

BMJ Open Generalisability of vaccine effectiveness estimates: an analysis of cases included in a postlicensure evaluation of 13-valent pneumococcal conjugate vaccine in the USA

Ruth Link-Gelles,¹ Daniel Westreich,² Allison E Aiello,² Nong Shang,¹ David J Weber,² Jennifer B Rosen,³ Tasneem Motala,⁴ Laurene Mascola,⁴ Jeffery Eason,⁵ Karen Scherzinger,⁶ Corinne Holtzman,⁷ Arthur L Reingold,⁸ Meghan Barnes,⁹ Susan Petit,¹⁰ Monica M Farley,^{11,12} Lee H Harrison,¹³ Shelley Zansky,¹⁴ Ann Thomas,¹⁵ William Schaffner,¹⁶ Lesley McGee,¹ Cynthia G Whitney,¹ Matthew R Moore¹

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For numbered affiliations see end of article.

Correspondence to

Dr Ruth Link-Gelles; hzt7@cdc.gov

ABSTRACT

Objectives External validity, or generalisability, is the measure of how well results from a study pertain to individuals in the target population. We assessed generalisability, with respect to socioeconomic status, of estimates from a matched case–control study of 13-valent pneumococcal conjugate vaccine effectiveness for the prevention of invasive pneumococcal disease in children in the USA.

Design Matched case–control study.

Setting Thirteen active surveillance sites for invasive pneumococcal disease in the USA.

Participants Cases were identified from active surveillance and controls were age and zip code matched.

Outcome measures Socioeconomic status was assessed at the individual level via parent interview (for enrolled individuals only) and birth certificate data (for both enrolled and unenrolled individuals) and at the neighbourhood level by geocoding to the census tract (for both enrolled and unenrolled individuals). Prediction models were used to determine if socioeconomic status was associated with enrolment.

Results We enrolled 54.6% of 1211 eligible cases and found a trend toward enrolled cases being more affluent than unenrolled cases. Enrolled cases were slightly more likely to have private insurance at birth ($p=0.08$) and have mothers with at least some college education ($p<0.01$). Enrolled cases also tended to come from more affluent census tracts. Despite these differences, our best predictive model for enrolment yielded a concordance statistic of only 0.703, indicating mediocre predictive value. Variables retained in the final model were assessed for effect measure modification, and none were found to be significant modifiers of vaccine effectiveness.

Conclusions We conclude that although enrolled cases are somewhat more affluent than unenrolled cases, our estimates are externally valid with respect to socioeconomic status. Our analysis provides evidence that this study design can yield valid estimates and the

Strengths and limitations of this study

- Strengths included population-based surveillance data and multiple data sources for estimating socioeconomic status (ie, case report form, parent interview and geocoding) at multiple levels (individual and neighbourhood).
- This was the first study to look at generalisability with respect to socioeconomic status in a vaccine effectiveness study.
- Weaknesses included no access to parent interview variables for unenrolled cases, the study potentially lacked sufficient power to identify effect measure modification, and no nationwide surveillance to compare results.

assessing generalisability of observational data is feasible, even when unenrolled individuals cannot be contacted.

INTRODUCTION

External validity, or generalisability, is the measure of how well results from a study pertain to individuals in the target population.^{1–3} Studies may fail to be generalisable to a target population when both of the following criteria are met: (1) selection/enrolment into the study is differential with respect to variable X (ie, the study population is not representative of the source population with respect to variable X, which is usually a potential confounder) and (2) variable X modifies the exposure–outcome relationship under study.^{1,4}

Increased external validity can be a major benefit of observational studies versus

randomised controlled trials (RCTs).^{2–9} Unlike in RCTs, where strict exclusion criteria are often used, observational studies usually enrol a broader subset of the population.³ This may be especially true in case–control studies, in which researchers commonly attempt to enrol *every* case of disease in a given surveillance population (eg, geographic area or hospital system).¹⁰ With the assumption that the study source population (the surveillance area) does not vary in a meaningful way from the target population (eg, an entire country), then results from observational studies may be more generalisable than those from RCTs.¹⁰

