstrates that PCV10 and PCV13 provide substantial protection against VT-IPD and overall IPD in young children despite low vaccine coverage. The predominance of serotype 19A and waning protection over time emphasize the importance of selecting 19A-containing formulations and booster schedules to inform timely national PCV introduction in Vietnam.

1. Introduction

Streptococcus pneumoniae is a leading cause of illness and death in children under five, responsible for an estimated 3.7 million cases and 294,000 deaths globally among HIV-uninfected children aged 1-59 months, with the highest

burden in low- and middle-income countries[1,2]. Pneumococcal conjugate vaccines (PCVs) have substantially reduced invasive pneumococcal disease (IPD) where implemented, and more than 170 countries have introduced PCVs into their national immunization programs, achieving marked declines in vaccine-type disease, ranging from 60 to 95% [1,3–6]. However, uptake across many Asian settings has been slower, hindered by limited local data to support policy adoption[6].

Vietnam carries a considerable burden of childhood pneumonia and invasive bacterial infections, ranking among the 15 countries with the highest pneumonia-related hospitalizations[7,8]. Over the past decade, sentinel surveillance systems have provided valuable information on circulating pneumococcal serotypes and antibiotic resistance, indicating that more than 80% of IPD cases are caused by serotypes covered by currently available PCVs, alongside a high prevalence of antibiotic resistance and a case fatality rate of 8.2% among bacterial meningitis cases[9,10]. However, PCVs have not yet been introduced into the national Expanded Program on Immunization (EPI). Instead, the ten-valent PCV (PCV10) and the thirteen-valent PCV (PCV13) have been available only in the private sector since 2014 and 2019, respectively, resulting in low coverage and inequitable access. Indirect evidence derived from vaccine sales data shows that PCV10 uptake among

children under five years of age during the study period was approximately 18%, with PCV13 coverage likely even lower.

Despite surveillance data describing circulating strains, real-world evidence on PCV effectiveness in Vietnam remains limited, including which vaccine formulations perform best, and how protection varies by age and time since vaccination. This evidence gap may have hindered national decision-making on PCV introduction, product selection, and dosing strategies. Reliance on effectiveness data from high-income countries may not adequately reflect outcomes in countries without established PCV programs, where serotype distribution, transmission dynamics, vaccination schedules, and waning immunity differ[2,11–14].

To address this gap, we conducted a matched case-control study among children aged 2-59 months in southern Vietnam to estimate the effectiveness of PCV against IPD. The primary objective was to evaluate vaccine effectiveness (VE) against vaccine-type IPD, with secondary analyses assessing all-serotype disease, serotype-specific protection, time since the last dose, and age at first dose vaccination. These findings provide the first real-world evidence of PCV performance in Vietnamese children and are intended to guide national deliberations on PCV introduction and vaccine formulation.

2. Methods

2.1. Study Setting and Population

The study was conducted in Vietnam, a lower-middle-income country with a gross domestic product (GDP) per capita of approximately US$4,700, and a national population of about 101 million in 2024[15,16]. A sentinel surveillance platform for invasive bacterial diseases has been established at three tertiary pediatric hospitals in Ho Chi Minh City (HCMC) (Children's Hospital No.1, Children's Hospital No.2, and City Children's Hospital) since 2012; these hospitals serve as referral centers in southern Vietnam (catchment population: 2.83 million children aged 2-59 months, accounting for 29.8% of the national under-five population)[17].

2.2. Study design

We conducted a matched case-control study between February 2022 and January 2025 to evaluate the effectiveness of one or more doses of PCV against IPD among children aged 2-59 months in southern Vietnam.

Cases: Cases were children hospitalized with clinical suspicion of invasive bacterial diseases (e.g., meningitis, bacteremic pneumonia, and pneumonia-associated sepsis), from whom specimens from normally sterile sites (blood, cerebrospinal fluid, or pleural fluid) were collected. Confirmed cases were defined by the identification of *Streptococcus pneumoniae* using routine culture. From March 2024, the study protocol was amended to additionally include cases with *S. pneumoniae* detected in cerebrospinal fluid by real-time PCR (RT-PCR). Isolates were sent to the Pasteur Institute in HCMC for

confirmation by optochin susceptibility testing and *lyt*A RT-PCR. Serotyping was performed via sequential triplex RT-PCR covering 21 serotypes[18]. Serogroup 6 (6A, 6B, 6C, and 6D) was further differentiated using the quadriplex RT-PCR assay[19]. These included all 13 serotypes in the PCV13, along with eight additional important serotypes or serogroups (such as 2, 11A/11D, 12F/12A/12B/44/46, 15A/15F, 16F, 22F/22A, 23A, and 33F/33A/37)[18,20]. We classified cases as vaccine-type IPD (VT-IPD) if the identified serotype was included in PCV10 (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F), with PCV13 additionally covering serotypes 3, 6A, and 19A. All remaining serotypes were deemed to be non-vaccine types (NVT).

