Distance to health services affects local-level vaccine efficacy for pneumococcal conjugate vaccine (PCV) among rural Filipino children

Elisabeth Dowling Root[a,1], Marilla Lucero[b], Hanna Nohynek[c], Peter Anthamatten[d], Deborah S. K. Thomas[d], Veronica Tallo[b], Antti Tanskanen[c,e], Beatriz P. Quiambao[b], Taneli Puumalainen[f], Socorro P. Lupisan[b], Petri Ruutu[g], Erma Ladesma[b], Gail M. Williams[h], Ian Riley[h], and Eric A. F. Simões[i]

[a]Department of Geography and Institute of Behavioral Sciences, University of Colorado Boulder, Boulder, CO 80309; [b]Research Institute for Tropical Medicine, Muntinlupa, 1781 Manila, Philippines; [c]Department of Vaccination and Immune Protection, National Institute for Health and Welfare, 00271, Helsinki, Finland; [d]Department of Geography and Environmental Sciences, University of Colorado Denver, Denver, CO 80217-3364; [e]Department of Clinical Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden; [f]Department for Promotion of Welfare and Health, Ministry for Social Affairs and Health, 00271, Helsinki, Finland; [g]Department of Infectious Disease Surveillance and Control, National Institute for Health and Welfare, 00300, Helsinki, Finland; [h]School of Population Health, University of Queensland, Herston, QLD 4006, Australia; and [i]Department of Pediatrics, University of Colorado School of Medicine and Department of Epidemiology and Center for Global Health, Colorado School of Public Health, Aurora CO 80043

Edited by Burton H. Singer, University of Florida, Gainesville, FL, and approved January 21, 2014 (received for review July 22, 2013)

Pneumococcal conjugate vaccines (PCVs) have demonstrated efficacy against childhood pneumococcal disease in several regions globally. We demonstrate how spatial epidemiological analysis of a PCV trial can assist in developing vaccination strategies that target specific geographic subpopulations at greater risk for pneumococcal pneumonia. We conducted a secondary analysis of a randomized, placebo-controlled, double-blind vaccine trial that examined the efficacy of an 11-valent PCV among children less than 2 y of age in Bohol, Philippines. Trial data were linked to the residential location of each participant using a geographic information system. We use spatial interpolation methods to create smoothed surface maps of vaccination rates and local-level vaccine efficacy across the study area. We then measure the relationship between distance to the main study hospital and local-level vaccine efficacy, controlling for ecological factors, using spatial autoregressive models with spatial autoregressive disturbances. We find a significant amount of spatial variation in vaccination rates across the study area. For the primary study endpoint vaccine efficacy increased with distance from the main study hospital from −14% for children living less than 1.5 km from Bohol Regional Hospital (BRH) to 55% for children living greater than 8.5 km from BRH. Spatial regression models indicated that after adjustment for ecological factors, distance to the main study hospital was positively related to vaccine efficacy, increasing at a rate of 4.5% per kilometer distance. Because areas with poor access to care have significantly higher VE, targeted vaccination of children in these areas might allow for a more effective implementation of global programs.

spatial epidemiology | spatial analysis | targeted intervention | randomized controlled trial | GIS

Of the estimated 7.6 million children under 5 who died in 2010, ∼1.39 million (18.3%) died from acute lower respiratory infections (ALRI) (1). Although ALRI mortality has decreased over the past decade, it remains the largest single cause of childhood mortality worldwide, particularly in less-developed countries in Africa, Southeast Asia, and the eastern Mediterranean (1–3). ALRI is caused by a variety of pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, respiratory syncytial virus and influenza virus (4). There are conflicting estimates in the scientific literature of the role each of these pathogens play in the overall burden of disease (1, 5, 6). O'Brien et al. suggest that *S. pneumoniae* is the leading cause of pneumonia, accounting for 826,000 (or 8%) of all deaths among children under 5 in 2000 (6). However, more recent estimates from the global burden of disease study (GBD) suggest a much smaller role for pneumococcus, accounting for only 168,000 ALRI deaths in children under 5 y in 2010 (2). Although the reporting years differ, and ALRI mortality has decreased over time, these significantly different estimates have sparked a debate about the proportion of ALRI mortality attributable to pneumococcus.

Pneumococcal conjugate vaccines (PCVs) have been shown to be effective against invasive pneumococcal disease across a diverse set of populations. A PCV9 vaccine showed an efficacy of 17% in South Africa (7) and 37% in the Gambia (8) against radiologically confirmed pneumonia; a PCV11 vaccine showed an efficacy of 23% in the Philippines (9); and a PCV10 showed an efficacy of 22% in Latin America (10). Drawing from these large vaccine trials, the World Health Organization (WHO) now recommends that PCVs be included in childhood immunization programs worldwide. Special emphasis is placed on countries with high childhood mortality (under 5 mortality rate of >50 deaths/1,000 births) where "high and equitable coverage" is advocated to maximize the impact of pneumococcal vaccines (11).