Unfortunately, due to issues related to tracking, contacting and enrolling participants, generalisability in observational studies may not be achieved, even when a priori exclusion criteria are minimal. In particular, the study population may differ from the source population by socioeconomic status (SES), which is frequently associated with characteristics that may affect enrolment probability.¹¹ For example, less-affluent individuals may lack a landline or frequently switch cell phone numbers, making them harder to reach; they may hold multiple jobs or have long commutes, making them less likely to answer their phone; they may have diminished use of or trust in the medical system, making them less likely to agree to enrolment; they may seek care at underfunded (eg, public) hospitals, which lack the resources to enrol participants.^{12–17} Alternatively, lower-SES individuals may be more likely to join a study that provides a monetary incentive for participating versus those of higher SES for whom the monetary incentive is lower.

While not always a problem, lack of representativeness by SES may reduce external validity if SES modifies the effect of the exposure–outcome relationship under study.^{18–20} One way to explore generalisability as it relates to SES is to evaluate differences in SES indicators between those selected into a study and those who were eligible, but not selected. Although some individual SES constructs, such as use of or trust in the medical system, may not be measured accurately, others, such as educational attainment, are more readily available. Additionally, other characteristics, such as recent immigration, insurance status and utilisation of prenatal care, can serve as proxies for harder-to-measure SES constructs, providing some context for the demographic characteristics of the underlying source and participant populations.

Extensive SES information is usually not available for individuals who are not enrolled in a study. We present an analysis of the external validity of estimates from a study with access to relatively detailed information on unenrolled cases, providing a rare opportunity to assess differences in key SES variables between enrolled and unenrolled cases. For variables with substantial differences, we assessed effect measure modification (EMM), using data from a large matched case–control study of 13-valent pneumococcal conjugate vaccine (PCV13).²¹

METHODS

Parent study and study population

PCV13 was introduced in the USA in 2010 as part of the routine childhood immunisation schedule.²²

After licensure, the Centers for Disease Control and Prevention (CDC) conducted a vaccine effectiveness (VE) evaluation in children aged 2–59 months with culture dates between 1 May 2010 and 31 May 2014 who were identified through the Active Bacterial Core surveillance (ABCs) system or one of three additional sites with similar surveillance procedures. This parent study has been previously published and is summarised in the online supplementary material—Methods for the current study.²¹ In addition to the exclusion criteria for the parent study, we excluded cases from two ABCs sites, Colorado and Maryland, because the necessary SES data were not available from those sites. The total annual surveillance population under 5 years of age was 4 249 724.

In the current study, almost 45% of cases were not enrolled, leading to concerns about representativeness with respect to SES (table 2). Further, past studies of invasive pneumococcal disease (IPD) and pneumococcal vaccines have provided some evidence for differential risk of IPD at different levels of individual SES, potentially due to the association of lower SES with IPD risk factors (eg, existing chronic or immunocompromising conditions, smoking exposure, household crowding).

Enrolment procedures

Enrolment procedures have been previously published.²¹ Briefly, cases were identified via routine surveillance and enrolled over the phone. Lists of eligible controls were obtained from local birth registries for children born in the same zip code in which the case resided when diagnosed with IPD and born within 14 days of the case. Detailed information on eligible and enrolled controls has been previously published.²³ Vaccine providers for cases and controls were contacted and state or city immunisation registries were reviewed to obtain vaccine and medical histories. Additional details on enrolment procedures have been previously published and are summarised in the online supplementary material for the present study.²¹ Both the parent study and the current analysis were approved by institutional review boards (IRBs) at CDC and surveillance sites. The current analysis was also approved by the IRB of the University of North Carolina-Chapel Hill.