Controls: Four neighborhood healthy controls were matched to each case by age group (2 to <12, 12 to <24, and 24 to 59 months) and pre-illness residential location. A 1:4 matching ratio was selected to optimize statistical efficiency in a context where IPD cases were relatively scarce, and community controls were more accessible, as additional controls beyond four confer minimal gains in power[21,22]. Age for cases was determined at the date of culture confirmation (index date), and age for controls at the enrollment date (reference date).

Exclusion criteria: Children were excluded if: (1) their parent(s) or legally acceptable representative(s) (LAR) were unable or unwilling to provide consent; (2) they lacked a birth certificate or hospital birth record; (3) they

resided outside the study catchment area; or (4) they had previously participated in a PCV trial in HCMC.

The study protocol received ethical approval from the Institutional Review Boards of the Pasteur Institute in HCMC (Ref: 46/GCN-PAS, approved on 15 September 2020) and all participating study hospitals. Written informed consent was obtained from parents or legal guardians of cases, and verbal informed consent was obtained for controls. The study was registered with the Thai Clinical Trials Registry (TCTR20201206002).

2.3. Enrollment Procedures and Data Collection

Cases: Eligible cases were identified through routine culture testing in the participating hospitals. After obtaining informed consent, the trainer study team interviewed parents/caregivers using structured questionnaires (*available in the supplementary material*). A schematic of study enrollment, laboratory procedures, and data collection is provided in **Figure 1.**

Controls: Four age- and neighborhood-matched community controls were recruited within 14 days of case identification. Controls were selected through using a structured H-shaped household search strategy; an expanding-circle approach was applied if not feasible[21]. Verbal consent was obtained because no biological specimens were collected.

For all participants, we gathered information on: (*i*) demographics and perinatal factors (age, sex, ethnicity, residence, birthweight, gestational age);

(*ii*) nutritional status (weight, height, breastfeeding); (*iii*) household characteristics and exposures (siblings, crowding, smoke exposure, daycare attendance); (*iv*) socio-economic status (maternal education, income, air conditioner); (*v*) medical history and vaccination records. Demographic and perinatal information was obtained from hospital medical records and official documents when available (e.g., birth certificates or child health insurance records). Nutritional status (weight and height) was assessed using direct measurements when feasible or caregiver report when direct measurement was not available. Household characteristics and socio-economic data were collected through structured caregiver interviews. Details on vaccination history ascertainment and classification of PCV exposure are described in *Section 2.4*. Clinical information for cases (symptom onset, hospitalization, clinical syndrome, laboratory results, treatment, outcome) was extracted from hospital records and completed by the study physician. Time-varying exposures (e.g., household smoke exposure, breastfeeding, daycare attendance, recent illness, and antibiotic use) were assessed for the 30 days preceding the index/reference date.

2.4. Vaccination history and PCV status

Routine vaccination history was verified through multiple independent sources, including immunization cards, the National Immunization Information System (NIIS), and commune-level health records, and discrepancies were adjudicated

by trained EPI staff. When documentation was unavailable, parental recall was recorded.

In Vietnam, PCV10 and PCV13 have been available exclusively in the private sector, without a national catch-up program. Age-specific schedules included a 3+1 schedule for infants <6 months, a 2+1 schedule for previously unvaccinated infants aged 7-11 months, and a two-dose schedule for children aged ≥12 months, with minimum intervals of one to two months between doses as recommended[2].

Given its central importance for VE estimation, PCV vaccination status underwent enhanced validation. In addition to the sources above, trained EPI staff cross-checked PCV information directly with vaccination centers where each child had received immunization. PCV data were complete for all vaccinated children, with no missing dates and no invalid doses identified. Children were classified as vaccinated if they received ≥1 valid PCV dose (≥6 weeks of age, ≥4 weeks between doses, and ≥14 days before the index/reference date). No children were excluded due to invalid dose timing. Children with no record, or with a single dose <14 days before the index/reference date, were considered unvaccinated.

2.5. Study Outcomes

The primary outcome was to evaluate the effectiveness of one or more doses of PCV10 and PCV13 against VT-IPD. Secondary objectives included

estimating VE against all-serotype IPD and against IPD caused by serotypes 6A and 19A to assess potential cross-protection. We further evaluated effectiveness by clinical syndrome, time since the last PCV dose (<6, 6-23, ≥24 months), and age at first vaccination (<6, <12, and >12 months).