Although PCVs have been widely used in United States, and more recently in Europe, they have generally not been widely adopted in other regions largely due to the high cost of integrating PCVs into national programs (12). The cost of implementing a universal PCV vaccination strategy, along with the recent findings from GBD 2010, suggests a need to reconsider the recommendations for universal PCV coverage shifting to a focus on vaccination strategies that target specific geographic subpopulations at greater risk for pneumococcal pneumonia.

Significance

Although pneumococcal conjugate vaccines (PCVs) are widely available in industrialized nations, the cost of these vaccines and the strategy of universal vaccination of infants, as endorsed by the World Health Organization, are daunting obstacles to the adoption of these vaccines in developing countries. Using spatial epidemiological methods to examine the spatial variation in vaccine efficacy (VE) in an 11-valent PCV trial in Bohol, Philippines, we suggest an alternative strategy to universal vaccination. Our main finding suggests that areas with poor access to healthcare have the highest VE. An alternative vaccination strategy could target vaccination to areas where children are most likely to benefit, rather than focus on nationwide immunization.

Author contributions: E.D.R., M.L., H.N., P.A., D.S.K.T., V.T., A.T., B.P.Q., T.P., S.P.L., P.R., E.L., G.M.W., I.R., and E.A.F.S. designed research; E.D.R. performed research; E.D.R. analyzed data; and E.D.R. and E.A.F.S. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[1]To whom correspondence should be addressed. E-mail: roote@colorado.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1313748111/-/DCSupplemental.

www.pnas.org/cgi/doi/10.1073/pnas.1313748111

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However, targeted interventions require a detailed analysis of the efficacy of the PCV vaccine that takes sociodemographic and geographic factors into account. Subpopulations with higher rates of vaccine-preventable disease could be targeted for vaccination, providing large cost savings to national health programs over universal vaccination approaches. These savings would only be realized if the costs associated with delivering a vaccine to disparate subpopulations is the same or lower than the average cost nationally and if the benefits of the vaccine (both direct and indirect) are the same or higher than the average benefits nationally. In this study, we use spatial epidemiological methods to examine the spatial variation in vaccine efficacy (VE) and model ecological factors that drive spatial patterns to suggest how targeted vaccine strategies can be developed.

Results

There was significant spatial variation in vaccination rates across the study area (Fig. 1*A*), ranging from 17% to 74%. Although the maps in Fig. 1 *A* and *B* provide evidence of pockets of high and low rates across the study area, the patterning of vaccination rates appears spatially random. We find no evidence of a distance decay pattern, meaning vaccination rates are not higher near the city of Tagbilaran (and the main study hospital) and lower in more distal areas. We also find striking spatial patterns of VE for all three endpoints that are statistically significantly different from the global mean (Fig. 2). VE also varied spatially, ranging from well below 0 to as high as 100%. VE was lowest in areas that were in and around Tagbilaran City with the highest population density and the main study hospital and higher in rural areas farther from the city. These results indicate that both vaccination and VE are not global phenomena, but rather vary spatially across the study area.

