Distance to health services modifies the effect of an 11-valent pneumococcal vaccine on pneumonia risk among children less than 2 years of age in Bohol, Philippines

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Abstract

Background: Both vaccine trials and surveillance studies typically use passive surveillance systems to monitor study outcomes, which may lead to under-reporting of study outcomes in areas with poor access to care. This detection bias can have an adverse effect on conventional estimates of pneumonia risk derived from vaccine trials.

Methods: We conducted a secondary analysis of a randomized, placebo-controlled, double-blind vaccine trial that examined the efficacy of an 11-valent pneumococcal vaccine (PCV) among children less than 2 years of age in Bohol, Philippines. Trial data were linked to the residential location of each participant using a geographical information system. The study was conducted using 11 729 children who received three doses of any study vaccine (PCV11) or placebo. Multivariate Cox proportional hazards models were used to examine major risk factors for pneumonia diagnosis and the relationship between distance to Bohol Regional Hospital (BRH) and vaccination with PCV with risk for pneumonia diagnosis.

Results: There was a significant interaction effect between distance from BRH and vaccination with PCV11 on pneumonia risk. Among children living 12 km from BRH, vaccination with PCV11 was associated with a decreased hazard ratio for radiographic pneumonia, compared with vaccination with the study placebo [0.57, 95% confidence interval (CI) 0.37–0.86]. However, for children living 1 km from BRH, there was little difference in risk of radiographic pneumonia diagnosis between children vaccinated with PCV11 and those given the study placebo.
Conclusion: Children living close to BRH had no documented reduction in the primary study outcome from PCV11, whereas those at greater distance experienced a substantial reduction. Because of detection bias caused by distance to BRH, in spatial analysis of vaccine trial results it may be necessary to adjust estimates of pneumonia risk and vaccine efficacy. Failure to consider the geographical dimension of trials may lead to under-estimates of efficacy which might influence public health planning efforts.

Key messages
- Among children living further than 6km from Bohol Regional Hospital, vaccinated children had lower rates of radiographic and severe pneumonia compared with unvaccinated children.
- This interaction was not apparent for children with non-severe pneumonia.
- These effects may be due to barriers to healthcare encountered in rural areas which prevent timely care so that children are not immediately brought in for care when a respiratory infection first develops.
- Vaccine trials and surveillance studies that do not consider detection bias related to geographical differences in access to care may lead to incorrect estimates of pneumonia risk and vaccine effectiveness.

Introduction
The worldwide burden of lower respiratory infection (LRI) is high—responsible for approximately 900 000 deaths among children < 5 years of age each year. Although estimates suggest a 50% reduction in LRI mortality over the past 20 years, it is still the leading cause of child mortality. Significant effort has gone into preventing pneumonia among children in low- and middle-income countries. Several large pneumococcal conjugate vaccine trials illustrate this potential. A pneumococcal vaccine (PCV9) showed an efficacy of 17% in South Africa and 37% in the Gambia against radiologically confirmed pneumonia; a PCV11 vaccine showed an efficacy of 23% in the Philippines; and a PCV10 showed an efficacy of 22% in Latin America. The estimated efficacies of these studies varied significantly, and the reasons for the differences have not been explored in depth.

Detection bias refers to systematic differences between groups in how outcomes are determined. It is a challenge for studies requiring passive surveillance to identify or diagnose study outcomes, as there are always inequalities in the types of people who actively seek care for health problems. Ali and Clemens suggest that geographical barriers can lead to differences in detection of study outcomes between study participants with good access to care vs those with poor access to care. In particular, in studies where the main trial health facility is located in a region that is difficult for some study participants to access, certain portions of the population may be less likely to report to the health facility when they become ill.

In this study, we re-analyse data from a PCV11 trial in Bohol, Philippines, to examine the major risk factors for pneumonia in the trial population and examine the effect of the PCV on risk of infection. We use spatial analytical techniques to explore how detection bias can affect conventional estimates of pneumonia risk derived from vaccine trials. We discuss how geographical data collection and spatial analysis can be used to ameliorate detection bias in areas where the ability of the enrolled trial population to access the main study hospital differs based on location of residence and the challenges of accessing healthcare.