2.6. Statistical Analysis

Sample size requirements were estimated using formulas for an unmatched case-control design with continuity correction, because reliable published estimates of within-set exposure correlation (*rho*) for matched case-control vaccine effectiveness studies were not available in this setting[23,24]. Assuming 30% PCV10 coverage among controls, an expected vaccine effectiveness of 72%[25], a two-sided α of 0.05, and 80% power (β = 0.2), this minimum required sample size was 51 VT-IPD cases. Surveillance data indicating that approximately 75% of pneumococcal isolates were vaccine-type supported a target enrollment of 72 IPD cases[10].

In matched designs, a non-zero value of *rho* reduces the number of discordant pairs and can increase the required sample size to maintain statistical power. To assess the robustness of our assumption, we considered plausible values of *rho* between 0.1 and 0.2, consistent with prior VE studies, which suggested that the required number of vaccine-type cases would remain close to the achieved sample size [23,26]. Although sample size calculations were based on unmatched formulas due to these constraints, all VE estimates were derived

using conditional logistic regression, which appropriately accounts for the matched design.

We used conditional logistic regression to estimate crude and adjusted odds ratios (ORs) for PCV vaccination among cases and controls[27–29]. VE was calculated with the formula, VE = (1 - adjusted ORs) × 100%. Potential confounders were identified a priori based on epidemiological relevance and further evaluated by adding candidate variables individually to the basic model. Covariates that altered the odds ratio for vaccination by at least 10% or were associated with *p*-values <0.10 were considered confounders and retained in the final adjusted multivariable model to balance bias control and model parsimony[28]. Matching variables (age group and neighborhood) were not included as covariates, as they were accounted for by the conditional likelihood. Model selection was guided by likelihood-based comparisons using Akaike's Information Criterion (AIC), and independent variables were assessed for collinearity using variance inflation factors (VIFs).

VE was estimated for ≥1 and ≥2 doses of PCV10, as these categories included sufficient numbers to allow stable estimation. For PCV13, dose-specific analyses beyond ≥1 dose were not undertaken because of limited sample size. The study was not powered to formally compare effectiveness across dose strata; therefore, dose-specific estimates are presented descriptively and should be interpreted cautiously.

Data were double-entered, audited monthly, and verified for completeness. Analyses were performed using Stata (version 18.5; StataCorp, College Station, TX, USA).

3. Results

Data collection began with a pilot phase in 2021, but the study implementation was delayed by the COVID-19 pandemic and formally resumed from February 2022 to January 2025. A total of 72 culture-confirmed IPD cases were included in the analyses, comprising four identified during the 2021 pilot and 68 enrolled during the main study period. Following the protocol amendment in March 2024, no IPD cases were identified by RT-PCR, as routine diagnostic practice at the participating hospitals relied primarily on culture-based methods. Over half of the cases were recruited from Children's Hospital 2, followed by City Children's Hospital (29.2%).

3.1. Participant characteristics

Among the 72 enrolled cases, meningitis was the most common clinical syndrome (36.1%), followed by pneumonia-associated sepsis (30.6%) and bacteremic pneumonia (18.1%). The median time from symptom onset to admission was 3 days (IQR, 2-5), and the median duration of hospital stay was 15 days (7-26). Overall, 12.5% of cases died during hospitalization (**Table 1**).

3.2. Serotype distribution and vaccination history

Overall, 37.5%, 77.8%, and 79.2% of IPD cases were caused by serotypes included in PCV10, PCV13, and PCV20, respectively (**Table 1**). Serotype 19A was the most common (26.4%), followed by 6A, 19F, and 6B. Non-vaccine serotypes 15A/F (6.9%) and 23A (2.8%) were also identified (*Table S1, Supplementary*). Twenty-seven cases (37.5%) had received ≥1 dose of any PCV (21 PCV10, 3 PCV13, 3 mixed schedules [PCV10+PCV13]). Among children who received ≥3 PCV10 doses, 88.9% (16/18) of infections were caused by non-PCV10 serotypes, particularly 19A and 15A/F (**Figure 2**).

3.3. Comparison of cases and controls

A total of 288 matched controls were included. Cases and controls were similar regarding sex, age group, maternal education, and exposure to household smoking. Several characteristics were significantly more frequent among cases, including underweight, daycare attendance, household hospitalization history, recent antibiotic use, and underlying comorbidities. In contrast, breastfeeding, receipt of routine childhood vaccines, and at least one dose of any PCV were more common among controls (all $p<0.05$). These variables were considered as potential confounders in adjusted VE estimation (**Table 2**).

