Examining The Relationship Between Pcv13, Respiratory Viruses, And Invasive Pneumococcal Disease In Massachusetts Children

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Examining the relationship between PCV13, respiratory viruses, and invasive pneumococcal disease in Massachusetts children

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Abstract

The landscape of the burden of invasive pneumococcal disease (IPD) in Massachusetts children has been shaped by both the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 as well as the relationship with respiratory viruses, like influenza and COVID-19. The implementation of non-pharmaceutical interventions (NPIs) and dramatic decline in non-COVID circulating respiratory viruses during the initial waves of the COVID-19 pandemic provided a unique opportunity to evaluate the relationship between respiratory viruses and IPD in Massachusetts children. Using weekly surveillance data for IPD, influenza, and COVID-19 in Massachusetts children 5 years of age and younger from the Massachusetts Department of Public Health, we evaluated the impact of PCV13, the temporal relationship between influenza and IPD, and the impact of NPIs and COVID-19 on the burden of IPD in Massachusetts children. We found that there was a 78% decline in observed IPD cases compared to the predicted cases had PCV13 not been implemented and PCV13 averted approximately 1,135 cases of IPD in Massachusetts children. We observed a strong temporal association between influenza and IPD, with both diseases peaking within a few weeks of each other during the winter each year. Lastly, we found that during the state of emergency and implementation of non-pharmaceutical interventions (NPIs) in Massachusetts for COVID-19 between March 2020 and June 15, 2021, there was a 62% decrease in the observed number of cases compared to the predicted case counts had no COVID-19 non-pharmaceutical interventions been implemented and as a result, approximately 18 cases of IPD were averted. Both PCV13 and COVID-19 interventions led to a drastic decline in the incidence of IPD in Massachusetts children. After the relaxation of NPIs in June 2021, cases of IPD and influenza rebounded to pre-pandemic levels. We would like to expand upon this research by including RSV in our analysis and expanding our research into older children and the elderly.
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Introduction

*Streptococcus pneumoniae* bacteria colonizes the nasopharynx of its hosts, and in most cases, does not cause disease.\(^1\)\(^2\) Approximately 60% of children up to the age of 5 in the United States have asymptomatic nasopharyngeal colonization of *S. pneumoniae*.\(^2\) Prior to the introduction of pneumococcal conjugate vaccines (PCV), pediatric populations in the United States faced significant morbidity and mortality due to *S. pneumoniae*.\(^3\)\(^5\) *S. pneumoniae* was the most prevalent cause of pneumonia, bacteremia, sinusitis, and otitis media in children under 5 years of age and it resulted in approximately 65,000 cases of IPD in children each year.\(^2\)\(^4\)\(^5\)

In 2000, the heptavalent pneumococcal conjugate vaccine (PCV7) was approved for infants and young children in the United States and it resulted in a 75-80% reduction in invasive disease incidence in children under 5 years old.\(^5\)\(^-\)\(^7\) Three years after the introduction of PCV7 in Massachusetts, the incidence of childhood IPD declined by 69%.\(^8\) Despite the clear successes of PCV7 in reducing the burden of IPD in the United States’ pediatric population, the selective pressures from PCV7 resulted in the phenomenon of “serotype replacement.” By 2007, 85% of pediatric IPD cases in Massachusetts were attributed to non-PCV7 serotypes with non-vaccine serotype 19A alone responsible for over a quarter of pediatric IPD cases.\(^9\)

In response to the increase in non-vaccine serotypes causing IPD, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed for use in infants and young children in 2010.\(^10\) PCV13 included the 7 serotypes from PCV7 as well as 6 additional serotypes.\(^10\) The potency of *S. pneumoniae* to cause invasive disease is largely dependent on the age of the host and serotype, with serotypes 19A, 7F, 33F, and 38, and 3 exhibiting the highest invasive capacity.\(^2\) In a study of Massachusetts children, *S. pneumoniae* serotypes 3, 19A, and 10A had significantly higher serotype specific invasive capacity in children under 2 years old compared to children over 2 years old.\(^2\)

The risk of developing invasive pneumococcal disease might also influenced by the synergistic relationship between respiratory viruses, particularly influenza, and pneumococcus. Evidence shows that infection with influenza increases susceptibility of host nasopharyngeal and respiratory epithelial cells to *S. pneumoniae* invasion.\(^11\) A proposed mechanism for this phenomenon is that the influenza neuraminidase helps clear mechanical barriers to mucosal bacterial adherence, essentially priming the host epithelial cells.\(^11\)\(^,\)\(^12\) The relationship between IPD and respiratory viruses has been observed through strong temporal associations between IPD and
Influenza. An association between significant increases in IPD incidence and influenza activity was observed in Denmark, with the most profound effect seen between the ages of 15 and 39 where 8.4% of IPD cases could be attributed to influenza activity. Similarly in Sweden, 12-20% of IPD cases during the respiratory season are attributed to influenza activity. The United States has observed similar patterns such as during the 2009 A/H1N1 pandemic when there was a significant increase in hospitalizations for pneumococcal pneumonia during high influenza activity, particularly in school age children.

