Impact of pneumococcal conjugate vaccine uptake on childhood pneumonia mortality across income levels in Brazil, Colombia, and Peru [version 1; peer review: 1 approved]

Kayoko Shioda¹, Cristiana M. Toscano², Maria Tereza Valenzuela³, William Valdez Huaracaya⁴, Joshua L. Warren⁵, Daniel M. Weinberger¹, Lucia H. de Oliveira⁶

¹Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA
²Department of Collective Health, Institute of Tropical Pathology and Public Health (IPTSP), Federal University of Goiás (UFG), Goiânia, Goiás, Brazil
³Department of Epidemiology and Public Health, Universidad de Los Andes, Santiago, Chile
⁴Universidad Peruana de Ciencias Aplicadas, Lima, Peru
⁵Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA
⁶Comprehensive Family Immunization Unit/FPL, Pan American Health Organization, World Health Organization, District of Columbia, USA

Abstract

Background: Pneumococcal conjugate vaccines (PCVs) have prevented deaths due to pneumonia among children. The effect may differ between higher- and lower-income populations due to various factors, such as differences in the distribution of pneumococcal serotypes, healthcare access, and PCV uptake. This study aims to evaluate an association between increasing PCV coverage and population-level declines in death due to pneumonia and its variation by socioeconomic status of subnational regions.

Methods: We analyzed municipality-level mortality data from 2005 and 2015 for children aged 2-23 months in Brazil, Colombia, and Peru. We fit Poisson regression models to estimate the relationship between changes in PCV uptake and deaths due to all-cause pneumonia among subnational regions with different income levels. We controlled for changes unrelated to PCV by using data on non-respiratory deaths over time.

Results: Uptake of the third dose of PCV varied across subnational regions and was higher in high-income regions. Higher uptake of PCV was associated with larger declines in pneumonia mortality. This association did not differ by income level of the region in Brazil and Colombia. In Peru, low-income regions observed larger declines in pneumonia deaths, but there was large uncertainty in the difference between the low- and high-income regions. We estimated that, with 90% coverage, there would be 4-38% declines in all-cause pneumonia mortality across income levels and countries.
Conclusions: Regions with higher PCV coverage experienced larger declines in pneumonia deaths, regardless of the income level. Having more reliable data on mortality records and vaccine uptake would improve the reliability of vaccine impact estimates.

Keywords
Pneumococcal conjugate vaccine, vaccine evaluation, vaccine coverage, vaccine uptake, Brazil, Colombia, Peru, income level, childhood pneumonia mortality

Corresponding author: Kayoko Shioda (kayoko.shioda@yale.edu)

Author roles: Shioda K: Formal Analysis, Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Toscano CM: Conceptualization, Data Curation, Funding Acquisition, Investigation, Project Administration, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Valenzuela MT: Data Curation, Resources, Validation, Writing – Review & Editing; Huaracaya WV: Data Curation, Resources, Validation, Writing – Review & Editing; Warren JL: Formal Analysis, Methodology, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Weinberger DM: Conceptualization, Formal Analysis, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; de Oliveira LH: Conceptualization, Funding Acquisition, Project Administration, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: DMW has received consulting fees from Pfizer, Merck, GSK, and Affinivax and is Principal Investigator on a research grant from Pfizer to Yale. These entities were not involved in any aspect of the current work. LO is a staff member of the Pan American Health Organization. The author alone is responsible for the views expressed in this publication, and they do not necessarily represent the decisions or policies of the Pan American Health Organization. Other authors do not have conflict of interest.

Grant information: This work was supported by the Bill and Melinda Gates Foundation [grant OPP1156865 to PAHO]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2020 Shioda K et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Shioda K, Toscano CM, Valenzuela MT et al. Impact of pneumococcal conjugate vaccine uptake on childhood pneumonia mortality across income levels in Brazil, Colombia, and Peru [version 1; peer review: 1 approved] Gates Open Research 2020, 4:136 https://doi.org/10.12688/gatesopenres.13187.1

First published: 22 Sep 2020, 4:136 https://doi.org/10.12688/gatesopenres.13187.1
Introduction