3.4. Vaccine Effectiveness

For the primary outcome of VT-IPD, substantial protection was observed for serotypes covered by both PCV10 and PCV13 (**Tables 3 and 4**).

Against PCV10-type IPD, the adjusted VE of PCV10-only was 86.3% (95% CI: 13.3 to 97.9) for ≥1 dose and 89.5% (95% CI: 16.1 to 98.7) for ≥2 doses. VE

estimates for PCV13-only and mixed schedules could not be derived because of sparse data (**Tables 3 and 4**).

For PCV13-type IPD, the adjusted VE for ≥1 dose was 71.1% (95% CI: 21.4 to 89.4) among children receiving PCV10-only and 85.1% (95% CI: 6.7 to 97.6) among those receiving PCV13-only. Estimates for ≥2 doses and mixed schedules were imprecise or not estimable due to small numbers (**Tables 3 and 4**).

Against all-serotype IPD, the adjusted VE was 65.1% (95% CI: 21.8 to 84.4) for PCV10-only, 84.4% (95% CI: 20.0 to 97.0) for PCV13-only, and 69.5% (95% CI: -76.2 to 94.7) for mixed schedules (PCV10+PCV13), with wide confidence intervals reflecting limited sample size (**Table 3**). No statistically significant protection was observed against non-PCV10-type IPD across vaccine schedules (**Tables 3 and 4**).

Adjusted VE against IPD caused by serotype 6A was 98.0% (95% CI: 55.1 to 99.9). VE estimates for serotypes 6B, 19F, and 19A were 83.6% (95% CI: -303.2 to 99.3), 62.8% (95% CI: -262.2 to 96.2), and -4.5% (95% CI: -426.4 to 79.3), respectively, with confidence intervals crossing zero. By clinical syndrome, adjusted VE was 74.0% (95% CI: 8.5 to 92.6) against meningitis and 81.6% (95% CI: 29.5 to 95.2) against pneumonia with bacteremia or sepsis. VE estimates against severe outcomes were 79.4% (95% CI: 36.1 to 93.4) for ICU admission and 90.4% (95% CI: -156.7 to 99.6) for in-hospital death (**Table 3**). The wide confidence intervals, including negative values and crossing zero,

296 reflect sparse data and limited precision rather than evidence of harmful vaccine
297 effects.

298 VE against all-serotype IPD declined with increasing time since the last dose
299 (**Table 5**). Adjusted VE against all IPD was 86.0% (95% CI: 53.3 to 95.8) within
300 <6 months, decreased to 43.1% (95% CI: -51.0 to 78.5) at 6-23 months, and
301 53.8% (95%CI: -79.8 to 88.1) after ≥24 months since the last dose. VE also
302 varied by age at first vaccination, with estimates of 80.6% (95% CI: -39.3 to
303 97.3) among children vaccinated at ≥12 months and 67.3% (95% CI: 27.1 to
304 85.3) among those vaccinated before 12 months of age (**Table 5**).

305 **4. Discussion**

306 This matched case-control study provides the first real-world evidence of
307 PCV effectiveness against IPD among Vietnamese children. Despite low
308 coverage and use restricted to the private sector, both PCV10 and PCV13
309 conferred substantial direct protection, underscoring the potential population-
310 level benefits that could be achieved through national immunization.

311 VE against vaccine-type and all-serotype IPD ranged from 65.1% to
312 86.3% for PCV10 and PCV13, consistent with findings from early-
313 implementation or low-coverage settings[25,30–33]. These estimates were lower
314 than those observed in mature immunization programs in high-income
315 countries, where high coverage and herd immunity drive effectiveness over 90%
316 for VT-IPD[27,28,34–36]. This contrast suggests that the full public health impact of

PCV in Vietnam is likely to increase substantially following national introduction, and that delaying rollout while awaiting newer formulations may prolong preventable disease burden.

Our findings have direct implications for vaccine product selection in Vietnam. In contrast to earlier surveillance studies that identified serotypes 6A/6B, 19F, and 23F as predominant causes of IPD, we observed a marked predominance of serotype 19A, accounting for more than one quarter of IPD cases use[10,17]. This temporal shift in serotype distribution may reflect selective pressure associated with partial PCV10 use over time[30,37,38] and mirrors global patterns reported in countries using PCV10 or mixed PCV10/PCV13 schedules[4,11,30,32]. Importantly, our results are consistent with recent hospital-based surveillance from northern Vietnam, which likewise identified serotypes 6A/6B and 19A as leading causes of IPD, suggesting a broadly consistent serotype distribution nationwide despite regional differences[39]. In both studies, more than 80% of IPD cases were attributed to serotypes included in PCV13. Taken together, these findings highlight a substantial gap in protection offered by PCV10 and indicate that vaccine formulations containing serotype 19A are more likely to provide broader protection in Vietnam. In this context, the planned introduction of PCV13 into Vietnam's national immunization program beginning in March 2026 is well aligned with the current epidemiology of IPD[40]. Although higher-valence vaccines (PCV15, PCV20)

may eventually provide broader coverage, uncertainties regarding availability, cost, and regulatory timelines in low- and middle-income settings argue for the timely introduction of currently available 19A-containing vaccines, accompanied by continued surveillance to guide future transitions.