Methods

Study area
The study was conducted in six municipalities in the southwest corner of Bohol Province in the central Philippines (Figure 1). This is a predominantly rural agricultural area covering 357 km² with a population of 149 000 in 2000. Between 1999 and 2000, the infant mortality rate in the region was 28 per 1000 births. The major causes of death were pneumonia and diarrhoea.

Procedures
The trial was a randomized, placebo-controlled, double-blind vaccine trial. The description of recruitment procedures, the vaccine, vaccine administration procedures and the definition of pneumonia are described in detail.
After obtaining signed informed consent from the parent/caregiver, study nurses vaccinated infants in one of 48 health centres in the study area. The PCV11 and placebo vaccines were allocated using block randomization. A list containing random permutations of the letters A to F was generated by sanofi pasteur; three of the letters were assigned the PCV11 and three the placebo. After enrolment, a child was assigned the next letter on the list in a blinded manner. Recruitment and vaccination occurred simultaneously in all parts of the study area between July 2000 and December 2003; follow-up ended on 31 December 2004. The geographical location of each child’s household of residence was collected using handheld Geographic Position System (GPS) and linked to study data in a Geographic Information System (GIS). If a child moved during the study period, a new GPS location was collected.

The main objective of the trial was to examine the efficacy of an 11-valent pneumococcal vaccine (PCV) among children less than 2 years of age, against radiographic pneumonia. Radiologically-defined pneumonia (WHO-PEP) was defined using standardized World Health Organization (WHO) methodology, as the presence of a dense opacity that could be a fluffy consolidation of a portion of a lobe, a whole lobe or the entire lung, often containing air bronchograms, and sometimes associated with pleural effusion in the lateral pleural space associated with a pulmonary infiltrate or an effusion large enough to obscure such an opacity. WHO definitions of pneumonia (non-severe, severe and very severe), were used to define the clinical endpoints. Pneumonia was present if a child had a history of cough and/or difficult breathing of less than 2 weeks’ duration, and presented with: (i) increased respiratory rate (rate 60/min if age 2 months, 50/min if age 2–11 months and 40/min if age 12–59 months); (ii) lower chest wall indrawing (severe); or (iii) cyanosis and/or inability to feed or drink (very severe). Case ascertainment was through passive means; pneumonia cases were diagnosed and recorded among children brought into one of three private hospitals or the main public government facility (Bohol Regional Hospital) by a caregiver. Of the 12194 children enrolled in the trial, 98.7% received all three doses of vaccine or placebo (Figure 2). Among these children, 3074 episodes of clinical pneumonia were recorded.

For the current analysis, we assessed risk of pneumonia diagnosis among children over the 2-year follow-up period using four study endpoints: radiographic pneumonia (WHO-PEP), all clinical pneumonia cases, severe/very severe clinical pneumonia alone and non-severe clinical pneumonia alone. Our previous work showed clear spatial variation in the rate of vaccination among the entire study population, and spatial and temporal variation in pneumonia morbidity rates in the study area. We reasoned that this variation over space and time necessitated a spatio-temporal approach to modelling pneumonia risk in order to accurately model the effect of the vaccine and the risk factors that contributed to pneumonia. Individual child covariates included sex, the weight-for-age z-score and whether or not the child received the PCV11 vaccine; household-level covariates included maternal education, the number of children in the household and the distance between the household and Bohol Regional Hospital (BRH: where 80% of all clinical pneumonia cases were received). Although some of these measures could change over time (e.g. weight, maternal education), they were included as time-invariant covariates in regression models as they were only collected once when the child was enrolled in the study. Several time-varying covariates which captured the changes in case rates and vaccination rates over time were also included in regression models. We used ArcGIS and the Python scripting language to generate a series of distance buffers around each child’s household of residence in the dataset—at 500 m, 1000 m and 2000 m—and aggregate trial data to each of these buffers for every month of the trial. This yielded 52 separate months of data for each of the three distance buffers. If a child moved during the study, the location of their household was adjusted when calculating these space-time variables. An area-level measure of PCV11 coverage (defined as children who
received PCV11 by the total number children enrolled in the study) for each child was calculated under the assumption that coverage in the area around a child’s home might affect the risk of pneumonia. Areas with higher levels of coverage should see lower risk of pneumonia if there is a measurable indirect effect of the vaccine. The pneumonia rate per 1000 children was defined as the number of clinical pneumonia cases by the total number of children enrolled in the study. A child’s own case, if the child was diagnosed with pneumonia, was not included in this rate.