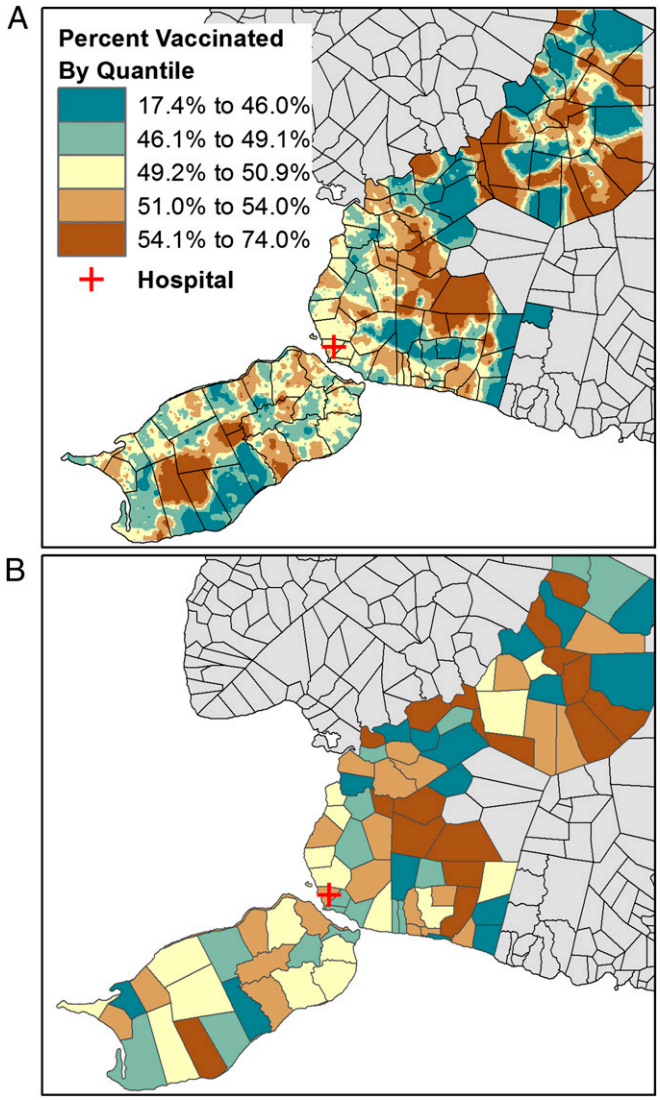

Fig. 1. Spatial variation in the percent of children vaccinated in the Bohol PCV11 trial calculated (*A*) using kriging to create a smoothed surface and (*B*) for the 92 government administrative units. Dark brown areas indicate areas with higher vaccination rates, yellow indicates areas with vaccination rates around the global mean (50%), and dark blue-green indicates areas with lower vaccination rates. See *SI Appendix*, Table S2 for summary statistics of data used for mapping.

Vaccine efficacy increased with distance from Bohol Regional Hospital (BRH; Table 1). For the primary study endpoint, radiographic pneumonia (WHO-PEP), VE ranged from −14% (95% confidence interval: −13–38; $P = 0.643$) for children living less than 1.5 km from BRH to 55% (95% confidence interval: 11–79; $P < 0.0001$) for children living greater than 8.5 km from BRH. The VE for children living >8.5 km from BRH was statistically significant and higher than the global VE estimated for the entire study population. We found similar results for the two other endpoints (Table 1) and in our sensitivity analysis, which used the intent-to-treat population (*SI Appendix*, Tables S9–S14 and Figs. S5 and S6). What is striking is that the rate of pneumonia decreases with distance among vaccine recipients, but there is no effect of distance demonstrated in placebo recipients. For radiographic pneumonia, the rate decreases from 13.4 per 1,000 person-years at <1.5 km to 6.4 at >8.5 km for vaccines, but actually increases slightly for placebo recipients from 11.7 to 14.2. This trend is even more apparent for severe/very severe pneumonia cases.

We found no evidence of an indirect effect of the vaccine (herd immunity) in a univariate analysis of VE and vaccine coverage (*SI Appendix*, Table S5); whereby nonvaccinated individuals are less likely to contract pneumonia if they are surrounded by large numbers of vaccinated individuals who cannot contract the disease. Vaccine efficacy did not decrease with increasing levels of vaccine coverage, a trend that we would expect to see if strong indirect effects were present in the study population. This is likely due to the fact that there were very few areas with particularly high PCV11 coverage, and this spatial heterogeneity is necessary for strong indirect effects of the vaccine to occur.

Table 2 and Fig. 3 show the results of the spatial autoregressive models with spatial autoregressive disturbances (SARAR), which indicate that VE increases with distance from BRH even after adjusting for confounding effects for both WHO-PEP ($\beta = 4.48$; $P < 0.0001$) and severe/very severe pneumonia ($\beta = 0.96$; $P < 0.0001$). For all clinical pneumonia, the distance coefficient is statistically significant, but the magnitude of the effect is small ($\beta = 0.72$; $P < 0.001$). Fig. 3 shows how, for all three endpoints, the VE–distance relationship begins to flatten out at greater distances, as indicated by the statistically significant coefficient for the distance polynomial term (in kilometers squared).

The inverse relationship between VE and vaccine coverage across all three endpoints provides evidence that higher local area vaccine coverage reduces placebo-group pneumonia incidence more rapidly, resulting in an indirect effect of the vaccine. This difference between univariate and multivariate results suggests that spatial heterogeneity in a variety of ecological factors—including density of children, household size, socioeconomic status, and average age—must be considered to examine the effect of neighborhood vaccine coverage on VE. This type of confounding is typically not an issue in randomized trials, as the randomization procedure automatically makes the treatment group allocation independent from any other factor that may be related to the outcome. However, because disease transmission and indirect protection are spatial processes, spatial distribution of factors related to the outcome must be considered to remove potential biases caused by spatial correlation. Other