Covariate assessment

Surveillance staff completed a standard case report form (CRF) for every IPD case identified through ABCs.²⁴ We included the following variables from the CRF (for all cases, whether or not enrolled in the parent study, table 1): hospitalisation status, length of hospitalisation and intensive care unit admission, outcome (survived/died), presence of an underlying condition that is a known risk factor for IPD and insurance status at IPD culture.^{22–24} Hospitalisation and ICU admission were

Table 1 Data sources and availability by case/control and enrolment status in a PCV13 vaccine effectiveness study

Data source	Enrolled case	Unenrolled case	Enrolled control	Unenrolled control
Case report form	✓	✓		
Parent interview	✓		✓	
Birth certificate	✓	✓	✓	✓
Geocoding/American Community Survey	✓	✓	✓	✓

PCV13, 13-valent pneumococcal conjugate vaccine.

combined into a three-level severity index: not hospitalised, hospitalised but not admitted to ICU and admitted to ICU.

Individual-level SES indicators

For cases and controls (regardless of enrolment status, [table 1](#)), study staff obtained variables from the birth certificate,²⁵ including: mother's race, ethnicity, education, source of payment for the birth and timing/initiation of prenatal care and gestational age, which were used to calculate the Adequacy of Prenatal Care Utilization (APNCU) Index.^{26 27} APNCU is a four-category variable that summarises how early in the pregnancy a woman initiated prenatal care and how many total prenatal care visits the woman received compared with how many are recommended by the American College of Obstetrics and Gynecology for a pregnancy of a given length.^{26 27} Insurance status and APNCU Index were analysed as measures of the individual's access to and use of the medical system.¹¹

Neighbourhood-level SES indicators

All enrolled and unenrolled children were geocoded, using a standard geocoding protocol (available from the authors on request). For children whose locations could not be confirmed, the most recent known address (from the birth certificate, state or city immunisation registry or medical chart) was used. Census tract data were merged with the 2013 5-year estimates from the American Community Survey (ACS), an annual survey conducted by the US Census Bureau, which includes demographic and SES indicators. These census-tract-level estimates can be a useful tool for understanding the context in which a child lives by complementing individual-level SES indicators.^{28 29}

Comparison groups

Importantly, in matched case-control studies, controls need not be representative of the source population with respect to the matching factor(s). In fact, if matching is done correctly, controls should resemble enrolled cases on the matching factor. This analysis, therefore, focuses on representativeness of enrolled cases with respect to eligible cases and leaves questions concerning controls for other analyses.²³

Statistical methods

Exploratory analyses compared differences in individual-level characteristics and ACS variables between enrolled and unenrolled cases. We also used the ACS variables to calculate a composite index of SES, based on the Socio-economic Position Index (SEP Index) created by Krieger *et al* for the Public Health Disparities Geocoding Project.³⁰ The SEP Index measures the major SES constructs of wealth, education and occupation at the neighbourhood level. Specifically, it includes: working class, unemployment, poverty, education, home prices and median family income (with home prices and median income reversed, so a higher SEP score indicates lower SES).³¹ p Values were calculated for continuous and categorical predictors via two-sided Wilcoxon rank-sum test and Fisher's exact test, respectively.

Because we had access to many SES-related variables through the CRF, birth certificates and ACS, it was not practical to assess every variable for EMM. Instead, we chose variables to assess for EMM in two ways. First, we decided a priori to assess as modifiers the SEP Index and the following individual-level variables that had p values

Table 2 Enrolment numbers, reasons for non-enrolment and geocoding status for cases of IPD identified in a PCV13 vaccine effectiveness study

Enrolment status	Cases, n (%)	Could not be geocoded, n (%)
IPD cases identified	1211†	21 (1.8)
Enrolled	661 (54.6)	9 (1.4)
Not enrolled	550 (45.4)	12 (2.2)
Could not locate/contact	194 (35.3)	4 (2.1)
Refused	177 (32.2)	5 (2.8)
No serotype available	158 (28.7)	2 (1.3)
Recurrent	11 (2.0)	1 (9.1)
Vaccine history not available	6 (1.1)	0
Resident of long-term care facility	4 (0.7)	0

†Excludes three children originally misclassified as ineligible and excluded from this analysis.