To determine the most relevant geographical scale at which to measure area-level pneumonia rates, vaccine coverage and population density, and as an added robustness check of our results, univariate and multivariate model results were examined using the data calculated at all three distance buffers. This allowed us to examine how results change if different geographical scales are used to measure area-level effects (e.g., scale dependencies). This analytical step was informed by a large body of research in the public health and social sciences, which
shows that the processes that affect health operate at a variety of geographical scales. All three geographical scales we examined showed similar results across all three area-level measures (results not shown); in particular, the results of the main effects of distance and PCV11 vaccination and the interaction between them did not change. The results for the 2000-m buffer were weak, suggesting this was too large a scale for measuring the potential disease diffusion process in this rural study area. The 500-m and 1000-m radius areas showed the strongest effects in univariate models predicting pneumonia risk. The final models included the level of vaccine coverage among children living within a 500-m radius and the pneumonia rate among children living within a 1000-m radius.

The ethics review boards of the Research Institute for Tropical Medicine in Philippines (RITM) and the National Public Health Institute of Finland (THL) approved this study. The trial is registered with ISRCTN (registry number 62323832).

Statistical analysis
The primary analysis on the per-protocol population included only participants who had received three doses of the study vaccine. In descriptive analyses, we fitted univariate Cox proportional hazard regression models (separate models for each endpoint) and verified that the proportionality assumption was satisfied for each potential covariate. The time-to-event variable for the Cox model analyses was defined as the time from the third dose of study vaccine (median of 3.9 months of age) to 24 months of age. Children were censored at the end of 24 months, at withdrawal, at death or when the clinical phase of the trial came to an end on 31 December 2004. Since we developed monthly area-level variables of pneumonia and vaccination rates, we also coded the endpoints by month. If a child was diagnosed with pneumonia any time during the month, they were coded as experiencing an event during that month. Multivariate Cox's proportional hazards models with space-time-dependent covariates of area-level vaccine coverage and pneumonia rates were used to examine the relative risk of pneumonia in the placebo group compared with the vaccine group, controlling for child and household covariates. Hazard ratios (HRs) were estimated by exponentiation of the coefficient for the covariates and the standard errors (SEs) for the coefficients were used to estimate P-values and 95% confidence intervals (CIs). In both univariate and multivariate analyses, potential spatial correlations in vaccine and pneumonia rates were accounted for using robust sandwich variance estimates clustered by barangay.

Table 1. Characteristics of the study sample by study endpoints, per protocol population