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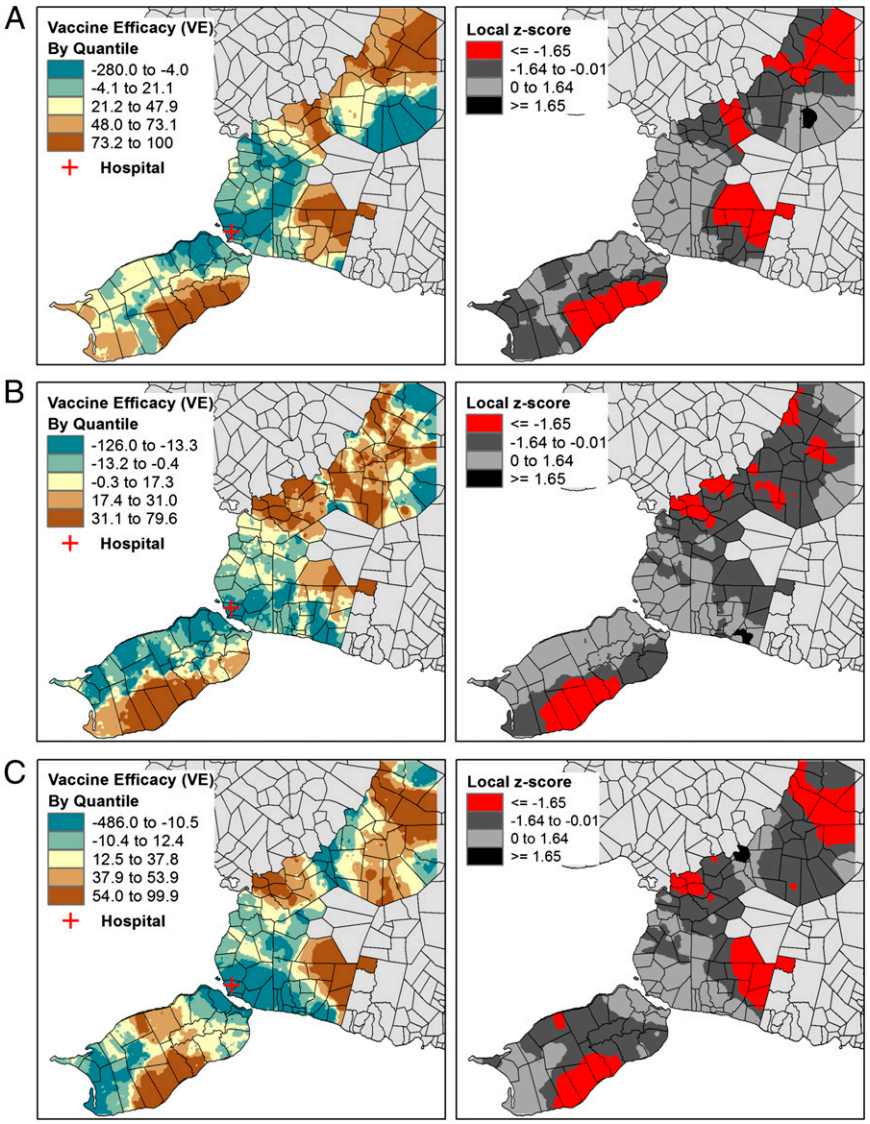

Fig. 2. Spatial variation in VE in the Bohol PCV11 trial for (*A*) WHO-PEP, (*B*) all clinical pneumonia, and (*C*) severe/very severe pneumonia. (*Left*) Endpoint displays the local VE surface map and (*Right*) the corresponding *z* score map. The *z* score indicates if the local-level efficacy measure is significantly different from the global (whole study area) mean VE. See *SI Appendix*, Table S4 for summary statistics of data used for mapping and *SI Appendix*, Table S1 for global means.

work has reported similar spatial effects with oral cholera vaccines in Bangladesh (13, 14).

Although we did examine the interaction between vaccine coverage and distance, this was not statistically significant (for WHO-PEP: $\beta = -0.01$; $P = 0.868$) and model fit statistics indicated a poorer fit. From this we conclude that vaccine coverage and distance are not colluding to affect VE, rather vaccine coverage and distance are separate effects.

We also see an inverse relationship between average children per household and VE. This relationship is likely due to the fact that one or two children in a household were included in the trial, so larger households were more likely to contain unvaccinated children who might contract and expose a vaccinated child to ALRI. Antibiotics are widely available from pharmacies without prescription, and may account for some of the local variation we observe, especially in outlying areas. Unfortunately, we have no measures of this.

Discussion

With a randomized vaccine trial, all individuals have equal likelihood of being assigned the vaccine as the placebo, but individual randomization does not necessarily translate to a spatially random distribution of vaccinated individuals. Some geographic areas may have higher rates of vaccinated children than others, which we demonstrate here in the case of the PCV11 trial in Bohol. Spatially uneven rates of vaccination, along with other ecological factors, have the potential to affect the disease risk and vaccine efficacy in localized areas. Although we found no evidence in this study of a spatial pattern of vaccination rates indicative of distance decay (e.g., areas farther from BRH did not exhibit lower rates of vaccination), a pattern such as this could confound the relationship between distance and VE.

