

## INTRODUCTION

Pneumonia is among the leading causes of hospitalization in children of the United States<sup>1</sup>, and one of the top ten causes of children deaths worldwide<sup>2</sup>. *Streptococcus pneumoniae*, or pneumococcus, remains a leading cause of bacterial pneumonia, and was still reported in approximately 4% of all pneumonias between 2010-2012 in children in the United States<sup>3</sup>. The mass introduction of vaccination against *Haemophilus influenzae* type b (Hib) in the United States in 1989, as well as the introduction of the seven-serotype vaccine against pneumococcus in 2000, and the 13-serotype vaccine of pneumococcus in 2010 have dramatically reduced the incidence of all-cause pneumonia in children<sup>4-6</sup>. A study reported an 80% reduction of invasive pneumococcal disease in children under-2 years of age after the seven-valent pneumococcal conjugate vaccination (PCV7) was first introduced in the United States<sup>7</sup>. The ten-valent pneumococcal conjugate vaccine (PCV10) is reported to reduce the frequency of pneumococcal carriage in children<sup>8</sup>.

Several comprehensive analyses report the impact of pneumococcal meningitis prevented by PCV7<sup>7,9,10</sup>. In Finland, the reduction of the rate of meningitis in children younger than 5 years was 65% after introducing PCV10 in their immunization schedule. Previous studies show that the reduction of invasive pneumococcal disease was 71% (95% confidence interval, 43-89), including pneumonia and meningitis.

Research has also been conducted on the reduction of pneumonia and meningitis mortality since mass PCV7 introduction<sup>7,11</sup>, but only a few studies show the protection of the 13-valent pneumococcal conjugate vaccine (PCV13), and fewer in the United States. We expand on these studies to show the reduction of PCV7 and PCV13 on all-cause pneumonia and all-cause meningitis, accounting for seasonality. Thus, our aim is to estimate the reduction in pneumonia

mortality rates during mass vaccination with PCV7 and PCV13 in the United States, relative to the prior non-vaccination period.

## **METHODS**

### **Study design**

We designed and carried out a before-after intervention ecological study to estimate the crude and adjusted impact of PCV on pneumonia and meningitis mortality in children of the United States before the COVID-19 pandemic, using age-specific interrupted time-series regression models.

Our study only uses anonymized, publicly available, secondary data; therefore, approval from an Ethics Committee was not required.

### **Data**

**Mortality:** Individual-level data (microdata) of deaths between 1994 and 2017 in the United States de-identified data were extracted from by the National Vital Statistics System of the National Center for Health Statistic of the Centers for Disease Control and Prevention, and published by the National Bureau of Economic Research<sup>12</sup>. The underlying causes of death were coded according to the 9<sup>th</sup> and 10<sup>th</sup> versions of the International Classification of Diseases (ICD). Data from 1994 to 1998 were coded in the 9<sup>th</sup> version, while causes of death from 1999 and 2017 were coded in the 10<sup>th</sup> version of the ICD. We grouped ICD codes in syndromes to measure the potential effects of PCV on mortality due to all-cause pneumonia and meningitis. This grouping is listed in Supplementary Table 1.

We retrieved data on deaths by age-groups (0-1, 2-11, 6-11, 12-24, 25-59, and 0-59 months old), according to year and month of death. We tested the change of mortality trends according to the

ICD coding using an interrupted time-series model, with a change in trend in January of 1999, the date of introduction of ICD-10. We did not find a significant change in the trend before and after the introduction of ICD-10 coding in the United States (Supplementary Figure 1).

**Population:** We used population estimates produced by the U.S. National Cancer Institute of the National Institute of Health<sup>13</sup>, according to age and calendar year. We used interpolation with natural splines to estimate the population at 0-1, 2-11, and 6-11 months, like other estimations in the literature<sup>14,15</sup>.