VE declined with increasing time since vaccination, with higher protection observed within six months of the last dose and a reduction of more than 30% after 24 months. Although confidence intervals were wide due to limited sample size, this pattern is consistent with waning immunity in the absence of booster doses, as reported in Taiwan and South Africa[30,32]. Notably, Australia historically implemented a 3+0 schedule and subsequently transitioned to a booster-containing schedule following higher rates of breakthrough IPD compared with settings using booster doses[11]. These findings reinforced the importance of booster-containing schedules to sustain long-term protection, particularly in settings such asVietnam, where vaccine coverage has been low before national introduction[2].

Consistent with other studies, low protection was observed against non-vaccine serotypes. As the diversity and circulation of non-PCV serotypes increase, sustained serotype surveillance will be essential to detect potential replacement following vaccine introduction and to inform future vaccine policy, including consideration of higher-valence or alternative vaccine approaches[27,28,32,34].

This study has several limitations. The modest sample size constrained the precision of time-, dose-, and serotype-specific estimates and precluded formal comparisons across multiple dose strata. Dose-specific VE estimates should therefore be interpreted cautiously, as higher dose categories included few vaccinated cases and the study was not designed to assess differences in uptake or effectiveness across dose strata. Second, neighborhood-based matching, although intended to control for some potential confounders, may have resulted in geographic overmatching. Given that access to PCV in Vietnam largely depends on private-sector availability and local socio-economic context, cases and controls from the same areas may have had similar vaccine access and uptake patterns, thereby biasing VE estimates toward the null. Similar effects have been noted in geographically matched vaccine studies[22,28,31,41,42]. Third, case ascertainment relied on culture-based diagnosis, which has limited sensitivity (despite high specificity), particularly among children pre-treated with antibiotics, potentially leading to under-ascertainment of true IPD and preferential inclusion of more severe cases. No PCR-positive, culture-negative cases were identified, reflecting routine diagnostic practice. Finally, data were collected from three tertiary children's hospitals in southern Vietnam, which may limit generalizability; however, these hospitals serve as major referral centers for severe pediatric disease. Larger, multi-site studies incorporating molecular diagnostics would strengthen the evidence base for national policy.

5. Conclusion

This matched case-control study provides the first real-world evidence from Vietnam demonstrating that PCV10 and PCV13 confer protection against IPD in children under five years of age. The predominance of serotype 19A and the observed decline in protection with increasing time since vaccination emphasize the importance of selecting vaccine formulations with broader serotype coverage and implementing schedules that sustain long-term protection. Together, these findings support timely and actionable evidence to guide the national introduction of PCV into Vietnam's EPI, including decisions on vaccine product selection and dosing strategies. Continued serotype surveillance will be essential to monitor vaccine impact, serotype shifts, and guide future vaccine policy refinements.

Author contribution

H.C.T., Q.D.P., and Thuong. V.N. conceived and designed the study. Thuong.V.N., Trung. V.N., Q.D.P., H.C.T., P.D.N., H.T.N., N.N.T.L., T.H.T., Q.D.N., N.T.N., and T.T.L. coordinated the study and collected the data. T.V.P. and D.T.T.V. conducted the laboratory procedures and serotyping analyses. H.C.T. drafted the first version of the manuscript. H.C.T. conducted the initial data analysis, and A.S. contributed to the statistical analyses and review of the manuscript. H.C.T., Thuong. V.N., and N.S. contributed to data analysis, interpretation, and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

CRediT authorship contribution statement

Hieu Cong Truong: Writing - review & editing, Writing - original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Quang Duy Pham:** Writing - review & editing, Methodology, Funding acquisition, Investigation, Conceptualization. **Trung Vu Nguyen:** Writing - review & editing, Resources, Supervision. **Phuc Duy Nguyen, Hung Thanh Nguyen, Nhan Nguyen Thanh Le, Tung Huu Trinh, Qui Dinh Nguyen, Nam Tran Nguyen, Trinh Tuyet Lam:** Writing - review & editing, Resources, Investigation. **Thanh Van Phan, Dai Thi Trang Vo**: Writing - review & editing, Investigation, Validation. **Antoine Soetewey:** Writing - review & editing, Validation. **Thuong Vu Nguyen:** Writing - review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Investigation, Conceptualization. **Niko Speybroeck:** Writing - review & editing, Visualization, Validation, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: Thuong Vu Nguyen reports financial support was provided by GSK. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

The data produced and analyzed in this study are not publicly accessible due to confidentiality and privacy restrictions. However, they can be obtained from the corresponding author upon reasonable request.