Our results illustrate that the VE of PCV11 was spatially varied across the study area and that the variation was positively related to distance from the main study hospital. In light of these findings we suggest that access to health services substantially modifies the effect of PCV. In Bohol, access is driven by how far a person lives from the area's main hospital, because travel is difficult in this rural setting. It could be postulated that VE is lower among urban populations closer to BRH because appropriate and timely treatment of pneumococcal pneumonia in placebo recipients, with good access to care and appropriate care-seeking behavior, reduces the rate of severe or radiographic pneumonia. Conversely, in rural areas, with logistical and economic barriers to access to care, children are brought to appropriate care at a later stage in the disease, resulting in a higher rate of severe ALRI and radiographic pneumonia in the placebo group. Given a fixed effect of vaccine on pneumonia outcomes

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Table 1. Vaccine efficacy by distance of child from BRH for three study endpoints, per protocol population

	Vaccine recipients		Placebo recipients			
Distance (km)*	Cases	Rate†	Cases	Rate†	VE (95% CI)	*P* value
Radiologic (WHO-PEP)						
<1.5	25	13.4	22	11.7	−14 (−13,38)	0.64
1.5–4.49	36	13.8	39	15.4	10 (−46,44)	0.65
4.5–8.49	22	10.7	34	16.6	35 (−14,64)	0.11
>8.5	13	6.4	29	14.2	55 (11,79)	**<0.01**
All clinical						
<1.5	409	219.3	321	170.9	−28 (−49,−11)	**<0.01**
1.5–4.49	374	143.8	395	155.6	8 (−7,20)	0.30
4.5–8.49	264	128.7	270	131.7	2 (−16,18)	0.79
>8.5	188	92.2	224	110.0	16 (−2,31)	0.07
WHO severity 2/3						
<1.5	128	68.6	88	46.8	−47 (−94,−11)	**<0.01**
1.5–4.49	129	49.6	138	54.3	9 (−17,29)	0.46
4.5–8.49	84	40.9	103	50.2	19 (−10,40)	0.16
>8.5	69	33.8	101	49.6	32 (6,51)	**0.01**

*Distance is measured from BRH. The study population was ordered into quantiles of distance (<1.5, 1.5–4.4, 4.5–8.4, and >8.5 km). Some inequalities in person-years of observation in the different quantiles occurred because quantiles were adjusted slightly to round categories to the nearest 500 m.
†Rate is reported per 1,000 person-years. Person-years used to calculate rates were as follows: <1.5 km = 1,878.8; 1.5–4.49 km = 2,539.1; 4.5–8.49 km = 2,050.3; and >8.5 km = 2,036.8.

among vaccine recipients, one would expect to see a differential VE based on distance (or access) to BRH. To further test this, we examined the rate ratio of severe/very severe pneumonia to nonsevere pneumonia by distance from BRH. There was a lower proportion of severe cases among placebo recipients at <1.5 km (relative risk = 0.38; $P < 0.001$) from the hospital compared with ≥8.4 km (relative risk = 0.82; $P = 0.14$), where children were more likely to become severely ill before gaining access to care (*SI Appendix*, Table S6). This difference was not apparent in the vaccinated population. Thus, children living farther away from the regional hospital in Bohol appear to derive the most benefit from PCV11 vaccination. This has implication for vaccine campaigns in resource-poor countries, where targeting vaccinations to specific populations may be a viable option.

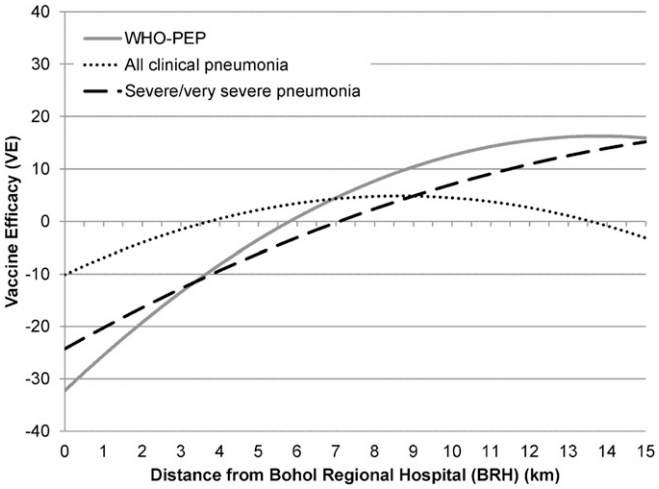

Fig. 3. Prediction plots for VE by distance from Bohol Regional Hospital. Prediction plots show the predicted VE by distance from BRH using the models presented in Table 2. Predicted values were plotted holding all variables constant at the mean (vaccine coverage = 50%; age at third dose = 4 mo; percent male = 50%; maternal education = 65%; density of children = 6 per km; average child per household = 3) and increasing the distance from hospital by 500-m increments. The spatial lag term (λ) was allowed to increase from −20% to 20% with increasing distance to simulate the changes in VE we observed with distance.