**Hib and PCV vaccination coverages:** We used an age-cohort model<sup>16</sup> to estimate the vaccination coverage of Hib and PCV in children of the United States and used these estimates to adjust the reductions of pneumonia mortality in 6-11, 2-11, 12-23, 24-59-, and 0-59-months old children.

We used data from the United States National Immunization Survey (NIS) from 1995-2019. The NIS survey has a complex sample, representative of the children between 19 and 35 months of the United States. This survey questions parents and their health providers for vaccination coverages in these children. We included surveyed children with data from the vaccine provider to estimate vaccination coverages at appropriate ages. Given the survey interviews children 19-35 months old, and the present study requires vaccine coverages at specified years and ages, we needed to construct an age-cohort model to estimate vaccination coverages in 6-11, 2-11, 12-23, 24-59-, and 0-59-months old children based on NIS data from children 19-35 months old. This means children surveyed in 2002 between 19 and 23 months old were vaccinated in 2000 and reported as vaccination estimate of 2000. The Supplementary Material details our methods. The final vaccination coverage of Hib and PCV estimates the percentage (using complex-sample weights) of children vaccinated by year of vaccination (Supplementary Figure 2).

## Statistical Analyses

We fitted models to the trends of monthly mortality rates for all outcomes by age-group, to estimate the reductions of mortality after PCV7 and PCV13 introduction in the United States.

Our interrupted time-series model fitted each series in crude and adjusted negative binomial regression models. Crude analyses included trend with a monthly indicator variable and an interaction between the trend and the intervention. We further adjusted the estimation by seasonality and Hib vaccine coverage between 1994 and 2017. We selected data from 1994 onwards because Hib coverage was available from the NIS after 1994.

Corticoid use was recommended for treatment of meningitis in the United States to reduce meningitis mortality (<https://doi.org/10.1086/425368>) after several trials showed reduction of meningitis-related adverse outcomes. Therefore, we adjusted the estimates of meningitis, meningitis mortality by adding an indicator of corticosteroid use for the treatment of meningitis in the United States, which was implemented after 2002 (2002-2003 as a transition period and 2004-2017 as the full implementation of this intervention)<sup>17</sup>.

The H1N1 pandemic in 2009 was also a potential confounder that increased pneumonia mortality in 2009. Therefore, we also introduced an indicator variable in 2009 for the analyses of all-cause pneumonia mortality to signal the circulation of the pandemic H1N1 virus in the United States.

To obtain the counterfactual estimated mortality rates without vaccination, we allowed a trend and slope change after the introduction of PCV7 (2000-2009) and PCV13 (2010-2017), using as reference the pre-PCV period (1994-1999). We estimated the fitted and counterfactual predictions of these models for each age-group. These models were adjusted by trend, seasonality, vaccination coverage of PCV7/PCV13 and H. influenzae type b, and corticosteroids introduction for the meningitis regression models, and the H1N1 pandemic for pneumonia

models. The exponentiated coefficient of the negative binomial regressions, i.e., the incidence rate ratio along with their 95% confidence intervals (CI), was used to calculate mortality reductions. The vaccine-attributable reductions were calculated according to the formula one minus the incidence rate ratio.

We also evaluated the seasonal variation of pneumonia and meningitis mortality after universal introduction of PCV using the wavelet power spectrum with the Morlet transform for each age-group. Wavelet powers were compared to white noise using 1,000 random simulations.

All mortality rates are reported per 100,000 pop. We used R (R version 4.1.1) for all analyses, using packages ‘WaveletComp’ and ‘ggplot2’ for wavelet power spectrum analyses and visualization, respectively. A p-value < 0.05 was considered statistically significant for all analyses.

We additionally did a MEDLINE search through PubMed with the following keywords:

“((((((pneumococcus) OR (pneumococcal)) OR (Streptococcus pneumoniae)) OR (S. pneumoniae)) AND (((mortality) OR (death)) OR (fatality))) AND ((vaccination) OR (vaccine)) AND (((children) OR (infants)) OR (pediatric)))”, published in English from January 1<sup>st</sup> of 2002 to August 15<sup>th</sup> of 2021, excluding those without assessment of impact in under-1 or under-5-year-old children. A total of 1,705 results were first obtained, arriving to eight studies showing the impact of pneumococcal conjugate vaccination (PCV) in mortality of under-1- and under-5-year-old children.