<table>
<thead>
<tr>
<th>Individual child variables</th>
<th>All Children (n = 11729)</th>
<th>Children w/ pneumonia (n = 1280)</th>
<th>Children w/o pneumonia (n = 10449)</th>
<th>Children w/ pneumonia (n = 717)</th>
<th>Children w/o pneumonia (n = 9432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated with PCV 11 (%)</td>
<td>50.1</td>
<td>50.9</td>
<td>50.8</td>
<td>50.9</td>
<td>50.8</td>
</tr>
<tr>
<td>Female (%)</td>
<td>48.0</td>
<td>48.6</td>
<td>48.8</td>
<td>48.6</td>
<td>48.8</td>
</tr>
<tr>
<td>Mean weight-for-age z-score</td>
<td>0.37 (1.05)</td>
<td>0.43 (1.06)</td>
<td>0.36 (1.05)</td>
<td>0.37 (1.05)</td>
<td>0.37 (1.05)</td>
</tr>
<tr>
<td>Mean mother’s education (years)</td>
<td>10.30 (3.53)</td>
<td>10.39 (3.52)</td>
<td>10.35 (3.53)</td>
<td>10.35 (3.53)</td>
<td>10.35 (3.53)</td>
</tr>
<tr>
<td>Mean no. children in the household (SD)</td>
<td>2.06 (1.93)</td>
<td>2.04 (1.92)</td>
<td>2.03 (1.92)</td>
<td>2.03 (1.92)</td>
<td>2.03 (1.92)</td>
</tr>
<tr>
<td>Mean distance from BRH (SD)</td>
<td>6090 (6001)</td>
<td>5040 (5375)</td>
<td>6281 (6089)</td>
<td>4672 (4952)</td>
<td>6098 (6004)</td>
</tr>
<tr>
<td>SD, standard deviation; BRH: Bohol Regional Hospital; w/ w/o, with without.</td>
<td></td>
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</tr>
</tbody>
</table>
We assessed interactions to examine whether the treatment effect differed between subgroups. Only the distance PCV11 interaction was statistically significant. To facilitate interpretation of the interaction effect, given that distance was a continuous variable in the model, point estimates were generated by producing exact hazard ratios and 95% confidence intervals (placebo vs PCV11 groups) at specific distances (1 km, 3 km, 6 km, 9 km, 12 km). These distances were arbitrarily chosen at equal intervals, and other distances showed the same trend. Hazard ratios for the interaction term show the treatment effect as a function of distance from Bohol Regional Hospital. Robustness checks included models where distance was treated as a categorical variable, and results were nearly identical (results available on request). Statistical analyses were done with SAS version 9.4 and R version 3.1.0.

## Results

Of the 12,194 children enrolled in the trial, 12,031 received all three doses. An additional 302 children could not be geocoded. The per-protocol study population for this analysis therefore comprised 11,729 children who received three doses of any study vaccine (PCV11 or placebo): 50.1% were vaccinated with PCV11, and 48% were girls. The mean $\mu_{\text{weight-for-age z-score}}$ weight for age $z$-score was $-0.37 (\pm 1.05)$, mothers had on average $10.3 (\pm 3.5)$ years of education, and there were approximately $2.06 (\pm 1.93)$ children per household. Table 1 shows child and family characteristics between infants and children experiencing a pneumonia episode and those who did not. Children with pneumonia were more likely to be boys, had a lower weight-for-age $z$-score, had a mother with a lower level of education, came from households with more children and lived closer to Bohol Regional Hospital ($P < 0.01$). Table 2 shows the same characteristics summarized by the distance from a child’s residence to BRH. Child and family characteristics differed significantly across all distances, with the exception of the rate of severe/very severe and radiographic pneumonia which showed no significant trend over distance. Figure 3 shows the rate of non-severe, severe/very severe and radiographic pneumonia by distance (categorized into $< 1$ km, 1–2.9 km, 3–8.9 km and $> 9$ km) and vaccination status (PCV11 vs placebo). The rate of non-severe pneumonia decreased with distance, and was similar between vaccinated and unvaccinated children. The rate of severe/very severe and radiographic pneumonia was similar across distance groups, with an elevated rate among placebo recipients living $> 6$ km from BRH.