Vaccination programs targeting pneumococcus are now established globally. Pneumococcal conjugate vaccines (PCVs) have effectively reduced the burden of disease and death due to pneumonia and other severe pneumococcal infections (e.g., sepsis, meningitis)\(^1\). For instance, national-level analyses found that estimated declines in pneumonia mortality among children 2–11 months of age were 8% (95% credible interval (CrI): 2 to 14%) in Brazil, 14% (-5 to 35%) in Colombia, and 36% (17 to 44%) in Peru\(^2\). The impact of PCVs on preventing deaths due to pneumonia could differ between higher- and lower-income populations. Differences in the etiology of pneumonia, the distribution of pneumococcal serotypes, and access to healthcare can influence the proportion of deaths that are preventable. Variations in vaccine uptake can also influence the overall reduction.

The countries in the Latin America and Caribbean region are ideal for conducting evaluations of the impact of PCVs. Countries in this region were among the first lower- and middle-income countries to introduce PCVs. The strong health and mortality data systems in these countries make it possible to perform detailed vaccine evaluation studies at a subnational level and to evaluate how variations in vaccine uptake relate to changes in rates of pneumonia deaths. The countries also have a wide variation in socioeconomic status at a subnational level, which provides a unique opportunity to compare the impact of PCV by income level. Therefore, this study aims to evaluate how the association between increasing vaccine uptake and population-level declines in death due to pneumonia varies by socioeconomic status in Brazil, Colombia, and Peru.

Methods

Mortality data and stratification

In a previous study, we evaluated the population-level impact of PCVs against pneumonia mortality at the national level in ten Latin American and Caribbean countries\(^1\). Among the 10 countries included in the national-level study, Brazil, Colombia, and Peru had subnational data on mortality, socioeconomic status, and vaccine coverage with a high spatial resolution, which enabled us to conduct this analysis. Mortality data were obtained from the National Mortality Information Systems. Both primary and non-primary causes of deaths were recorded for Brazil and Peru, while only primary causes were available for Colombia. The cause of death was classified using the International Statistical Classification of Diseases and Related Health Problems tenth revision (ICD-10) codes. Each country conducted standardized data cleaning and quality control\(^3\). We extracted mortality data for children at the municipality level that were available during the study period (2005-2015). The quality of mortality data was assessed and reported in the previous study\(^4\). Durations of pre- and post-PCV periods for each country are described in Table 1.

An outcome of our analysis was all-cause pneumonia deaths, defined as having an ICD-10 code in the range of J12-J18. For Brazil and Peru, we used J12-J18 recorded as either primary or non-primary causes of death as the outcome in the main analysis, and used J12-J18 recorded as the primary cause of deaths as the outcome in the sensitivity analysis. For Colombia, we used J12-J18 recorded as the primary cause of death as the outcome, as they did not have data on non-primary causes of death.

We analyzed data for children 2–23 months of age, as our previous national-level analysis did not detect any changes in pneumonia mortality among older children (24–59 months of age) following the introduction of PCV in any of the ten countries we analyzed\(^5\). Children under two months of age were not included in the analysis for both biological and practical reasons\(^6\).

For Brazil and Colombia, we classified municipalities into three income levels (low, medium, and high) using the Gross Domestic Product (GDP) per capita for the year of PCV introduction.

### Table 1. Descriptive statistics for Brazil, Colombia, and Peru.

<table>
<thead>
<tr>
<th></th>
<th>Brazil</th>
<th>Colombia</th>
<th>Peru</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PCV period</td>
<td>January 2005 - February 2010 (5 years and 2 months)</td>
<td>January 2005 - October 2011 (6 years and 10 months)</td>
<td>January 2005 - July 2009 (4 years and 7 months)</td>
</tr>
<tr>
<td>Post-PCV period</td>
<td>March 2010 - December 2015 (5 years and 10 months)</td>
<td>November 2011 - December 2015 (4 years and 2 months)</td>
<td>August 2009 - December 2014 (5 years and 5 months)</td>
</tr>
<tr>
<td>Total number of J12-18 among children 2–23 months of age in the study period (coded as primary or non-primary causes of death)(^1)</td>
<td>16,303</td>
<td>4700 (primary only)</td>
<td>6854</td>
</tr>
<tr>
<td>Total number of J12-18 among children 2–23 months of age in the study period (coded as primary cause of death)(^1)</td>
<td>35,259</td>
<td>4700</td>
<td>5818</td>
</tr>
<tr>
<td>Weighted average of PCV third dose coverage in the last year of the study period</td>
<td>91.7% in 2015</td>
<td>91.1% in 2015</td>
<td>81.8% in 2014</td>
</tr>
</tbody>
</table>