## **RESULTS**

### **Mortality before PCV vaccination**

**Table 1** shows the mortality rates and percent reduction for all-cause pneumonia and meningitis for the pre-vaccination, PCV7, and PCV13 time periods. Between 1994 and 1999, a total of 209,828 deaths for all-causes occurred in children 0-59 months old, for a rate of 180.3 deaths per 100,000 pop. For 0-1 months old children during the pre-vaccination period, the all-cause mortality rate was 286.1 per 100,00 pop., while for 2-11 months of age this rate was 19.7 deaths per 100,000 pop. All-cause pneumonia was reported as the cause of 1.9%, 0.9%, and 4.2% of all-cause deaths among 0-59, 0-1, and 2-11 months of age, respectively. All-cause meningitis was reported as the cause of deaths in 0.5%, 0.2%, 0.9%, of children 0-59, 0-1, and 2-11 months of age, respectively.

During the pre-vaccination period, 312 all-cause pneumonia deaths occurred annually in infants 2-11 months old, for a rate of 0.8/100,000 pop., while for all-cause meningitis, there were 70 deaths (0.2/100,000 pop.) in this age-group (Table 1).

### **Reductions of mortality by age-group**

During the time of PCV7 administration, there were statistically significant adjusted reductions in all-cause pneumonia for children: 2-11 months old (22%; 95% CI, 10 to 32); 12-23 months old (33%; 95% CI, 12 to 49); 24-59 months old (29%, 95% CI, 10 to 45); and the combined 0-59 months old (13%; 95% CI, 4 to 21). There was a not statistically significant increase in adjusted all-cause pneumonia for children 0-1 months (-12%; 95% CI, -29 to 3). Deaths by all-cause pneumonia during the PCV13 period followed a similar pattern; the adjusted reduction of mortality in children 2-11 and 6-11 months old compared to the pre-vaccine counterfactual were higher than those found with PCV7 (Table 1).

We found statistically significant reductions of all-cause meningitis in children 0-1 months old during PCV7 compared to the counterfactual. The reductions of all-cause pneumonia and

meningitis mortality during PCV13 were larger compared to PCV7 in infants 6-11 months old. Children 24-59 years old had a significant reduction of pneumonia mortality during PCV13. No other age-group showed a statistically significant different adjusted reduction of pneumonia or meningitis mortality in PCV13 compared to PCV7. The monthly mortality trends for all-cause pneumonia are shown in Fig. 2, and for all-cause meningitis in Fig. 3.

Further adjustments by removing the effect of Hib coverage did not change the statistical significance of reductions in mortality in the pneumonia outcome (Supplementary Table 2), while removing Hib coverage as a confounder for all-cause meningitis moved the significance to the null in the adjusted models of 2-11, 6-11, 12-32, and 24-59 months old.

We further estimated secular trends during the pre-vaccination period (1994-1999), stratifying the trend into two time-periods, the assumed pre-intervention period (1994-1996) and the post-intervention period (1997-1999). We did not find any trend for all-cause pneumonia in the data for any of the age-groups (Supplementary Table 3).

### **Reductions of seasonality**

Fig. 1 and Fig. 2 shows the trends for each vaccination period, with the seasonal component. Fig. 3 shows, through wavelet analysis, that the annual (12-month in y-axis) seasonal pattern of pneumonia deaths was significant before and after PCV7 vaccination. There was a reduction of the amplitude of seasonality after PCV7 from every 8-16 month to 10-11 months in children 2-11 years old. There were no significant seasonality changes after PCV13 introduction in this age group. On the other hand, for children from 12-23 months the annual seasonality disappears around and after the introduction of PCV13. In children 0-59 months old, the seasonality does not disappear, although it is reduced from pre-vaccine levels. Meningitis seasonality is reduced in 0-59 months old children from around 2004 onwards.