Multivariate Cox proportional hazards regression (Table 3) indicated that the association between pneumonia and child- and area-level risk factors were, for the most part, similar for radiographic, non-severe and very severe pneumonia. Children of mothers with higher levels of education had a decreased risk of pneumonia: HR 0.92 (95% CI 0.87–0.97) for radiographic pneumonia and 0.95 (95% CI 0.93–0.96) for non-severe pneumonia. A greater number of children in the household increased the risk for non-severe (HR 1.07, 95% CI 1.03–1.10), severe/very severe (HR 1.11, 95% CI 1.07–1.15) and radiographic pneumonia (HR 1.16, 95% CI 1.10–1.23). Each additional neighborhood pneumonia case per 1000 increased a child’s risk of pneumonia by 3% across all study endpoints (HR 1.03, 95% CI 1.02–1.04). The area-level measure of the percent of children vaccinated with PCV11 was not related to

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### Table 2. Characteristics of the study sample by distance from Bohol Regional Hospital, per protocol population

<table>
<thead>
<tr>
<th>Distance of child’s residence from BRH</th>
<th>&lt; 1 km</th>
<th>1 km–6 km</th>
<th>6 km–12 km</th>
<th>&gt; 12 km</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual child variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All clinical pneumonia rate (per 1000)</td>
<td>196.1 (8.6)</td>
<td>158.8 (4.2)</td>
<td>126.8 (6.2)</td>
<td>90.3 (5.5)</td>
</tr>
<tr>
<td>Non-severe pneumonia rate (per 1000)</td>
<td>133.4 (7.1)</td>
<td>101.9 (3.4)</td>
<td>80.7 (4.9)</td>
<td>46.8 (4.0)</td>
</tr>
<tr>
<td>Severe/very severe pneumonia rate (per 1000)</td>
<td>62.7 (4.9)</td>
<td>58.6 (2.5)</td>
<td>46.0 (3.7)</td>
<td>43.4 (3.9)</td>
</tr>
<tr>
<td>Radiographic pneumonia rate (per 1000)</td>
<td>14.4 (2.3)</td>
<td>14.9 (1.3)</td>
<td>15.1 (2.1)</td>
<td>11.8 (1.9)</td>
</tr>
<tr>
<td>Vaccinated with PCV11 (%)</td>
<td>49.1</td>
<td>50.2</td>
<td>49.9</td>
<td>49.6</td>
</tr>
<tr>
<td>Female (%)</td>
<td>47.3</td>
<td>48.6</td>
<td>47.3</td>
<td>47.4</td>
</tr>
<tr>
<td>Mean weight-for-age z-score (visit 1) (SD)</td>
<td>$-0.32 (1.0)$</td>
<td>$-0.29 (1.0)$</td>
<td>$-0.53 (1.1)$</td>
<td>$-0.36 (1.1)$</td>
</tr>
<tr>
<td>Mean mother’s education (years) (SD)</td>
<td>12.1 (3.1)</td>
<td>10.5 (2.1)</td>
<td>9.6 (3.3)</td>
<td>8.4 (3.3)</td>
</tr>
<tr>
<td>Mean no. children in the household (SD)</td>
<td>1.7 (1.7)</td>
<td>2.1 (1.9)</td>
<td>2.3 (1.9)</td>
<td>1.6 (1.7)</td>
</tr>
<tr>
<td><strong>Area-level variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pneumonia rate (per 1000 children) (SD)</td>
<td>4.9 (4.7)</td>
<td>3.3 (4.5)</td>
<td>2.5 (9.6)</td>
<td>2.0 (8.3)</td>
</tr>
<tr>
<td>Mean percent vaccinated with PCV11 (SD)</td>
<td>50.1 (3.6)</td>
<td>49.8 (9.1)</td>
<td>50.7 (15.2)</td>
<td>50.5 (21.6)</td>
</tr>
</tbody>
</table>

SD, standard deviation; BRH, Bohol Regional Hospital.
pneumonia diagnosis. Covariate-adjusted survival curves can be found in Figures S1-S4 (available as Supplementary data at IJE online).