\(^1\)These numbers are before filtering out regions with sparse data. The study periods include both pre- and post-PCV periods. 

Abbreviation: PCV, pneumococcal conjugate vaccine.
For Peru, these three categories of the income level were created based on a five-level income level indicator, reflecting the per capita income in the year of PCV introduction. This indicator is obtained from household surveys and is based on quintiles of household per capita expenditure as it relates to the costs of a “basic consumption basket.”29,30 These income categories were defined for each country separately and cannot be directly compared across countries. We then created subnational regions by grouping municipalities based on these three income-level categories in each of the departments (n=32 in Colombia and n=25 in Peru) or states (n=27 in Brazil). For example, Peru had 75 possible combinations of departments and income levels; however, there were only 68 subnational regions simply because some strata did not exist (e.g., no low-income regions in Lima). Furthermore, we excluded subnational regions from the analysis if there were less than ten all-cause pneumonia mortality per year on average. After this exclusion, we had 49 subnational regions in Brazil (11 low-, 25 medium- and 13 high-income regions), 16 in Colombia (12 medium- and four high-income regions), and 23 in Peru (five low-, 10 medium-, and eight high-income regions) in the final analysis.

PCV coverage data
Brazil introduced the 10-valent PCV with a 3+1 schedule (2, 4, and 6 months + 12–18 months of age) in March 2010. Colombia introduced the 10-valent PCV in November 2011 and used a 2+1 schedule (2 and 4 months + 12 months of age). Peru introduced the 7-valent PCV with the 2+1 schedule in August 2009 (2 and 4 months + 12 months of age), and switched to the 10-valent PCV with the 2+1 schedule in December 2011.

Data on the PCV third dose coverage (i.e., last primary dose for Brazil and booster dose for Colombia and Peru) by year were obtained from the National Immunization Programs at the municipality level in all three countries. For Colombia and Peru, we first conducted linear interpolation for missing coverage data, if there were any, in each municipality. We then calculated a weighted average of the coverage in each subnational region. We used the population size of each municipality as a weight for Brazil and Colombia. For Peru, a total number of deaths during the study period in each municipality was used as a weight, as municipality-level population data were not available.

Statistical analysis
To estimate changes in pneumonia mortality among children after the introduction of PCVs, we fit the following Poisson regression model to the data from each country separately such that

$$ Y_{i,t} | \lambda_{i,t} \sim \text{Poisson}(\lambda_{i,t}) $$

$$ \ln(\lambda_{i,t}) = \beta_0 + \beta_1 x_{i,t} + \theta_i y_{i,t} + \phi_{i,t}. $$

The outcome, $Y_{i,t}$, is the number of all-cause pneumonia deaths in subnational region $i$ in year $t$. To control for unmeasured temporal factors affecting pneumonia mortality, we included all-cause deaths other than those caused by respiratory illness as a covariate in the model ($x_{i,t}$) where $\beta_0$ represents the region-specific regression parameter that describes the association between this covariate and deaths and $\beta_1$ is the region-specific intercept. To account for potential overdispersion and unexplained correlation in deaths across time, we included an observation-level random effect, $\phi_{i,t}$, that follows a first order autoregressive process. The weighted average of the PCV third dose coverage in subnational region $i$ in year $t$ is given as $y_{i,t}$ and the region-specific vaccine effect, $\theta_i$, is modeled as a function of region-level socioeconomic status such that

$$ \theta_i = \gamma_1 I_{low} + \gamma_2 I_{med} + \gamma_3 I_{high} + \eta_i, $$

where $I_{low}$, $I_{med}$, and $I_{high}$ are indicator variables for the income level. The remaining variation in $\theta_i$ that is not explained by the effect of income level is captured by $\eta_i$ which are modeled using independent Gaussian distributions with zero mean and shared variance parameter.

