





RESEARCH ARTICLE

Impact of pneumococcal conjugate vaccine uptake on childhood pneumonia mortality across income levels in Brazil, Colombia, and Peru [version 1; peer review: 1 approved, 2 approved with reservations]

Kayoko Shioda ¹, Cristiana M. Toscano², Maria Tereza Valenzuela³, William Valdez Huarcaya⁴, Joshua L. Warren⁵, Daniel M. Weinberger ¹, 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

V1 First published: 22 Sep 2020, 4:136
<https://doi.org/10.12688/gatesopenres.13187.1>
Latest published: 22 Sep 2020, 4:136
<https://doi.org/10.12688/gatesopenres.13187.1>

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

Open Peer Review

Reviewer Status   

	Invited Reviewers		
	1	2	3
version 1			
22 Sep 2020	report	report	report

1. **Tamara Pilishvili**, Centers for Disease Control and Prevention, Atlanta, USA

2. **Robert Simon Heyderman** , University College London, London, UK

3. **Edward Kim Mulholland**, University of Melbourne, Melbourne, Australia
London School of Hygiene and Tropical Medicine, London, UK

Any reports and responses or comments on the

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

article can be found at the end of the article.

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; **Huarcaya 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](https://creativecommons.org/licenses/by/4.0/), 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, 2 approved with reservations]** 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., septicemia, meningitis)¹⁻⁷. 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 Peru⁷. 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 countries⁷. 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 control⁸. 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 study⁷. 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 analyzed⁷. Children under two months of age were not included in the analysis for both biological and practical reasons⁷.

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.

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

¹These 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.”^{9,10} 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

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

$$\ln(\lambda_{i,t}) = \beta_{0i} + \beta_{1i} x_{i,t} + \theta_i v_{i,t} + \phi_{i,t}$$

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 β_{1i} represents the

region-specific regression parameter that describes the association between this covariate and deaths and β_{0i} 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 $v_{i,t}$ and the region-specific vaccine effect, θ_i , is modeled as a function of region-level socioeconomic status such that

$$\theta_i = \gamma_1 I_{low_i} + \gamma_2 I_{med_i} + \gamma_3 I_{high_i} + \eta_i$$

where I_{low_i} , I_{med_i} , and I_{high_i} are indicator variables for the income level. The remaining variation in θ_i that is not explained by the effect of income level is captured by η_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)¹¹. 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 methods¹².

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 methods¹².

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)¹³. 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)¹³. 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.

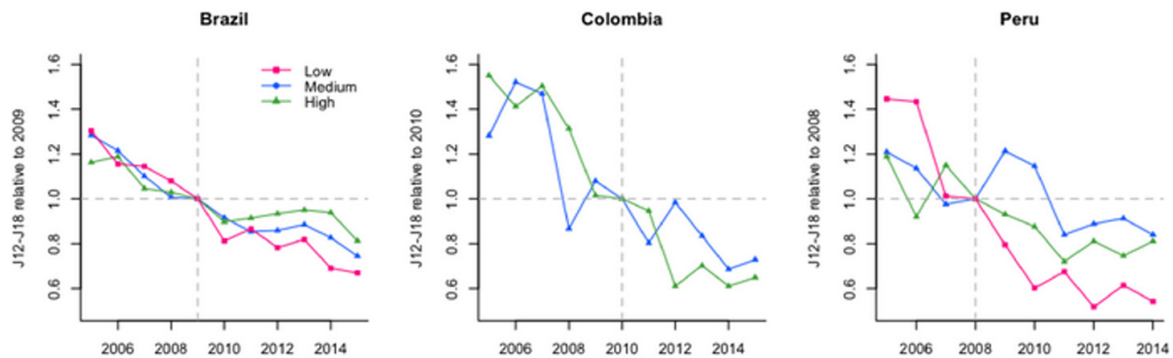
With 90% uptake of the vaccine, we estimated declines in all-cause pneumonia would range from 4–38% in low-income regions, -4–23% in medium-income regions, and 8–25% in high-income regions (Table 2). The estimates for individual regions had a high degree of uncertainty due to small numbers of deaths (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)¹². 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)¹³, and this shift exaggerated the estimated impact of PCV when analyzing the primary cause of death only.