There was an important interaction effect between distance from BRH and vaccination with PCV11 (Figure 4; Table S3, available as Supplementary data at IJE online). Among children living 1 km from BRH, the hazard ratio for radiographic pneumonia was similar between children vaccinated with PCV and those given the study placebo (1.10, 95% CI 0.84–1.46). The hazard ratio for PCV11 vs placebo decreased with distance from BRH: among children living 12 km from BRH it was 0.57 (95% CI 0.37–0.86). This represents a 43% reduced risk for PCV11 vs placebo among children living far away from the main study hospital. For severe/very severe pneumonia, results were similar though attenuated. The HR decreased from 1.24 (95% CI 1.03–1.49) among children living 1 km of BRH to 0.72 (95% CI 0.56–0.93) among children living 12 km from BRH—a 28% reduction in risk for children receiving PCV11. There was no interaction effect for non-severe pneumonia.

In order to ensure that the geographical distribution of deaths among the study population did not bias results, all-cause mortality and pneumonia-related mortality by distance quintile were examined (Tables S1 and S2, available as Supplementary data at IJE online). Results indicate that the all-cause mortality rate for the population living less than 1 km from BRH was 5.12 per 1000 (95% CI 2.97–8.82) and for children living more than 12 km from BRH was 4.22 (95% CI 2.50–7.13). Poisson regression models indicate no difference between the closest (< 1 km) and furthest (> 12 km) children [risk ratio (RR) 0.83; 95% CI 0.39–1.75]. Numbers were much smaller for pneumonia-related deaths, but results were nearly identical.
Our results suggest that children living a greater distance from comprehensive health services, such as those available at the large regional hospital, derive greater benefit from vaccination with PCV11. In particular, children living 9 km or more from the regional hospital and who received the vaccine had a decreased risk of developing clinically severe/very severe pneumonia or radiographic pneumonia compared with placebo recipients. This effect was not apparent for children with non-severe pneumonia. It is well known that non-severe pneumonia is for the most part viral, and in fact none of the three trials in Africa\(^3,4\) or our trial in Asia\(^5\) showed an impact of pneumococcal vaccine on non-severe pneumonia. However, all three trials showed an impact on severe/very severe and radiographic pneumonia, suggesting a role for the pneumococcus in their causation and commensurate with the specific distance effects demonstrated here.

What might be the explanation for these distance effects? It is possible that limited access to healthcare in rural areas prevents timely care, as children are not immediately brought in for care when a respiratory infection first develops. Failure to come in early allows a viral lower respiratory tract infection to progress to a pneumococcal pneumonia, many of which are due to vaccine serotypes and present clinically as severe/very severe or radiographic pneumonia. This would be more evident in the placebo group, given a fixed effect of vaccine on pneumonia outcomes among vaccine recipients.

We also found that vaccinated children living close to the hospital (<1 km) appear to have higher rates of severe pneumonia and very severe pneumonia, which might explain the finding of a higher rate of severe pneumonia in the placebo group. However, our multivariate analysis included covariates which controlled for differences in urban areas.\(^18,19\) A full explanation of this finding is outside of the scope of the current study and future studies will further evaluate the risk factors for pneumonia among children in the urban centre of Tagbilaran City.

Distance to health services often plays a vital role in health-seeking behaviour, particularly in low-income countries where mobility often incurs social and economic costs. Patients are often monitored via hospital-based passive-surveillance systems in vaccine trials. If a person lives far away from the study health facilities, they may be less likely to report to these facilities, which could lead to under-reporting.