Spatial analysis of the PCV11 trial indicates that geographic targeting may be a good strategy for vaccination in this region. Although we have not yet replicated these analyses in other regions, it is possible that limited access to health services may lead to similar patterns in other geographic regions. Evidence suggests that barriers to access related to travel time, distance, and cost are ubiquitous in developing countries (15, 16). However, there are also other factors, such as care-seeking behaviors, socioeconomic status, and population density, which determine which subpopulations are at higher risk for disease (17). Many of these factors also have a geographic expression; theoretical and empirical evidence from public health, geography, and sociology indicate that people with similar characteristics cluster in space, creating larger spatial patterns within a population (18, 19). Thus, spatial analysis of PCV trial data in other regions may similarly provide insight to which populations should be targeted

Table 2. Predictors of local-level vaccine efficacy, per protocol population

	WHO-PEP			All clinical pneumonia			Severe/very severe clinical pneumonia		
Independent variable	Estimate	SE	*P* value	Estimate	SE	*P* value	Estimate	SE	*P* value
Vaccine coverage (%)	−2.19	0.28	<0.0001	−0.77	0.11	<0.0001	−1.59	0.15	<0.0001
Average age at third dose (months)	9.36	6.04	0.1214	16.50	4.18	<0.0001	1.99	3.80	0.6008
Male children (%)	−0.43	0.20	0.0309	−0.91	0.10	<0.0001	−0.74	0.09	<0.0001
Maternal education 14+ years (%)	−1.17	0.12	<0.0001	0.05	0.01	0.0001	−0.10	0.03	0.0002
Density of children (per km^2)	0.85	0.29	0.0036	−0.52	0.08	<0.0001	0.52	0.12	<0.0001
Average no. children per household	−13.63	2.63	<0.0001	6.81	1.03	<0.0001	−1.80	0.52	0.0005
Distance to hospital (km)	4.48	0.71	<0.0001	0.72	0.21	0.0008	0.96	0.22	<0.0001
Distance to hospital (km^2)	−0.26	0.04	<0.0001	−0.25	0.02	<0.0001	−0.10	0.01	<0.0001
Spatial lag of VE (λ)	0.77	0.04	<0.0001	0.82	0.03	<0.0001	0.89	0.01	<0.0001
AIC		96129			82169			95829	
Moran's I for SARAR residuals		−0.015			−0.0003			−0.034	

Note: Numbers in the three estimate columns are the SARAR model regression coefficients for each endpoint; numbers in the SE columns are the corresponding SEs for the regression coefficients; exact *P* values are also provided for each estimate. The λ, or spatially weighted value of VE, is also shown, along with corresponding SE and *P* values. We examined the Akaike Information Criterion (AIC) to find the best model fit; lower AIC values suggest better model fit. Models shown here represent the lowest AIC among all models specified for each endpoint. For each endpoint, we also show the Moran's I value for the regression residuals.

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for vaccination. In this study we use evidence from our research to suggest that distance could be used to target vaccination, but we acknowledge that other factors could and should also be used for targeting in other settings.

We do not suggest that pneumococcal conjugate vaccines should not be introduced into developing countries. Rather, given the history of slow uptake of new vaccines in developing countries, in part because of the cost and complexity of these new vaccines, alternative strategies should be considered (20, 21). Although the GAVI Alliance has committed to provide significant funding to support the implementation of PCVs in eligible countries through the advance market commitment (AMC), funding through the AMC is only a 5 y commitment of support, after which countries are expected to support immunization themselves (22). The end of funding will create a significant financial burden for many countries. For example, a recent study from Gambia, which estimated the total incremental costs to the Gambian government of introducing PCVs, found that with a PCV price of US$7 per dose, the cost of introducing PCV was US$1,647,074 or US$24.67 per fully immunized child. The costs decreased to US$864,394 with a vaccine price of US$3.50 (12). These costs are high for a country with a $10 per capita annual general government expenditure on health (23). Researchers have suggested that introduction of new vaccines might require modification of surveillance and delivery strategies (20). In this study, we develop one such strategy for determining where, or with which subpopulations, vaccination could begin.

More generally, these findings impact the design and interpretation of future vaccine and other intervention studies. The effect of access to healthcare may differentially impact the results of epidemiological studies examining the effect of vaccination programs in rural areas compared with urban areas. Providing good access to care, or implementing a trial in an area with good access, may act to reduce observed vaccine efficacy. Differential access to healthcare across study areas may explain some of the controversial results obtained in previous studies (e.g., 37% VE in Gambia vs. 17% in South Africa), as the settings for these trials were very different. This also suggests that future studies should be conducted in settings that are representative of average country conditions or in multiple sites that represent the different setting that exist within a country.

Methods

Study Area. Bohol Province in central Philippines consists of 47 municipalities that are divided into smaller regions called barangays. The region covered in this study consists of six districts in the southwest corner of Bohol. It is a predominantly rural agricultural area covering 357 km^2 with a population of 149,000 in 2000.