IPD, invasive pneumococcal disease; PCV13, 13-valent pneumococcal conjugate vaccine.

<0.2 in the exploratory analyses for differences between enrolled and unenrolled: maternal education, insurance status at birth and APNCU. Second, to ensure we did not miss any variables for the EMM assessment that may be strong modifiers *and* related to representativeness, we used predictive modelling to select additional ACS variables to assess for EMM. Many of the available ACS variables measured similar metrics (both to other ACS variables and to the individual variables); therefore, we fit a series of models to narrow the selection. All models fit were logistic regression, using backward selection and retaining variables with a p value of <0.2.

We first fit a single predictive model including all individual-level variables (ie, CRF and birth certificate variables), requiring the model to retain the following CRF variables: severity, outcome, underlying condition status, child's race/ethnicity and insurance status at IPD culture. This model also included interaction terms between child's race/ethnicity and maternal education and between child's race/ethnicity and APNCU. We divided the ACS variables into four categories—demographics, wealth, work and household characteristics—for inclusion in separate models to reduce the number of ACS variables used. Four models were run, including all individual-level variables retained from the first model and each category of the ACS variables. Lastly, we fit the final predictive model, which included all individual-level variables and interaction terms (regardless of whether they were retained in the first model) and any variables retained in the ACS models. As with the first model, we required the model to retain the CRF variables.

Any variables included in the final model predicting enrolment were assessed as potential modifiers, in addition to the SEP Index and individual-level variables chosen a priori. All the individual-level variables were already categorical. Variables not applicable to and/or not available for controls (ie, all CRF variables) were excluded. Child's race/ethnicity, underlying condition status and insurance status at IPD were collected as part of the parent interview/provider follow-up for enrolled children and could therefore be assessed for EMM. The ACS variables were continuous, so we dichotomised them at the median for the EMM analysis (online supplementary table). To assess variables as modifiers, we fit conditional logistic regression models for each variable with IPD caused by 1 of the 13 serotypes included in the vaccine as the outcome, receipt of one or more doses of PCV13 as the exposure and an interaction term between each variable of interest and PCV13 receipt.²¹ Because power to assess interaction terms is reduced, we used a p value <0.2 as our cut-off for the likelihood ratio χ^2 value for the interaction term and then did a Bonferroni adjustment by the total number of variables assessed for EMM to account for multiple comparisons. Therefore, $\alpha < 0.015$ for the likelihood ratio test was considered an indication of modification and cause for concern about generalisability.

RESULTS

Enrolment

The annual population of children under age 5 in the catchment area for the parent study was approximately 4.7 million, which was reduced to 4.2 million with the exclusion of Colorado and Maryland. We identified 1214 cases of IPD in children in the catchment area for this analysis. Three children were initially miscategorised as ineligible by surveillance personnel and enrolment was not attempted, leaving 1211 cases in our analysis, 661 (54.6%) of whom were enrolled (table 2). Of the 550 cases not enrolled, 194 (35.3%) could not be located/contacted, 177 (32.2%) refused and 158 (28.7%) did not have a pneumococcal isolate available for serotyping. The remaining 21 children were not enrolled for other reasons.

Table 3 Characteristics of eligible cases by enrolment status:

a) ABCs case report form			
Characteristic	Enrolled (n=661)	Not enrolled (n=550)	p Value*
Median age, median months (IQR)	21 (11–37)	22 (12–37)	0.27
Child's race			
White, non-Hispanic	262 (42.2)	217 (43.1)	0.41
Black, non-Hispanic	157 (25.3)	139 (27.6)	
Other, non-Hispanic	64 (10.3)	55 (10.9)	
Hispanic	138 (22.2)	92 (18.3)	
Unknown	40	47	
Insurance status at time of IPD culture			
Private	207 (49.9)	205 (47.7)	0.83
Public	254 (47.0)	208 (48.4)	
Military	2 (0.4)	2 (0.5)	
Uninsured	15 (2.8)	15 (3.5)	
Other/unknown	120	120	
Hospitalised	454 (68.8)	354 (66.4)	0.38
Median length of stay in days (IQR)	5 (3–10)	5 (2–10)	0.65
ICU	124 (31.9)	89 (29.0)	0.46
Survived	648 (98.8)	511 (97.0)	0.04
Chronic condition	9 (1.4)	5 (0.9)	0.59
Immunocompromising condition	64 (9.7)	64 (11.6)	0.30