## DISCUSSION

Our analysis of individual-level vital statistics data shows a significant reduction in mortality due to pneumonia and meningitis after the mass introduction of PCV7 and PCV13 in the United States. Despite availability of vaccination and other medical interventions, pneumonia is one of the top causes of childhood deaths worldwide<sup>2</sup>. We show a substantial reduction of all-cause pneumonia mortality rates in infants and children 2-11 months of age in the United States. These reductions of all-cause pneumonia accelerated after the introduction of PCV13 in infants 6-11 months old, with 43% more reductions of all-cause pneumonia. The reductions of all-cause meningitis were more modest, and located in children 24-59 months old during PCV13. These substantial reductions suggest that the introductions of PCV7 and later PCV13, adjusted by trend, seasonality, PCV and Hib vaccine coverage, and the H1N1 pandemic, were associated with decreasing pneumonia and meningitis mortality in infants and children of the United States. These adjustments consider the previous trends of mortality, potentially caused by better life conditions and well-being, better healthcare treatments, and other life-saving interventions, and paint a scenario of strong effects of PCV7/PCV13 for reducing illness and mortality. Taking the entire evidence into context, including vaccine trials and observational studies (Table 3), PCV7/PCV13 are life-saving intervention for infants and children worldwide, and efforts should be made to improve the rollout and increase vaccination coverage in countries worldwide. Previous cohort studies have shown the reduction in pneumonia cases and hospitalizations due to PCV7, and death reduction in the United States due to invasive pneumococcal disease<sup>7,11</sup>. A previous analysis of PCV7 showed a reduction of 25% in deaths due to invasive pneumococcal disease<sup>11</sup>. In an analysis of all-cause pneumonia in 10 states, children under 2 years of age had a 28% reduction of cases and an 80% reduction of invasive pneumococcal disease<sup>6</sup>. A cohort



study from Denmark studied the reductions of mortality secondary to invasive pneumococcal disease after PCV7 and PCV13. Despite the reductions of mortality in children under-2 years of age in the Denmark study were not significant, the incidence rate ratio showed a reduction of invasive pneumococcal disease of 53% for PCV7 and 71% for PCV13.

In a systematic review, we found eight studies<sup>14,18–24</sup> assessing the reduction of mortality after the introduction of one or several of PCV7/PCV10/PCV13 in countries worldwide. All studies in infants, except one in Ecuador, show significant reductions of mortality, ranging from 10% in Brazil to 79% in South Africa (Table 2).

For 0-59 months old children, the annual seasonality of all-cause pneumonia and did not change. Conversely, in 12-23 months old children, the annual seasonal pattern disappeared around the time of introduction of PCV13 in 2010. The H1N1 pandemic, and the recommendation of influenza vaccination for children  $\geq 6$  month could explain the difference in seasonality behavior between both age groups and the disappearing of the annual seasonality starting in 2009 among children 12-23 months old.

Vaccination hesitancy is currently an issue in the United States; a recent survey shows that 6.1% of parents in the United States are hesitant to vaccinate their children.<sup>25</sup> Vaccination trials for PCV7, PCV10, and PCV13 did not show a high rate of adverse reactions or complications for vaccinated infants and children, suggesting that pneumococcal vaccines have a good safety profile<sup>26</sup>. There is no evidence that pneumococcal vaccination is linked to any serious adverse effect, and their impact is substantial to reduce mortality of pneumococcal-related outcomes.