Procedure and Participants. Between July 2000 and December 2004, a randomized, placebo-controlled, double-blind vaccine trial [International Standard Randomised Controlled Trial Number (ISRCTN) 62323832] was conducted in Bohol to examine the efficacy of an 11-valent pneumococcal vaccine among children less than 2 y of age. The description of recruitment procedures, the vaccine, vaccine administration procedures, definition of study endpoints, and trial results have previously been published in detail elsewhere (9). In brief, enrollment and vaccination of infants took place in 48 government primary health care centers. The PCV11 and placebo vaccines were allocated using block randomization at the individual level. Mothers and caregivers were encouraged to bring their children to one of three private hospitals or the main public government facility (Bohol Regional Hospital) for any illness that they experienced at any time during the study. No "catch-up" vaccination was conducted in the study area. Only the cohort of children born into the study area between the start and the end of the study period was randomized into the trial. Because children were randomized from the same baseline population, they are assumed to have the same background pneumonia rate.

A total of 12,194 children were enrolled, of which 98.7% received all three doses of the vaccine. Only 142 children were partially vaccinated (e.g., received <3 doses) and these children were included in the intent-to-treat (ITT) analyses, but not the per-protocol (PP) results that we present here. The geographic location of each child's household of residence was collected using handheld GPS (24). We linked these geographic data to the study population in a geographic information system (GIS). Approximately 302 households could not be located during the study period. We also excluded a small isolated population of 228 children in the northeast corner of the study area because the data showed that this population was likely receiving health care services outside of the study area and, therefore, study endpoints were not accurately captured for this population. To avoid reporting bias, we chose to exclude this population in the final analysis. The final spatial sample size was 11,501 children for the PP population. The Consolidated Standards of Reporting Trials (CONSORT) diagram for flow of participants into the trial is shown in *SI Appendix*, Fig. S1.

Definitions of Pneumonia. Community-acquired pneumonia (CAP) was defined as pneumonia with onset either in the community or in a hospital but less than 72 h after admission into the hospital. Several definitions of CAP were used throughout the trial, of which two are reanalyzed in this study. First, was the primary trial endpoint, radiologically defined CAP (WHO-PEP), defined as presence of dense or diffuse infiltrates on a chest radiograph. Second, clinical pneumonia was classified using the WHO severity grades as nonsevere, severe, and very severe in infants and children with cough and/or difficult breathing. Fast breathing alone defined nonsevere pneumonia; chest-wall indrawing identified severe pneumonia; and the presence of cyanosis, the inability to feed or drink, and convulsions were the hallmarks of very severe pneumonia. During the follow-up period, 3,074 clinical episodes of WHO-defined pneumonia were recorded.

Independent Variables. As part of the trial, sociodemographic data were collected for children and their families. Individual child and family characteristics were aggregated to 2.5 km neighborhoods (for the all clinical pneumonia and severe/very severe pneumonia analyses) and 3 km neighborhoods (for the WHO-PEP analysis) around each child for use in spatial models (*SI Appendix*, Fig. S2). After creating a distance buffer of 2.5 and 3 km around each child, data were aggregated to each of these buffers to create the following independent variables: percentage of children vaccinated, the average age of children at their third dose of vaccine/placebo, percentage of children who were male, percent of mothers with 14 or more years of education (a proxy for family socioeconomic status), the density of children, and the average number of children per household. Distance was measured as the Euclidean distance from the location of each child's house to BRH.

Statistical Analysis. The primary analysis in this study was performed on the per-protocol population using both primary and secondary endpoints. Only children who received all three doses of the study vaccine with a minimum interval of 21 d between doses were included. An episode of pneumonia was included if it occurred 14 or more days after the third doses and before the date of exit from the trial.

Vaccine coverage was calculated by dividing the number of children who received all three doses of the vaccine by the total number of children (who received three doses of vaccine or placebo) enrolled in the trial. Rates of experiencing an endpoint episode were calculated per 1,000 person-years of observation for the vaccine and placebo groups. Efficacy of the vaccine in preventing a child experiencing an episode was calculated as: $100 \cdot (1 - RR)\%$, where RR is the rate ratio PCV11: placebo. A P value for the difference between rates and 95% confidence intervals (95% CI) for the RR were calculated using a Poisson regression model. Rates of experiencing an endpoint episode and VE were also calculated by distance quartiles from Bohol Regional Hospital and by quartiles of vaccine coverage using the same methods. Statistical analyses were performed using SAS v9.3.

Prior analyses of this trial only reported global vaccine efficacy measures (9). Following previously established ecological vaccine trial methods (14, 25), this study examines efficacy at a local level by calculating VE for neighborhoods, defined as a series of distance buffers around each child in the study, and ranging in size from 500 m to 10 km. We call these areas neighborhoods because they surround a child's household of residence and represent the neighboring population. The PCV11 trial data were linked to the geographic location of each child's household of residence in a GIS. Efficacy of the vaccine in preventing a child experiencing an episode was calculated as:

$$VE_i = \left(1 - \frac{ARV_i}{ARU_i}\right) \cdot 100,$$

where VE_i is the vaccine efficacy in neighborhood i, ARV_i is the vaccinee incidence rate in neighborhood i, and ARU_i the nonvaccinee incidence rate in neighborhood i. The local VE was calculated for 14 different buffer sizes for 11,501 neighborhoods. Rates of experiencing an end point were calculated using episode counts for each child and person-years of

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observation. Detailed methods for calculating neighborhood-level VE are provided in *SI Appendix*, Fig. S2 and Table S3.