*p Value is from Wilcoxon rank-sum test for continuous variables and from Fisher's exact test for categorical variables. ABCs, Active Bacterial Core surveillance; ICU, intensive care unit; IPD, invasive pneumococcal disease.

Table 3 b) Birth certificate variables

Characteristic	Enrolled (n=661)	Not enrolled (n=550)	p Value*
Maternal race/ethnicity, n (%)			
White, non-Hispanic	268 (46.7)	206 (44.8)	0.22
Black, non-Hispanic	127 (22.1)	127 (27.6)	
Hispanic	52 (9.1)	36 (7.8)	
Other, non-Hispanic	127 (22.1)	91 (19.8)	
Unknown	87	90	
Maternal education level, n (%)			
Less than high school	110 (20.2)	99 (22.7)	<0.01
High school or equivalent	130 (23.9)	136 (31.2)	
Some college	146 (26.8)	115 (26.4)	
College degree or more	158 (29.0)	86 (19.7)	
Unknown	117	114	
Source of payment for birth, n (%)			
Private	228 (48.2)	151 (39.8)	0.08
Public/state	223 (47.2)	209 (55.2)	
Uninsured	8 (1.7)	9 (2.4)	
Other	14 (3.0)	10 (2.6)	
Unknown	188	171	
Adequacy of Prenatal Care Utilization, n (%)			
Adequate plus	183 (34.9)	135 (32.8)	0.16
Adequate	186 (35.5)	157 (38.1)	
Intermediate	67 (12.8)	37 (9.0)	
Inadequate	88 (16.8)	83 (20.2)	
Unknown	137	138	
Gestational age, median weeks (IQR)†	39 (38–40)	39 (38–40)	0.57
Prenatal care initiation, median month (IQR)†	2 (2–3)	3 (2–4)	0.01
Total prenatal care visits, median (IQR)†	12 (10–16)	12 (10–18)	0.94

*p Value is from Wilcoxon rank-sum test for continuous variables and from Fisher's exact test for categorical variables.

†Included in calculation of Adequacy of Prenatal Care Utilization Index.^{26 27}

Differences between enrolled and unenrolled cases

Enrolled and unenrolled cases were of similar age (median age: 21 and 22 months, respectively) and race/ethnicity (42% and 43% white, non-Hispanic, respectively, $p=0.41$; [table 3a](#)). Enrolled children were slightly more likely to survive their illness (98.8% vs 97.0%, $p=0.04$).

Mothers of enrolled and unenrolled children had a similar racial/ethnic distribution ([table 3b](#)). Maternal education was somewhat different between the two groups, with 44.1% of mothers of enrolled children having no college education compared with 53.9% of mothers of unenrolled children ($p<0.01$).

The SEP Index was similar in enrolled and unenrolled cases ($p=0.07$; [table 3c](#)). A number of characteristics differed between the two groups, including proportion with an income above US\$60 000, proportion disabled and proportion of households occupied ($p<0.01$ for all).