A. J12-J18 (unadjusted)



B. J12-J18 (adjusted for all-cause deaths other than respiratory illness)

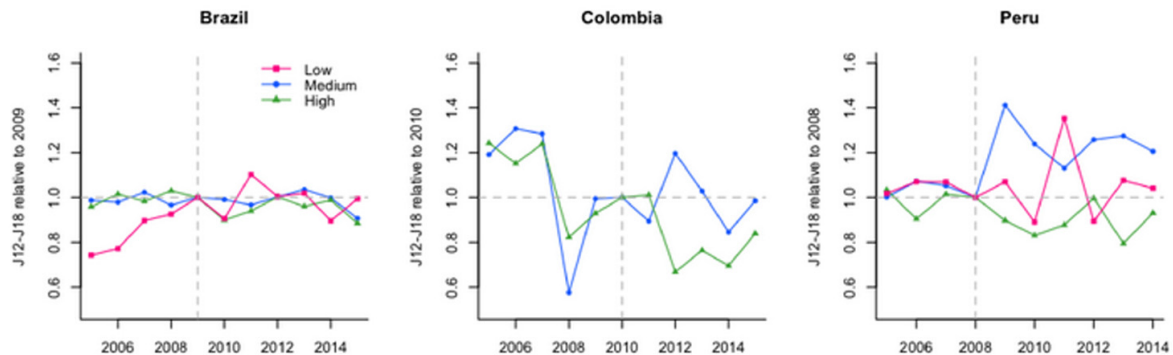


Figure 1. Time series for all-cause pneumonia mortality (ICD-10 code: J12-J18) relative to the counts in the final year of the pre-PCV period by income level among children aged 2-23 months in Brazil, Colombia, and Peru. Pink, blue, and green lines represent estimates for low-, medium-, and high-income 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.