Disclaimer Statement

446 The findings and conclusions presented in this publication are those of the
447 author and do not necessarily represent the official stance of the Vietnamese
448 Ministry of Health or the Pasteur Institute in Ho Chi Minh City.

449 **Supplementary material**

450 Supplementary data associated with this article are available in the online
451 version.

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Table 1. Characteristics of invasive pneumococcal disease cases (N=72)

	Cases (N=72)
Age in months, mean ± SD	23.7 ± 15.1
Clinical syndrome, n (%)	
Meningitis	26 (36.1)
Pneumonia-associated sepsis	22 (30.6)
Bacteremic pneumonia	13 (18.1)
Other syndromes	11 (15.3)
Microbiological diagnosis, n (%)	
Blood culture	46 (63.9)
CSF culture	11 (15.3)
Pleural effusion culture	5 (6.9)
Blood + CSF	8 (11.1)
Blood + Pleural fluid	1 (1.4)
Blood + CSF + Pleural fluid	1 (1.4)
Medical care and outcomes	
Time from symptom onset to admission, day (median, IQR)	3 (2-5)
Length of stay, day (median, IQR)	15 (7-26)
Deaths, n (%)	9 (12.5)
Dominant serotypes identified, n (%)	

19A	19 (26.4)
6A	10 (13.9)
19F	8 (11.1)
6B	7 (9.7)
Serotype group, n (%)	
PCV10	27 (37.5)
PCV10-SII	56 (77.8)
PCV13	56 (77.8)
PCV15	56 (77.8)
PCV20	57 (79.2)
Non-PCV10	45 (62.5)

Abbreviation: SD, standard deviation; CSF, cerebrospinal fluid; PCV10, ten-valent pneumococcal conjugate vaccine, including serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F; PCV10-SII, another ten-valent pneumococcal conjugate vaccine, including PCV10 serotypes minus 4 and 18C, and plus 6A and 19A; PCV13, thirteen-valent pneumococcal conjugate vaccine, including PCV10 serotypes added sertoypes 3, 6A, and 19A; PCV15, expands upon PCV13 by including two additional serotypes, 22F and 33F; PCV20, PCV15 added 5 serotypes 8, 10A, 11A, 12F, 15B, 22F, 33F; Non-PCV10, serotypes not included in PCV10[2].

Table 2. Comparison of characteristics of cases and controls.

	Cases (N=72)	Controls (N=288)	*p*-value* (matched)
Demographic			
Sex, male	36 (50.0)	149 (51.7)	0.792
Age (months), mean ± SD	23.7 ±14.9	23.7±15.1	
Age group, months			
2-<12	17 (23.6)	65 (22.6)	
12-<24	24 (33.3)	103 (35.8)	0.507
24-<59	31 (43.1)	120 (41.7)	0.947
Nutritional status+			
Underweight (weight-to-age Z-score <2)	8 (11.1)	8 (2.8)	0.005
Currently breastfeeding	11 (15.3)	77 (26.7)	0.043
Childcare and exposures			
Daycare attendance	39 (54.2)	90 (31.3)	<0.001
Exposure to cooking smoke	5 (6.9)	10 (3.5)	0.143
Person smoking cigarettes in the house	31 (43.1)	128 (44.4)	0.822
Crowding (>2 people sleeping in the same room as the child)	7 (9.7)	15 (5.2)	0.168
Socio-economic characteristics			
Maternal education less than 12 years	43 (59.7)	192 (65.8)	0.318