Enrolment prediction model

In the individual-level model, three variables—maternal education, APNCU and the interaction between race/ethnicity and maternal education—were retained in addition to the five variables that we required ([table 4](#)). The model yielded a concordance (c-) statistic of 0.639, indicating only marginal predictive ability (0.5 is equal to a coin flip).³² Retaining these eight variables and adding demographic, wealth, work and household variables from the ACS yielded similarly low c- statistics of 0.632, 0.652, 0.643 and 0.655, respectively. The final predictive model included IPD severity, outcome, underlying condition status, child's race/ethnicity, insurance status at IPD culture, maternal education, APNCU, race/ethnicity and maternal education interaction, as well as the following census tract variables: per cent of tract of white race, earning <US\$30 000, earning \geq US\$60 000, disabled,

Table 3 c) American Community Survey

Characteristic	Enrolled (n=661)	Not enrolled (n=550)	p Value (univariate)*	p Value (multivariable model)
Successfully geocoded, n (%)	652 (98.6)	538 (97.8)	0.28	N/A
White race	56.1 (17.6–81.9)	58.9 (19.8–83.9)	0.26	<0.01
Household income <US\$30 000	28.1 (17.3–38.5)	29.9 (18.9–42.1)	0.03	<0.01
Household income ≥US\$60 000	41.1 (29.4–57.8)	38.2 (25.1–53.8)	<0.01	<0.01
Mean hours worked (annually)	38.1 (36.8–39.3)	38.0 (36.7–39.2)	0.39	0.05
Disabled workers	10.1 (7.5–13.5)	11.2 (8.2–16.0)	<0.01	<0.01
Working class	60.3 (52.6–69.8)	62.3 (52.5–69.8)	0.36	<0.01
Occupied houses	92.4 (88.1–95.8)	91.3 (86.4–94.7)	<0.01	0.07
SEP Index†, median (IQR)	1.5 (–1.4–4.5)	2.1 (–0.8–4.9)	0.07	N/A

Unless otherwise noted, all measurements are the median per cent (IQR) by census tract.

*p Value is from Wilcoxon rank-sum test for continuous variables and from Fisher's exact test for categorical variables.

†Socioeconomic Position Index. Higher value indicates higher level of deprivation.³⁰

N/A, not applicable.

working class, occupied households and mean hours worked. This model had a concordance statistic of 0.703, indicating only slightly better predictive ability than the single ACS category models.

Effect measure modification

None of the individual-level variables retained in the prediction model were found to be significant modifiers of the effect of PCV13 receipt on IPD caused by 1 of the 13 serotypes in the vaccine (figure 1A). Likewise, none of the ACS variables (including SEP Index) assessed as modifiers had a p value <0.015 for the likelihood ratio test (figure 1B).

DISCUSSION

We assessed the external validity of VE estimates from a postlicensure evaluation of PCV13 in children in the USA. Despite a small trend toward enrolled cases being more affluent than unenrolled cases, the differences were minimal and most did not meet a priori definitions of significance. Additionally, we did not find EMM of VE by any SES variables and therefore conclude that lack of generalisability to the broader source population is of minimal concern in the current study. Our results provide some evidence that study designs based on population-based surveillance systems can be generalisable, even with relatively low case enrolment (54.6% in the

Table 4 Prediction models for case enrolment

Mode	Variables in model (n)		AIC	c-statistic
	Start	After selection		
Individual level	11	7 (IPD severity, outcome, underlying condition status, race/ethnicity, insurance at the time of IPD culture, maternal education, race/ethnicity×maternal education)	717.840	0.639
ACS: demographics	26	9 (individual level from above+per cent: white race, speaks English)	927.995	0.632
ACS: wealth	18	11 (individual level from above+per cent: living abroad 1 year ago, earning <US\$30 000, earning ≥US\$60 000, per capita income)	927.838	0.652
ACS: work	16	10 (individual level from above+per cent: mean hours worked, disabled, working class)	932.599	0.643
ACS: household	30	14 (individual level from above+per cent: owner-occupied housing units, households with one resident, households without children <18 years, crowded households, households with plumbing, households with kitchens, occupied housing units)	896.747	0.655
Final (all individual level, plus retained ACS variables)	27	15 (individual level from above+APNCU Index, per cent: white race, earning <US\$30 000, earning ≥US\$60 000, disabled, working class, occupied houses, mean hours worked)	690.606	0.703

ACS, American Community Survey; AIC, Akaike information criterion; APNCU, Adequacy of Prenatal Care Utilization; IPD, invasive pneumococcal disease.