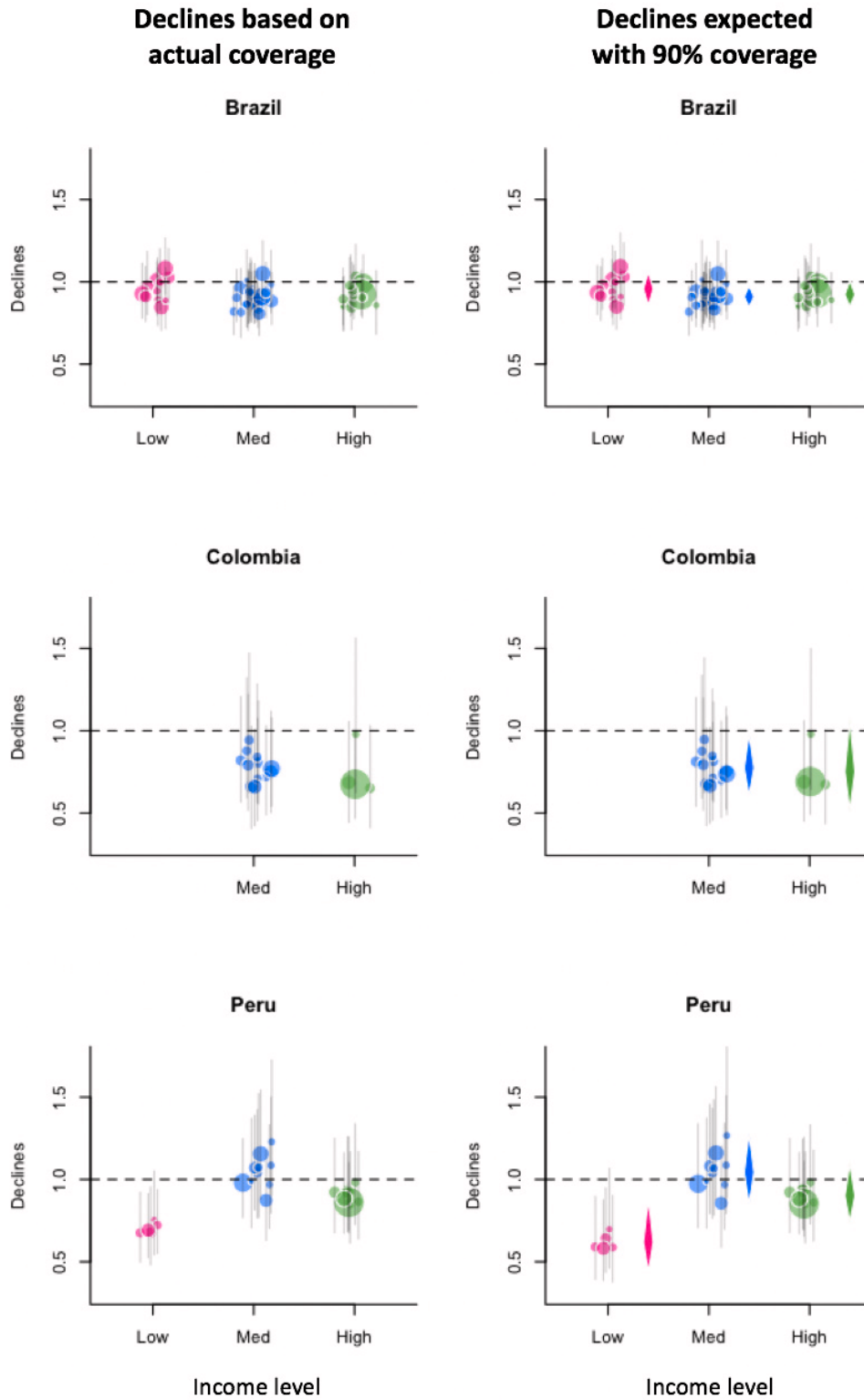


Figure 2. Declines in all-cause pneumonia estimated based on actual coverage in the last year of the study period or with the 90% coverage. Pink, blue, and green bubbles represent the point estimates for low-, medium-, and high-income subnational regions in each country. Grey bars are the 95% CrIs. The 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.