Posterior medians were used as point estimates and the 95% highest density CrIs were calculated to quantify uncertainty. All analyses were performed in R (Vienna, Austria)31. The aggregated time series data and code can be found in the following GitHub repository:https://github.com/weinbergerlab/PAHO_subnational. A stable copy of the repository is available from https://zenodo.org/badge/latestdoi/291341482. More details on the model, such as the information on prior distributions, can be found in the Extended data, Supplementary methods32.

Estimation of the impact of PCV by income level
We evaluated how the population-level impact of PCV changes by income level in a few different ways. First, we quantified declines in all-cause pneumonia deaths based on the actual coverage in the last year of the study period in each subnational region. Next, to compare the effect of PCVs between regions while holding vaccine uptake constant, we estimated declines in all-cause pneumonia deaths that would be expected with 90% uptake of the third dose of PCV. More details on the calculations are described in the Extended data, Supplementary methods32.

Results
Variation in vaccine uptake at subnational level in Brazil, Colombia, and Peru
The uptake of PCV increased rapidly within a few years after introduction in all countries, but there was variation by region (Extended data, Figure S1)31. For example, although the average uptake of the third dose was 82% at the national level in the last year of the study period in Peru (Table 1), average uptake varied from 55% to 100% between regions. Uptake of the third dose was higher in more affluent regions (Extended data, Figure S2)31. For example, in Peru, the median uptake was 67%, 88%, and 90% in low, medium, and high-income regions, respectively, in 2014.

Declines in all-cause pneumonia mortality by PCV uptake and income level
All-cause pneumonia mortality declined over time across income levels and countries, and these declines started before the introduction of PCV (Figure 1A). This trend became unclear after adjusting for all-cause mortality other than those caused
by respiratory illness (Figure 1B). In the last year of the study period, most subnational regions across countries observed declines in all-cause pneumonia deaths with large uncertainties, while low-income regions in Peru experienced larger declines (Figure 2). Higher uptake of the third dose of PCV was associated with additional declines in pneumonia deaths in most of the regions in all three countries (Figure 3). In Peru, this association was especially strong in low-income regions, while it was modest among high-income regions and not clear among medium-income regions.

With 90% uptake of the vaccine, we estimated declines in all-cause pneumonia would range from 4–38% in low-income regions, 4–23% in medium-income regions, and 8–25% in high-income regions (Table 2). The estimates for individual regions had a high degree of uncertainty due to small numbers of deaths (Figure 2). There was no evidence that the effect of the vaccine on pneumonia deaths differed between high- and low-income regions in Brazil and Colombia. In Peru, estimated declines in pneumonia mortality were largest among low-income regions. The estimated decline in pneumonia mortality in low-income regions was 52% (95% CrI: 14%, 90%) and 38% (2%, 76%) smaller than that in medium-income regions and high-income regions, respectively.

Sensitivity analyses
For Brazil and Peru, we repeated the analysis but only included deaths where pneumonia was recorded as the primary cause of death as the outcome variable. This modification did not appreciably change the estimated declines in Brazil, while it increased the estimated impact of PCV in Peru (Extended data, Table S1). The discrepancy in Peru was due to changes over time in the proportion of pneumonia deaths recorded as the primary cause vs contributing cause of death (Extended data, Figure S3), and this shift exaggerated the estimated impact of PCV when analyzing the primary cause of death only.