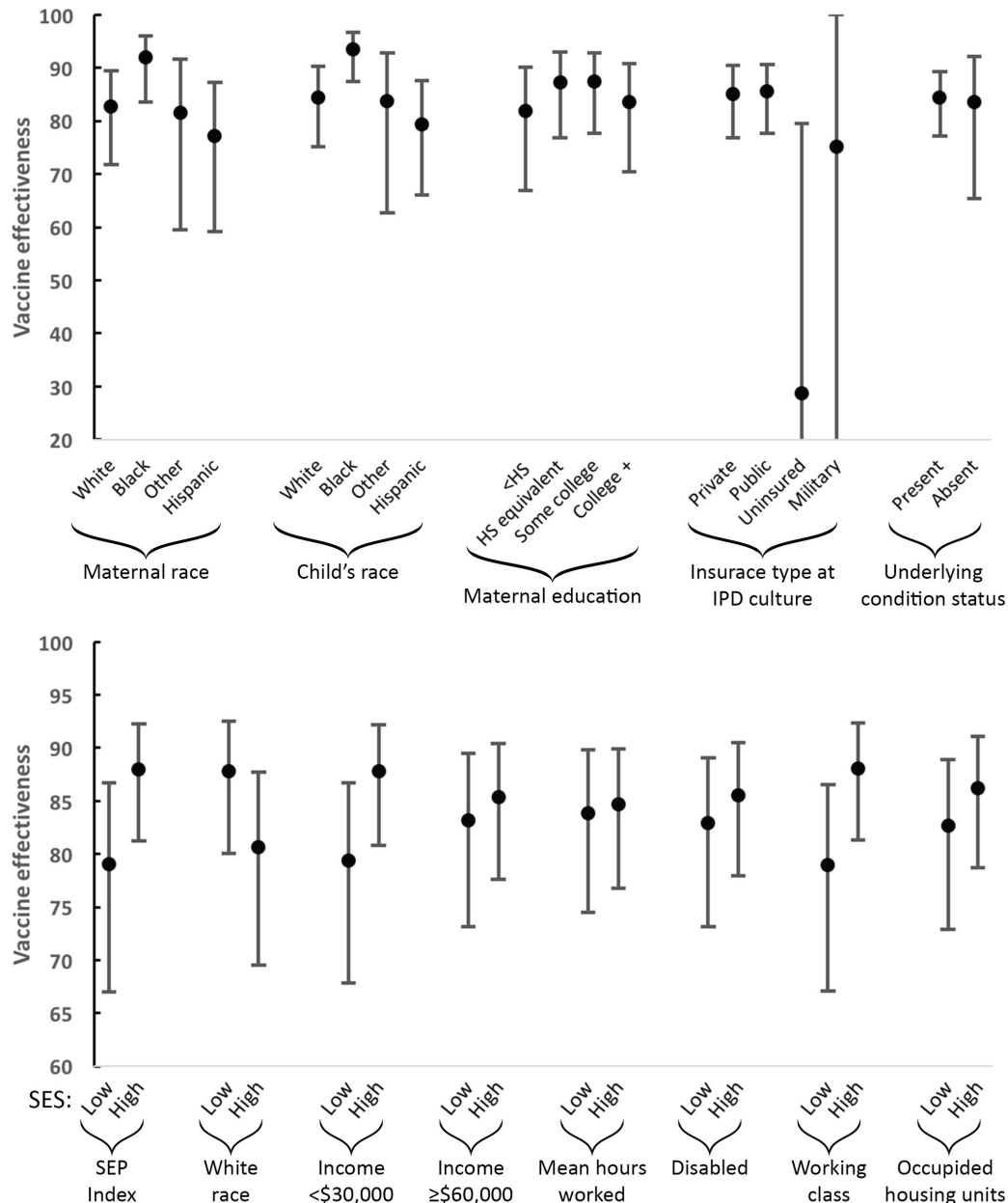


Figure 1 Vaccine effectiveness (and 80% CIs) for characteristics retained in the final predictive model, stratified as indicated. (A) Individual-level variables; (B) American Community Survey variables, divided at median. IPD, invasive pneumococcal disease; SEP, Socioeconomic Position Index; SES, socioeconomic status.

current study)—in particular, when researchers conduct extensive investigations to obtain contact information and provide incentives to encourage enrolment.