### Table 3. Multivariate Cox regression models by study endpoint, per protocol population

<table>
<thead>
<tr>
<th>Individual child variables</th>
<th>All clinical pneumonia</th>
<th>Non-severe pneumonia</th>
<th>Severe/very severe pneumonia</th>
<th>Radiographic pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received vaccine</td>
<td>1.91 (1.08–3.38)</td>
<td>1.05 (0.56–1.99)</td>
<td>5.66 (2.19–14.64)</td>
<td>7.06 (1.67–29.77)</td>
</tr>
<tr>
<td>Female</td>
<td>0.80 (0.71–0.89)</td>
<td>0.84 (0.75–0.93)</td>
<td>0.71 (0.61–0.83)</td>
<td>0.79 (0.62–1.01)</td>
</tr>
<tr>
<td>Weight-for-age z-score (at visit 1)</td>
<td>0.95 (0.91–1.00)</td>
<td>0.97 (0.92–1.02)</td>
<td>0.93 (0.86–1.00)</td>
<td>0.99 (0.87–1.14)</td>
</tr>
<tr>
<td>Mother’s education (years)</td>
<td>0.94 (0.93–0.96)</td>
<td>0.95 (0.93–0.96)</td>
<td>0.94 (0.92–0.97)</td>
<td>0.92 (0.87–0.97)</td>
</tr>
<tr>
<td>No. children in the household</td>
<td>1.08 (1.05–1.11)</td>
<td>1.07 (1.03–1.10)</td>
<td>1.11 (1.07–1.15)</td>
<td>1.16 (1.10–1.23)</td>
</tr>
<tr>
<td>Log(distance) from BRH(^a)</td>
<td>0.79 (0.74–0.85)</td>
<td>0.73 (0.68–0.79)</td>
<td>0.92 (0.83–1.03)</td>
<td>0.99 (0.84–1.18)</td>
</tr>
<tr>
<td>Received vaccine * log(distance)(^b)</td>
<td>0.92 (0.86–1.00)</td>
<td>1.00 (0.92–1.09)</td>
<td>0.80 (0.71–0.91)</td>
<td>0.76 (0.63–0.92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Area-level variables(^b)</th>
<th>All clinical pneumonia</th>
<th>Non-severe pneumonia</th>
<th>Severe/very severe pneumonia</th>
<th>Radiographic pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia rate (per 1000 children)</td>
<td>1.03 (1.02–1.04)</td>
<td>1.03 (1.02–1.04)</td>
<td>1.03 (1.02–1.03)</td>
<td>1.03 (1.02–1.04)</td>
</tr>
<tr>
<td>Percent vaccinated with PCV11</td>
<td>1.00 (0.98–1.01)</td>
<td>1.00 (0.98–1.02)</td>
<td>0.99 (0.98–1.01)</td>
<td>1.00 (0.98–1.03)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; BRH, Bohol Regional Hospital.

\(^a\)Distances are in kilometres (km).

\(^b\)Pneumonia rate (per 1000 children) was constructed using a 1000-m buffer area; percent vaccinated with PCV11 was constructed using a 500-m buffer area.
detection bias. Our findings support the existence of such bias but also suggest that detection bias differs by severity of disease. Descriptive characteristics of the study population by distance indicate that the non-severe pneumonia rate decreases with distance from BRH from 135.7 (< 1 km) to 70.6 (> 12 km) (P < 0.001); this effect did not exist for severe/very severe and radiographic pneumonia. This in itself if quite interesting, and suggests that care-seeking behaviour differs by severity of disease, and that detection bias in this setting is driven by the interaction between access and severity. It is likely that the difference in pneumonia rates with distance is related to the effect of travel time and distance on care seeking behaviour. In areas near BRH, where there are few barriers to care, families bring children in regardless of severity of illness. In areas far away, with geographical (distance) and economical (cost) barriers, families appear to only seek care for severe cases. Detection bias, therefore, is most apparent when examining non-severe disease.

This has two implications for interpretation of our results. First, if detection bias does not occur among severe cases, then the true protective effect of the vaccine is observed among children with severe disease. Our results show that children living 9 km or more from the regional hospital and who received the vaccine had a decreased risk of developing clinically severe/very severe pneumonia or radiographic pneumonia compared with placebo recipients. This effect was not apparent for children with non-severe pneumonia. In order to avoid the challenges presented by detection bias in vaccine trials, it is important to ensure that all study subjects can reach and use health facilities in the study area. Knowledge of the spatial distribution of the population and the barriers they face in accessing care (both physical and socioeconomic) should be considered in the choice or establishment of health facilities used to provide key services during the vaccine study. Spatial data (e.g. GPS and GIS) can provide the spatial information necessary to examine the distribution of the population, locate study health facilities, delineate and create trial areas and, subsequently, analyse trial data.