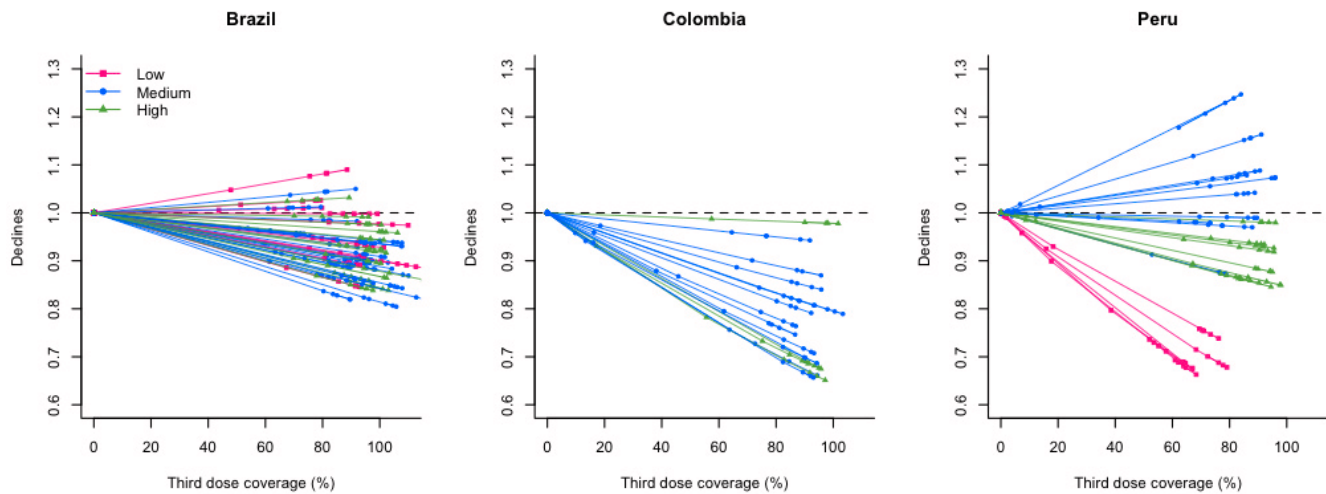


Figure 3. Estimated declines by PCV third dose coverage for each region. Pink, blue, and green dots represent estimates for low-, medium-, and high-income subnational regions in each country. Horizontal dashed line indicates one, meaning that there were no changes in all-cause pneumonia mortality. Abbreviation: PCV, pneumococcal conjugate vaccine.

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.

Country	Estimated declines (95% CrIs) by income level associated with 90% uptake of third dose of PCV		
	Low	Medium	High
Brazil	0.96 (0.86, 1.06)	0.91 (0.85, 0.97)	0.92 (0.85, 1.01)
Colombia	-	0.77 (0.61, 0.98)	0.75 (0.51, 1.07)
Peru	0.62 (0.44, 0.88)	1.04 (0.85, 1.28)	0.90 (0.74, 1.10)

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^{1–7}. 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 uncertainty⁷.

A previous study reported larger PCV-associated declines in pneumonia mortality among children in low-income municipalities in Brazil⁶, 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 study⁷. 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.4011097>¹⁴.

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

Figshare: OnlineSupplement.pdf; <https://doi.org/10.6084/m9.figshare.12934901.v1>¹².

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.

Figshare: Supplementary Figures; <https://doi.org/10.6084/m9.figshare.12957887.v1>¹³.

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.

Analysis code available from: https://github.com/weinbergerlab/PAHO_subnational.

Archived analysis code at time of publication: <http://doi.org/10.5281/zenodo.4011097>¹⁴.

All data and code are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

Acknowledgments

We thank Carlos Andrés Castañeda-Orjuela and Diana Patricia Diaz 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

1. Kupek E, Vieira ILV: [Impact of PCV10 pneumococcal vaccine on mortality from pneumonia in children less than one year of age in Santa Catarina State, Brazil]. *Cad Saude Publica*. 2016; 32(3): e00131414. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Diaz J, Terrazas S, Bierrenbach AL, et al.: Effectiveness of the 10-Valent Pneumococcal Conjugate Vaccine (PCV-10) in Children in Chile: A Nested Case-Control Study Using Nationwide Pneumonia Morbidity and Mortality Surveillance Data. *PLoS One*. 2016; 11(4): e0153141. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Becker-Dreps S, Amaya E, Liu L, et al.: Changes in childhood pneumonia and infant mortality rates following introduction of the 13-valent pneumococcal conjugate vaccine in Nicaragua. *Pediatr Infect Dis J*. 2014;