Generalisability can be a major benefit of observational vaccine studies over RCTs^{8,33}; however, it is rare for reports on either study type to provide extensive information on how their study population differs from their source or target population.^{1,34} We used a novel approach to assessing generalisability with respect to SES, exploring a mix of variables chosen a priori and through predictive modelling. We had access to more detailed information on unenrolled cases than is typical; however, the data we assessed were collected without patient contact and therefore could be gathered more routinely in observational studies. Our analysis shows that assessing and reporting

on generalisability may be feasible even when it is not possible to interview unenrolled cases.

Postlicensure VE studies are common tools to assess the ‘real-world’ effectiveness of vaccines, and as with similar studies, cases were identified from a disease surveillance system.^{35–38} Generalisability of results with respect to SES from vaccine studies is an important component of assessing the overall quality of a study, as well as the utility of results beyond the study population. Thus, although we found little cause for concern in the current analysis, this conclusion may not be applicable for vaccines for diseases, such as rotavirus, which are spread differently and therefore may have different risk factors and potential modifiers. Likewise, if case identification or enrolment methods are different, representativeness to the source

population could be lacking. Since SES has been identified as a significant risk factor for many vaccine-preventable diseases, other postlicensure vaccine studies may find more substantial cause for concern. However, careful selection of case and control populations, regardless of the disease under study, can yield results, such as these, which are generalisable to the underlying source population.

Our study had some limitations. We did not have access to variables collected during the parent interview (eg, household income) for unenrolled cases and so could not explore differences between enrolled and unenrolled cases for these variables. We may have also lacked sufficient power to identify EMM in our study. For example, the confidence limits for VE among those without insurance were extremely wide. Likewise, a VE study of the 7-valent pneumococcal conjugate vaccine (a more limited valency, but otherwise identical, vaccine) in a similar population to the current analysis found clear evidence of EMM by underlying condition status.³⁷ We did not identify EMM by underlying condition status but only had two matched sets with underlying conditions and discordant vaccination status (required to contribute to a conditional analysis) in our study. Additionally, we were not able to compare cases eligible for our study (ie, the source population) with cases throughout the USA (ie, the target population) because active, population-based surveillance for IPD does not exist nationwide.

We identified minimal external validity concerns in a PCV13 VE study in children in the USA. Nevertheless, future VE studies should take care to enrol as broad a subset of cases as possible, especially focusing on children from lower-SES areas. Additionally, every effort should be made to gather at least basic SES information so that study populations can be compared with source populations and estimates can be understood in context.

Author affiliations

¹National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

²Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

³New York City Department of Health and Mental Hygiene, New York City, New York, USA

⁴County of Los Angeles Department of Public Health, Los Angeles, California, USA

⁵Bureau of Epidemiology, Utah Department of Health, Salt Lake City, Utah, USA

⁶Emerging Infections Program, Institute for Public Health, University of New Mexico, Albuquerque, New Mexico, USA

⁷Minnesota Department of Health, St Paul, Minnesota, USA

⁸Department of Epidemiologia, California Emerging Infections Program, Oakland, California, USA

⁹Colorado Emerging Infections Program, Denver, Colorado, USA

¹⁰Connecticut Department of Public Health, Hartford, Connecticut, USA

¹¹Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia, USA

¹²Infection Disease Section, Medical Specialty Care Service Line, Atlanta VA Medical Center, Atlanta, Georgia, USA

¹³Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

¹⁴New York State Department of Health, Albany, New York, USA

¹⁵Oregon Public Health Division, Oregon Emerging Infections Program, Portland, Oregon, USA

¹⁶Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

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