Low household income[++]	48 (66.7)	238 (82.6)	0.003
Medical history and comorbidities			
Underlying medical condition	10 (13.9)	4 (1.4)	<0.001
Antibiotic use in the previous 30 days	24 (33.3)	40 (13.9)	<0.001
Hospitalization history	19 (26.4)	27 (9.4)	<0.001
Vaccination history			
≥3 doses DTP-Hib-polio vaccine	48 (66.7)	241 (83.7)	<0.001
≥ 1 dose influenza vaccine	17 (23.6)	123 (42.7)	0.001
≥ 1 dose measles vaccine	25 (34.7)	153 (53.1)	0.001
Pneumococcal vaccination status			
≥ 1 dose any PCV[#]	27 (37.5)	143 (49.7)	0.046
≥ 1 dose PCV10 only	21 (29.2)	107 (37.2)	0.084
≥ 1 dose PCV13 only	3 (4.2)	23 (8.0)	0.118
≥ 1 dose Mixed PCV (PCV10+PCV13)[$]	3 (4.2)	13 (4.5)	0.562
≥ 2 doses any PCVs[@]	22 (30.6)	121 (42.0)	0.06
≥ 2 doses PCV10 only	19 (27.5)	92 (33.3)	0.129
≥ 2 doses PCV13 only	0	16 (5.8)	NE
≥ 2 doses Mixed PCV (PCV10+ PCV13)	3 (4.2)	14 (4.5)	0.630
≥ 3 doses Mixed PCV (PCV10+ PCV13)	18 (25.0)	100 (34.7)	0.096

***** Matched *p*-values were estimated using conditional logistic regression. [+] Nutritional status based on the WHO Child Growth standards. [++] Low household income was defined as a monthly income <3 million VND × household size[43]. [#]Any PCV refers to

receipt of PCV10, PCV13 or mixed schedules**.** [$]Mixed PCV refers to children receiving both PCV10 and PCV13 in any sequence.
[@]At least 2 doses do not distinguish between primary or booster doses.
Abbreviations: SD, standard deviation; DTP, diphtheria-tetanus-pertussis; Hib, *Haemophilus influenzae* type b; PCV, pneumococcal conjugate vaccine; PCV10, 10-valent PCV; PCV13, 13-valent PCV; NE, Not estimable.

Table 3. Vaccine effectiveness (≥1 dose) against invasive pneumococcal disease, stratified by vaccine serotype, specific serotype, and clinical syndrome.

Exposure[++]	Cases[*] (N=72)	Controls[*] (N=288)	Crude VE (%) (95% CI)	Adjusted VE (%) (95% CI)[$$]
PCV10-type IPD (n=27)				
PCV10 only	4	32	65.2 (-12.3 to 89.2)	86.3 (13.3 to 97.9)
PCV13 only	1	6	64.1 (-250.5 to 96.3)	74.7 (-347.1 to 98.6)
Mixed PCV10 + PCV13	0	4	NE	NE
PCV13-type IPD (n=56)				
PCV10 only	14	96	53.4 (5.0 to 77.1)	71.1 (21.4 to 89.4)
PCV13 only	2	17	72.2 (-37.4 to 94.4)	85.1 (6.7 to 97.6)
Mixed PCV10 + PCV13	2	9	46.8 (-200.7 to 90.6)	78.4 (-142.6 to 98.1)
All IPD (n=72)				
PCV10 only	21	107	41.2 (-7.3 to 68.8)	65.1 (21.8 to 84.4)
PCV13 only	3	23	65.4 (-30.8 to 90.8)	84.4 (20.0 to 97.0)
Mixed PCV10 + PCV13	3	13	33.9 (-168.4 to 83.7)	69.5 (-76.2 to 94.7)
Non-PCV10-type IPD (n=45)				
PCV10 only	17	75	23.8 (-57.2 to 63.1)	40.6 (-40.8 to 74.9)
PCV13 only	2	17	65.7 (-75.6 to 93.3)	71.0 (-61.4 to 94.8)
Mixed PCV10 + PCV13	3	9	-15.0 (-413.5 to 74.2)	21.0 (-292.8 to 84.1)

Specific pneumococcal serotype				
6A (n=10), PCV10 only	1	23	93.9 (48.6 to 99.3)	98.0 (55.1 to 99.9)
6B (n=7), PCV10 only	1	7	62.3 (-267.4 to 96.1)	83.6 (-303.2 to 99.3)
19A (n=19), PCV10 only	9	27	-81.1 (-440.4 to 39.3)	-4.5 (-426.4 to 79.3)
19F (n=8), PCV10 only	1	9	64.5 (-226.5 to 96.1)	62.8 (-262.2 to 96.2)
Overall by clinical syndrome				
Meningitis (n=26), Any PCV	8	52	60.9 (-5.3 to 85.4)	74.0 (8.5 to 92.6)
Bacteremic or sepsis with pneumonia (n=35), Any PCV	16	77	34.9 (-44.3 to 70.6)	81.6 (29.5 to 95.2)
ICU admission (n=37), Any PCV	11	77	67.1 (24.3 to 85.7)	79.4 (36.1 to 93.4)
Death (n=9), Any PCV	2	18	85.8 (-43.2 to 98.6)	90.4 (-156.7 to 99.6)