To determine whether the spatial heterogeneity in VE observed in maps was random or a statistical departure from the global (whole study area) VE mean, we computed local *z* scores of the ratio of the incidence in vaccinees to the incidence in placebo recipients (25). The *z* score for neighborhood *i* is calculated as:

$$z_i = \frac{\bar{x}_i - \mu}{\sigma\sqrt{\sum_j w_{ij}}},$$

where $\bar{x}_i$ is the mean of the log of the incidence rate ratio for neighborhood *i*, μ the global mean of the log of the incidence rate ratio, σ the SD of the log of the incidence rate ratio, and w_{ij} the weight assigned to neighborhood *j*. We compared these to a standard *z* distribution and used a standard 95% confidence level, in this case $|z_i| > 1.65$, to accept the hypothesis of an extreme local value. A statistically significant negative *z* score indicates higher vaccine efficacy than the global mean.

Spatial interpolation methods were used to create smoothed surface maps for the entire study area to visualize the local vaccination rate, local VE, and *z* scores. Interpolation is the process of obtaining a data value at an unsampled location based on surrounding measurements (26). Using an inverse distance weighted algorithm in ArcGIS 10.0 and the neighborhood measures of vaccination and VE, we created two sets of maps: a continuous smoothed surface for vaccination rates and surface maps for VE by endpoint with corresponding local *z*-score maps. These smoothed maps are descriptive in nature, and are meant as a tool for visually communicate spatial patterns of VE.

In univariate analyses, we examined the relationship between VE and the distance of each child's household from BRH. The study population was ordered into quartiles based on distance from BRH then the incidence of disease among vaccinees and placebo recipients, and VE were calculated for each quartile of distance and examined for trends. To test for indirect effects of the vaccine and possible confounding effect of high levels of indirect protection, we conducted a similar univariate analysis using level of vaccine coverage in a 1-km radius area around each child, and ordered the study population into quartiles based on level of vaccine coverage. VE was calculated for each quartile of vaccine coverage and examined for trends.

SARARs implemented in *R* v.2.13.0 were used to measure the relationships between local-level VE and distance to BRH, controlling for ecological factors aggregated to the neighborhood scale. Results from our initial ordinary least squares (OLS) regression models suggested high spatial correlation among model residuals (Moran's I ranged from 0.56 to 0.49; $P < 0.001$; *SI Appendix*, Fig. S3). Based on this and the results of Lagrange multiplier tests we determined that a spatial regression model that included both a spatial lag term (which models the spread of disease) and a spatial error term (which controls for spatial autocorrelation among observations) was appropriate for this dataset. Formally the SARAR model is (27):

$$y = \rho Wy + X\beta + (\lambda Wu + \epsilon),$$

where *y* is a vector of observations of the dependent variable; *Wy* is a spatially lagged dependent variable for weight matrix *W*; *X* is a matrix of observations of the explanatory variables; *Wu* is a spatially lagged error term for weight matrix *W*; ϵ is the vector of the independently and identically distributed error terms; and ρ, λ, and β are parameters. The spatial error term accounts for the spatial autocorrelation in VE that we induced by calculating neighborhood VE (because there are many overlapping circles that share data; *SI Appendix*, Fig. S4 for SARAR residuals). In addition, the use of the 2-km fixed distance spatial weights accounts for nearly all spatial correlation, which we tested using Moran's I statistic. As a sensitivity analysis other spatial weights matrices (1 and 2.5 km) were examined with similar results.

ACKNOWLEDGMENTS. This study is part of the research of the Acute Respiratory Infection Vaccine (ARIVAC) Consortium. We are indebted to the Consortium study team and the following collaborators—The Data Safety Monitoring Board: Kim Mulholland (chair), Keith Klugman, Mary Ann Lansang (local safety monitor), David Sack, Pratap Singhashivanon, Peter Smith, and Chongsuphajaisiddhi Tan; National Institute of Health and Welfare (formerly National Institute of Public Health KTL): Tarja Kaijalainen, Kaisa Jousimies; and Research Institute for Tropical Medicine (RITM): Vernoni Ermata Dulalia, Leilani T. Nillos, Sanofi Pasteur, S. Arnoux, F. Bailleux, S. B. Chir, E. Boutry, J. M. Chapsal, Y. Couedel, V. Delore, H. DyTioco, E. Feroldi, J. Lang, J. R. Maleckar, M. Moreau, R. Ryall, D. Schulz, D. Teuwen, S.Vital, and C. Zocchetti.

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