Our study uses ICD-10<sup>th</sup> to assign deaths by all-cause pneumonia and all-cause meningitis. We are restricted to the information reported on the death certificate at time of death, therefore other interventions may confound the associations we found, including improvements overtime of

sanitation, healthcare delivery, or other known and unknown confounders. Our results approximate the true effect of PCV7/PCV13 on pneumococcal disease, and studies using individual-level vaccination and mortality data may be required to replicate our results. The main limitation of this observational study is the ecological nature of the aggregated analysis, which precludes knowing the vaccination status of those who died. Despite this, the temporal association of the introduction of PCV7 and PCV13 in the US with substantial reductions in pneumococcus-associated mortality among the target age-groups; and the specificity of such association makes it unlikely to be explained solely by improvement in general health conditions or other social drivers of childhood mortality different from immunization. Thus, our results suggest that the mass introduction of PCV7 and PCV13 may have partially contributed to the observed reductions in childhood mortality. We adjusted our results by seasonality and Hib vaccine coverage, with little change in the predicted reductions of all-cause mortality. Another limitation of our study may be the introduction of information bias derived from improper classification of deaths. The diagnosis of pneumococcal is difficult, even in the United States. Although this is a plausible source of error, by including all-cause pneumonia and meningitis as the main outcomes, we are underestimating the potential effectiveness of PCV7/PCV13 vaccination, aiming to lower the potential misclassification bias of the diagnosis of pneumococcal disease. The coverage of vital statistics in the United States is high, leaving little room for the possibility of selection bias in these analyses. The World Bank reports a coverage of death registration >98% for the entire study period, deeming low the likelihood of this bias. The change in ICD coding in 1999 may also have been an issue, although we did not find any change in trend after the introduction of ICD-10<sup>th</sup> coding in 1999 in the United States. Improvements in the medico-legal system could have improved the ICD-10<sup>th</sup>

coding of reported deaths over time, which could increase the estimates of all-cause pneumonia and all-cause meningitis, biasing results towards the null hypothesis, and therefore suggesting the estimates of death reduction are higher than estimated in the present analysis. Our results may have also been influenced by atypically large flu seasons in the United States. We adjusted by the H1N1 epidemic period in 2009, for the unusual numbers of epidemic deaths that occurred during the time-period. After 2009, H1N1 became endemic and joined the other flu viruses as seasonal.

The estimations may also be biased to the null hypothesis because the United States enacted the Affordable Care Act in 2010 (Obamacare), this because the law increased the number of insured population, potentially decreasing the number deaths after 2014. Despite this, children had special insurance before the Affordable Care Act (i.e., Medicaid), that limits this potential bias. We also constructed an alternative scenario during the pre-vaccination period, where we simulated an intervention from 1997-1999, and found adjusted trends were not reduced without vaccination, strengthening the inference of our results (Supplementary Table 3).

## **CONCLUSION**

PCV7 and PCV13 are associated to a reduction of pneumonia and meningitis mortality in infants and children of the United States.

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## Legend

**Figure 1. Monthly mortality trends with vaccination (black) and the counterfactual without vaccination (red), for all-cause pneumonia in children of the United States.**

**Note:** Dots are observed monthly data-points. This model was adjusted by trend and seasonality.

**Figure 2. Monthly mortality trends with vaccination (black) and the counterfactual without vaccination (red), for all-cause meningitis in children of the United States.**

**Note:** Dots are observed monthly data-points. This model was adjusted by trend and seasonality.

**Figure 3. Reduction of seasonality for all-cause pneumonia and all-cause meningitis mortality using wavelet analyses, in children of the United States.**

**Note:** The  $x$ -axis of the figures is calendar time, where black vertical lines signal the introduction of PCV7, while purple vertical lines show the introduction of PCV13. The  $y$ -axis is the period where seasonality is stronger, where for example, the  $y$ -axis in the number 12 means that the trend repeats every 12 months. The Panels in this figure show a significant reduction of 12-month seasonality after 2010 (after PCV13 introduction), in infants between 12-23 months old for all-cause pneumonia and all-cause meningitis. This pattern repeats for all-cause meningitis in 0–59-month-old children. The black dots show significant trends at every  $y$ -axis month values during  $x$ -axis years (with a  $P < 0.05$  threshold); this means black dots at 12 months in the  $y$ -axis are significant trends every 12 months for the years in the  $x$ -axis.