- 33(6): 637–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Becker-Dreps S, Blette B, Briceño R, *et al.*: **Changes in the incidence of pneumonia, bacterial meningitis, and infant mortality 5 years following introduction of the 13-valent pneumococcal conjugate vaccine in a “3+0” schedule.** *PLoS One.* 2017; **12**(8): e0183348.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 5. Suarez V, Michel F, Toscano CM, *et al.*: **Impact of pneumococcal conjugate vaccine in children morbidity and mortality in Peru: Time series analyses.** *Vaccine.* 2016; **34**(39): 4738–4743.
[PubMed Abstract](#) | [Publisher Full Text](#)
 6. Schuck-Paim C, Taylor RJ, Alonso WJ, *et al.*: **Effect of pneumococcal conjugate vaccine introduction on childhood pneumonia mortality in Brazil: a retrospective observational study.** *Lancet Glob Health.* 2019; **7**(2): e249–e256.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 7. de Oliveira LH, Shioda K, Valenzuela MT, *et al.*: **Declines in pneumonia mortality following the introduction of pneumococcal conjugate vaccines in Latin American and Caribbean countries.** *Clin Infect Dis.* 2020; ciaa614.
[PubMed Abstract](#) | [Publisher Full Text](#)
 8. Pan American Health Organization: **Lineamientos básicos para el análisis de la mortalidad.**
[Reference Source](#)
 9. Mancero X: **Medición de la pobreza por ingresos - Actualización metodológica y resultados.** 2019.
[Reference Source](#)
 10. **II. MARCO CONCEPTUAL.** Accessed August 29, 2020.
[Reference Source](#)
 11. Plummer M: **rjags: Bayesian Graphical Models using MCMC.** R package version 4-7. 2018.
[Reference Source](#)
 12. Shioda K, de Oliveira L, Toscano CM, *et al.*: **OnlineSupplement.pdf.** *figshare.* Online resource. 2020.
<http://www.doi.org/10.6084/m9.figshare.12934901.v1>
 13. Shioda K, Weinberger D, Toscano CM, *et al.*: **Supplementary Figures.** *figshare.* Figure. 2020.
<http://www.doi.org/10.6084/m9.figshare.12957887.v1>
 14. Shioda K, Weinberger D: **weinbergerlab/PAHO_subnational 0.2 (Version 0.2).** *Zenodo.* 2020.
<http://www.doi.org/10.5281/zenodo.4011097>

Open Peer Review

Current Peer Review Status:   

Version 1

Reviewer Report 21 December 2020

<https://doi.org/10.21956/gatesopenres.14392.r30085>

© 2020 Mulholland E. This is an open access peer review report 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.



Edward Kim Mulholland

¹ Department of Infectious Disease Epidemiology, Department of Paediatrics, University of Melbourne, Melbourne, Vic, Australia

² Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

This is a very timely and appropriate piece of research. In the past some (including this reviewer) have argued that PCVs have the potential to increase inequity in child survival unless high coverage is reached in the poorest communities. This research addresses this issue in 3 countries of the Americas where quality mortality data are available at subnational level.

In each country departments or states are categorized into 3 levels based on income data from other sources. Then the pneumonia mortality rates were evaluated by income level and time. To account for important differences in PCV coverage by income, the authors extrapolated to a hypothetical PCV coverage level of 90%. This seems particularly important in Peru where PCV coverage ranged from 67% to 94% in the 3 strata. Exactly how this extrapolation was done is unclear to this reviewer. Logically the relationship between PCV coverage and mortality is non-linear as the unvaccinated will be at higher risk, regardless of income level, and this effect may be more acute at lower income levels. Figure 2 seems to show that this adjustment had little effect on the conclusions.

Figure 3 which shows estimated mortality declines with PCV coverage is a bunch of straight lines with various data points on it. What does this mean?

On Page 5, "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." This seems a polite way to put this. The graph seems to show increasing mortality among most of the middle income regions. This probably reflects issues with data, but it is difficult to conclude that. At least it should be discussed.

As a reader it is a little difficult to really understand the paper without the basic pneumonia mortality data in the 3 strata against which the trends are being analysed. All data are presented

relative to the year of vaccine introduction, 2009, 2010 and 2008 for Brazil, Colombia and Peru respectively. The 3 countries have all seen substantial falls in child mortality over the period which predated PCV introduction, so the key question seems to be what was the impact of PCV, over-and-above the declines that were taking place. That would appear to be presented in Figure 1, which seems to show that there was no significant decline in any of the 3 countries, once non-pneumonia mortality trends were accounted for.

Figure S3 is difficult to follow, probably because of the legend.