Second, the overall rate of pneumonia was likely higher than our data suggest, since many non-severe cases from households located far from BRH were not diagnosed. This finding has larger implications for any surveillance study using passive hospital- or clinic-based case ascertainment methods. Such bias would be worse for studies with one or two major study sites where passive case ascertainment takes place. Surveillance estimates will need to be adjusted to account for this distance-based detection bias. This requires knowledge of the spatial distribution of the population and statistical techniques which can incorporate spatial relationships when estimating disease rates. Our findings support recommendations to strengthen surveillance systems and burden of disease data both before and after vaccine introduction.20,21 Many bilateral donors and non-governmental organizations (NGOs) provide some technical support for the development of surveillance, monitoring and data management programmes,22 but there is still significant need to strengthen such systems. In light of our findings, we suggest that such monitoring efforts should routinely collect geographically explicit data in order to understand geographical heterogeneity in the population and burden of disease. Population census databases which collect basic demographic data on a regular
basis are very important tools which should be used for lower respiratory infection (LRI) surveillance, prevention and control programmes. Many low- and middle-income countries have infrequent and inadequate census programmes, which could be improved to provide support for the design, implementation and analysis of vaccine trials and, more generally, for disease surveillance efforts.

Detection bias could also explain the difference in efficacy against reported radiographic pneumonia between the South African, Gambian and Philippine PCV trials, because the barriers to accessing care differed greatly between these sites. The South African trial (vaccine efficacy of 17%) was conducted in a peri-urban area outside Johannesburg, where study participants all had good geographical access to care. The Gambian trial (vaccine efficacy of 37%) was conducted in a group of rural communities where access was uniformly difficult. The South African vaccine trials (vaccine efficacy of 17%) was conducted in an area where some trial participants lived near the study hospital whereas others had difficulty accessing the main study hospital. The results of these trials lend further support to our conclusions. If access to care is good (South Africa), children in the placebo group would receive antibiotics earlier, decreasing vaccine effectiveness; whereas with poor access to care (Gambia), severe/very severe and radiographic pneumonia would develop in the placebo recipients, increasing vaccine efficacy given a fixed effect on vaccine recipients. A comparative study of these different trials would further strengthen our understanding of how access to care in low-income countries may bias conventional estimates from vaccine trials and surveillance studies. Our findings also support the need for multi-site studies so that geographical/contextual factors can be examined and considered.

This study has a few limitations. Though geographical data were collected using GPS technology, the gold standard for geographical studies, some children enrolled in the study could not be located. We assessed the difference in demographic characteristics between children we located and those that were not and found no significant differences, suggesting geocoding errors did not bias study results. Additionally, the area-level variables are subject to small-numbers problems, especially in more sparsely populated areas. Our previous work used extensive geostatistical techniques to choose a geographical level of analysis that would minimize small-number problems, so we are confident that area-level rates accurately represent small-area disease dynamics.

We have shown that detection bias can have an adverse effect on conventional estimates of pneumonia risk derived from vaccine trials. These findings are supported by our earlier work on the same PCV11 trial in the Philippines, where we found that areas located further from BRH had higher estimates for vaccine protective efficacy than areas closer to BRH. In this trial, detection effects tended to bias the overall estimates of vaccine efficacy downward, especially since a majority of the population lived in the city of Tagbilaran and had good access to hospital care. Only with the use of geographical data and spatial analysis was it possible to estimate geographically explicit vaccine efficacy measures and see the effect of diagnosis on distance. Including a geographical dimension in pneumonia vaccine trials may lead to better estimates of the true potential vaccine effect, by taking into account geographical distance and partially accounting for access to care biases.

Supplementary Data

Supplementary data are available at IJE online.

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