[++]Reference group consisted of children with no prior PCV vaccination for all exposure categories. [*]Numbers shown in the "Cases" and "Controls" columns represent the number of vaccinated (exposed) individuals contributing to each matched analysis. [$$]VE was calculated as (1 - OR) × 100, where ORs were obtained from conditional logistic regression. Adjusted VE models varied by outcome: (i) PCV10-type and non-PCV10-type IPD: sex, low income, maternal education, daycare, hospitalization history; (ii) PCV13-type IPD, all-serotype IPD, and clinical syndrome: sex, low income, maternal education, daycare, hospitalization history, antibiotic use, comorbidities; (iii) Serotype-specific IPD: sex, maternal education, daycare, antibiotic use, comorbidities. For all stratified analyses, including vaccine serotype, serotype-specific, and clinical syndrome-specific outcomes, cases were defined according to the outcome of interest, and controls were restricted to the corresponding age- and neighborhood-matched community control sets. Other IPD cases were not included as controls. NE: not estimable due to zero discordant pairs.

Abbreviation: VE, vaccine effectiveness; CI, confidence intervals; NE, not estimable; PCV, pneumococcal conjugate vaccine; IPD, invasive pneumococcal disease.

Table 4. Vaccine effectiveness (≥2 doses) against invasive pneumococcal disease, stratified by vaccine serotype.

Exposure[++]	Cases (N=72)	Controls (N=288)	Crude VE (%) (95% CI)	Adjusted VE (%) (95% CI)[$$]
PCV10-type IPD (n=27)				
PCV10 only	3	27	69.9 (-11.1 to 91.9)	89.5 (16.1 to 98.7)
PCV13 only	0	5	NE	NE
Mixed PCV10 + PCV13	0	4	NE	NE
PCV13-type IPD (n=56)				
PCV10 only	12	71	53.9 (2.8 to 78.2)	72.2 (19.6 to 90.4)
PCV13 only	0	12	NE	NE
Mixed PCV10 + PCV13	2	9	40.9 (-231.7 to 89.5)	76.7 (-167.2 to 98.0)
All IPD (n=72)				
PCV10 only	19	92	39.2 (-136.0 to 67.5)	62.1 (13.1 to 83.5)
PCV13 only	0	16	NE	NE
Mixed PCV10 + PCV13	3	13	29.1 (-187.0 to 82.5)	67.2 (-88.1 to 94.3)
Non-PCV10-type IPD (n=45)				
PCV10 only	16	65	18.6 (-70.5 to 61.1)	34.0 (-59.7 to 72.7)
PCV13 only	0	11	NE	NE
Mixed PCV10 + PCV13	3	9	-18.5 (-425.4 to 73.3)	19.2 (-296.8 to 83.5)

[++] Reference group consisted of children with no prior PCV vaccination for all exposure categories. [$$]Adjusted VE models varied by outcome: (i) PCV10-type and non-PCV10-type IPD: sex, low income, maternal education, daycare, hospitalization history; (ii) PCV13-

type IPD and all-serotype IPD: sex, low income, maternal education, daycare, hospitalization history, antibiotic use, comorbidities. NE: not estimable due to zero discordant pairs.
Abbreviation: VE, vaccine effectiveness; CI, confidence intervals; NE, not estimable; PCV, pneumococcal conjugate vaccine; IPD, invasive pneumococcal disease.

Table 5. Effectiveness of one or more doses of any pneumococcal conjugate vaccines against invasive pneumococcal disease, stratified by time since the last dose and age at first vaccination.

Exposure[++]	Cases (N=72)	Controls (N=288)	Crude VE, % (95% CI)	Adjusted VE, % (95% CI)[$$]
Time since the last dose (months)				
<6	5	53	73.2 (25.8 to 90.3)	86.0 (53.3 to 95.8)
6-23	15	61	24.3 (-55.1 to 63.0)	43.1 (-51.0 to 78.5)
24-<60	7	29	21.3 (-111.8 to 70.8)	53.8 (-79.8 to 88.1)
Age at first PCV dose (months)				
<6	22	109	40.2 (-10.4 to 67.6)	66.1 (23.1 to 85.1)
<12	25	127	41.7 (-5.2 to 67.7)	67.3 (27.1 to 85.3)
12-<60	2	16	62.2 (-74.6 to 91.8)	80.6 (-39.3 to 97.3)

[++] The reference group for all comparisons was no PCV vaccination. [$$] All models were adjusted for sex, low income, daycare attendance, hospitalization history, recent antibiotic use, and comorbidity status. Time since the last dose was calculated based on the interval between the most recent PCV dose and the index date. Age at first dose refers to the child's age when receiving the initial PCV dose.
Abbreviation: VE, vaccine effectiveness; CI, confidence intervals; PCV, pneumococcal conjugate vaccine.