In conclusion, as a reader I was reassured that PCV is associated with reduced child pneumonia mortality in most communities in the 3 countries, but this is quite in line with overall changes in child mortality in those countries so it is difficult to attribute the decline to PCV.

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

Partly

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

Partly

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

Partly

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

I cannot comment. A qualified statistician is required.

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.

Reviewer Expertise: Infectious disease epidemiology; vaccinology, paediatrics

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, however I have significant reservations, as outlined above.

Reviewer Report 18 December 2020

<https://doi.org/10.21956/gatesopenres.14392.r30069>

© 2020 Heyderman R. This is an open access peer review report 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.



Robert Simon Heyderman 

NIHR Global Health Mucosal Pathogens Research Unit @UCL, University College London, London, UK

This study sets out to evaluate how the association between increasing vaccine uptake and population-level declines in death due to pneumonia in children 2-23 months varies by socioeconomic status in Brazil, Colombia, and Peru. The authors have recently published an evaluation of the population-level impact of PCVs against death due to pneumonia in children under 5 years of age. The value of such national level analyses is size but the datasets from Peru and Colombia are modest. The analysis is confounded by heterogeneity of vaccine programmes and falling pneumonia death rates before vaccine introduction. These data nonetheless would be a valuable addition to the literature.

I have some suggestions that could improve the quality of the manuscript:

TITLE: The authors have specifically focused on children 2-23 months of age – this should be reflected in the title.

INTRODUCTION:

Although it may seem obvious, the authors should introduce what is already known and why differences in pneumonia deaths related to socioeconomic status between and within countries may be expected.

METHODS:

1. This analysis is highly dependent on the coding of pneumonia episodes in each country, uniformity of practice between countries and over time. The reader is pointed to a WHO document on standardized data cleaning and quality control which is in Spanish. Some further detail should be provided. Have any checks been done to ascertain miscoding? Do the authors have any data to demonstrate the fidelity of the coding.
2. The authors state that income level was ascertain in “household surveys”. Were these undertaken by the national governments?
3. To provide a context for the data, the authors should state the approximate birth cohorts for each country and the total number of deaths during the same period.
4. To account for overdispersion, an observation-level random effect was included in the analysis. Is there evidence that this was successful?
5. Were permissions required to use this national data?

RESULTS:

1. Table 1 shows that the total number of J12-18 among children 2–23 months in Brazil coded as primary or non-primary causes of death is 16,303 4700 and the total number of J12-18 among children 2–23 months of age in the study period coded as primary cause of death is 35,259. Is this the correct way around?

2. The authors provide the weighted average of PCV third dose coverage in the last year of the study period in the main text but the rapidly of vaccine uptake and the difference between and within countries are best illustrated by Figure S1 which should be included in the main manuscript.
3. To understand trends, all-cause pneumonia has been adjusted for all-cause mortality other than respiratory illness but the underlying trend could be in infectious diseases only. What is the overall trend in non-pneumonia infectious diseases? Has this been used to adjust all-cause pneumonia?
4. Figure 3 is referred to in the statement “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”. An analysis should be provided to confirm what seems to be apparent visually.

DISCUSSION:

1. The statement, “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”, should include a statement about the uncertainty.
2. Limitations should include: the number of pneumonia deaths were relatively modest in Peru and Columbia; heterogeneity in schedules and vaccine valency which may be particularly relevant for younger ages; and the estimates of vaccine coverage.
3. The main conclusion is that “in three middle-income countries in South America, regions with higher PCV coverage experienced larger declines in pneumonia deaths”. This needs to be formally substantiated in the results (see above).

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

Partly

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?

Partly

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

I cannot comment. A qualified statistician is required.

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.

Reviewer Expertise: Microbial Pathogenesis; Mucosal Immunity; Vaccine Preventable Diseases

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, however I have significant reservations, as outlined above.

Reviewer Report 21 October 2020

<https://doi.org/10.21956/gatesopenres.14392.r29638>

© 2020 Pilishvili T. This is an open access peer review report 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.



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.