Figure 1. Time series for all-cause pneumonia mortality (ICD-10 code: J12–J18) relative to the counts in the final year of the pre-PCV period by income level among children aged 2–23 months in Brazil, Colombia, and Peru. Pink, blue, and green lines represent estimates for low-, medium-, and high-income subnational regions in each country. Vertical dashed lines represent the final year in the pre-PCV period in each country. Abbreviations: ICD–10, International Statistical Classification of Diseases and Related Health Problems tenth revision; PCV, pneumococcal conjugate vaccine.
Figure 2. Declines in all-cause pneumonia estimated based on actual coverage in the last year of the study period or with the 90% coverage. Pink, blue, and green bubbles represent the point estimates for low-, medium-, and high-income subnational regions in each country. Grey bars are the 95% CrIs. The size of bubbles is proportional to the number of all-cause pneumonia deaths in the last year of the pre-PCV period. Horizontal dashed line indicates one, meaning that there were no changes in all-cause pneumonia mortality. In panels on the right, diamonds represent the average declines in each income level. Abbreviations: PCV, pneumococcal conjugate vaccine; CrI, credible interval.
Table 2. Average declines in all-cause pneumonia mortality among children aged 2–23 months expected with the 90% coverage of PCV by income level in Brazil, Colombia, and Peru.

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated declines (95% CrIs) by income level associated with 90% uptake of third dose of PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Brazil</td>
<td>0.96 (0.86, 1.06)</td>
</tr>
<tr>
<td>Colombia</td>
<td>-</td>
</tr>
<tr>
<td>Peru</td>
<td>0.62 (0.44, 0.88)</td>
</tr>
</tbody>
</table>

The outcome for Brazil and Peru is J12-J18 coded as either primary or non-primary causes of death. The outcome for Colombia is J12-J18 coded as the primary cause of death.

Abbreviations: PCV, pneumococcal conjugate vaccine; CrI, credible interval.

Discussion

Using spatially disaggregated data, we evaluated whether the population-level effect of PCV among children 2–23 months of age varies between income levels in Brazil, Colombia, and Peru. High-income regions had higher coverage of the third dose of PCV. The estimated decline in all-cause pneumonia deaths associated with increasing PCV uptake was similar across income levels in Brazil and Colombia, while there was a larger decline among low-income regions in Peru.

To date, seven post-licensure studies have evaluated the impact of PCV on pneumonia mortality, all of which were conducted in Latin American and Caribbean regions\(^1\). These studies used various datasets and methods, and the magnitude of reported effects varied. For example, Diaz et al. conducted a nested case-control study in Chile and estimated that pneumonia deaths declined by 71.5% (95% CI: 9.0-91.8%)\(^2\). On the other hand, a multi-country study conducted time series analysis and did not find declines in Guyana and Honduras due to large uncertainty\(^7\).

A previous study reported larger PCV-associated declines in pneumonia mortality among children in low-income municipalities in Brazil\(^6\), while we did not see differences across income levels. That study used three indicators (human development index, children in poverty, and maternal primary education), while we used GDP per capita in the year of PCV introduction. Among children 2–23 months of age, the previous study found the largest decline in low-income regions only when municipalities were grouped based on maternal primary education. Our income classification based on GDP is most closely related to their HDI-based classification. With this HDI category, the previous study found that medium-level regions observed slightly larger declines than low- and high-level regions, which is consistent with our findings for Brazil (Figure 2 and Table 2).

Data sparsity often becomes an issue when working with subnational data. As death is a rare clinical outcome compared to others (e.g., hospitalizations, outpatient visits), both our outcome (J12–18) and controls (other ICD-10 chapters) had small counts per unit time at subnational level. To reduce the noise introduced by sparse counts, we aggregated data by year. When aggregating time series data by a larger time interval, models will be fit to fewer data points, which may also cause an issue, such as increased uncertainty in estimates.

Our study has some limitations. The quality of mortality data varied by country and changed over time, as discussed in detail in the national-level study\(^7\). To minimize the influence of data quality, each country collected and cleaned the data using standardized methodology in collaboration with the Pan American Health Organization (PAHO). We also controlled for changes in data quality by including the control cause of death in the model, assuming that changes in data quality affect both...
the outcome and the control. Our results, however, should be interpreted carefully. Regarding the data on PCV uptake, some municipalities in Brazil had unreliable data exceeding 100% with abrupt increases and decreases. We defined the income level of each municipality using the data in the year of PCV introduction, although the income level could change over time. For trend adjustment, we were only able to include one control cause of death (all-cause deaths other than those caused by respiratory conditions) due to data sparsity. In Peru, even common control causes of death only had 0–2 deaths per year in many regions. However, we believe that all-cause deaths were able to successfully adjust for some key trends because its estimated coefficient was different from zero in many regions.

One challenge with the type of analysis conducted here is that vaccine uptake data tend to be less reliable at local scales. Estimating both the numerator (number of children vaccinated) and denominator (number of children eligible for the vaccine) becomes more challenging at small spatial scales. Because the vaccine uptake data were measured with error, the estimates for the association with pneumonia deaths could be biased towards zero. This trend was clear especially among small low-income regions in Peru which were filtered out from the final analysis. Having higher quality data on vaccine uptake at a local level could facilitate robust estimates of vaccine impact in other countries and regions.

In conclusion, in three middle-income countries in South America, regions with higher PCV coverage experienced larger declines in pneumonia deaths, regardless of the income level. Focusing public health efforts on increasing the vaccine coverage could prevent additional childhood deaths.

Data availability
Underlying data
Zenodo: AHO_subnational 0.2; http://doi.org/10.5281/zenodo.401109714.

Subfolder ‘Data’ contains the aggregated time series data used in this study. Data are also available at https://github.com/weinbergerlab/PAHO_subnational/tree/master/Data.

br.meso.v1.csv, co.meso.v1.csv, and pr.dept.inc.v1.csv include time series for subnational-level mortality data for Brazil, Colombia, and Peru, respectively. pr.cov.by.dept.inc.csv includes the PCV coverage data for Peru.

Extended data

This file contains the following extended data:

- Supplementary methods
- Table S1. Average declines in all-cause pneumonia mortality among children aged 2–23 months expected with the 90% coverage of PCV by income level in Brazil and Peru using J12-18 coded as the primary cause of death as an outcome.


This file contains the following extended data:

- Figure S1. Uptake of the third dose of pneumococcal conjugate vaccines by subnational region in Brazil, Colombia, and Peru.
- Figure S2. Coverage of PCV third dose in the last year of the study period by income level in Brazil, Colombia, and Peru.
- Figure S3. Proportion of J12-J18 recorded as the primary cause of deaths among J12-J18 recorded as any causes of deaths in Brazil and Peru.


All data and code are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Acknowledgments
We thank Carlos Andrés Castañeda-Orjuela and Diana Patricia Díaz Jimenez from the National Institutes of Health, Colombia; and Juan Pablo Alzate Granados from the Fundación Universitaria de ciencias de la Salud, Colombia; for support in data collection and review.

References


Open Peer Review

Current Peer Review Status: ✔

Tamara Pilishvili
Respiratory Disease Branch, National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

This is an important study contributing to the body of literature documenting PCV impact on mortality. The authors apply complex analytic methods to evaluate association between increasing vaccine uptake and pneumonia-related deaths by socioeconomic factor. The paper is well written and methods are clearly explained.

Specific comments:

- Declines in mortality are reported; however, for all estimates wide CrIs and all estimates cross the null value. Is the conclusion about the declines observed in all countries in the last year of study warranted given high level of uncertainty around the estimates? Perhaps the conclusion and corresponding statements in the results could be softened.

- How do the authors explain increases in mid-income regions in Peru and mid- and low-income regions in Brazil? Several lines for corresponding regions in Fig 3. suggest there were increases in deaths and the lines are above the dotted “null” line as vaccine coverage increases.

- Changes in coding practices over time could have contributed to observed trends. This should be included as a limitation.

- Unreliable PCV coverage data is mentioned in limitations without explanation of how this was resolved in the analysis (e.g. >100% coverage or unstable coverage estimates).

- Have any control “exposures” been evaluated, in addition to adjusting for “control cause of deaths”? If an association is found between control “exposures” (e.g. vaccine uptake other than PCV) that should not be associated with pneumonia-related deaths, this could indicate that the model is not adjusting for time-dependent confounders.

A couple of minor comments:
Table 1. Number of deaths for Brazil appear to be flipped - numbers are higher for pneumonia as primary-only cause of death than for pneumonia as primary or secondary cause of death.

Figure 1B interpretation in the text suggests that after adjusting for non-respiratory causes of death, the trends became “unclear”. From the figure, it appears that for most strata there was no longer a downward trend before or after PCV introduction.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.