Emerging evidence suggests a complex relationship between the novel, SARS-CoV-2 respiratory virus and IPD. During the 2020 COVID-19 pandemic, many countries experienced declines in IPD and non-COVID respiratory virus incidences thought to be due to the implementation of non-pharmaceutical interventions (NPIs) aimed at reducing the pandemic severity. A study of Switzerland found that during the peak of COVID-19 in 2020, the number of observed IPD cases was lower than expected and an increase in IPD cases correlated with the relaxation of COVID-19 NPIs. Similarly, during the 2020-2021 COVID-19 pandemic periods, there was a 65% reduction of IPD in Catalonia, Spain and a 50% reduction of IPD in Israel for children under 5 years old. A study in France found that the effectiveness of NPIs at reducing IPD incidence was largely due to the decrease in other respiratory viruses. IPD incidence in children 15 years old and younger in France declined by 63% during the COVID-19 with 53% and 40% of the decline being attributed to the decrease in RSV and influenza cases, respectively. Despite the lower IPD burden during the 2020-2021 pandemic, the pneumococcal carriage rate, density, and distribution of serotypes did not change during this period.

In this study, comprehensive population based IPD surveillance data in Massachusetts children aged 5 and younger was used to quantify annual IPD incidence over the previous two decades. Then, a negative binomial regression model was used to examine the impact of PCV13 implementation on IPD in Massachusetts children. Lastly, we illustrated the temporal association between influenza, COVID-19, and IPD in Massachusetts children and used a Poisson regression model to examine how implementation of NPIs during the COVID-19 pandemic impacted the number of IPD cases in Massachusetts children.
Methods

Data Sources

Infectious disease surveillance data of weekly confirmed cases of invasive pneumococcal disease, influenza, and COVID-19 for children 5 years of age and younger in Massachusetts were obtained from the Massachusetts Department of Public Health (MADPH) Bureau of Infectious Disease and Laboratory Sciences (BIDLS).\(^ \text{26} \) Weekly surveillance data was available from January 2003 until December 2022 for influenza and COVID-19 and from January 2003 until December 2023 for IPD. A confirmed case of IPD required isolation of *S. pneumoniae* from a normally sterile site as well as clinically compatible symptoms.\(^ \text{22} \) A confirmed COVID-19 case required a positive molecular test and excluded at-home antigen tests.\(^ \text{23} \) Testing and reporting requirements for influenza changed over the course of the study. From 2003 until October 2017, a confirmed influenza case required a positive PCR, culture, or rapid influenza test. After October 2017, positive rapid influenza tests reported to MADPH on paper were no longer included in confirmed influenza case counts. Following September 2018, rapid influenza tests were excluded from confirmed influenza case counts. It must be noted that from 2020 to 2022, screening and surveillance of infectious diseases were impacted by the COVID-19 pandemic. Population data from 2002 to 2022 for children aged 5 and younger in Massachusetts were obtained from the Census Bureau’s Population Estimates Program (PEP) and were used to calculate IPD incidence.

Incidence of IPD for children under 5 years of age in the United States was obtained from the Active Bacterial Core surveillance (ABCs) in the CDC’s Emerging Infections Program (EIP).\(^ \text{24} \) ABCs is an active surveillance system operating in 10 states encompassing approximately 44 million US residents and is used to estimate national incidence of various infectious diseases, including *S. pneumoniae*. A confirmed IPD case is defined as isolation of *S. pneumoniae* or detection of *S. pneumoniae* nucleic acid from a normally sterile site or isolation of *S. pneumoniae* from a wound in addition to necrotizing fasciitis or streptococcal toxic shock syndrome.\(^ \text{25} \) Vaccination coverage data for children in the United States and Massachusetts were obtained from the National Immunization Survey (NIS) using the CDC’s ChildVaxView.\(^ \text{27} \) Between 2007 and 2011, vaccine coverage rate was the estimated coverage of 4 or more doses of PCV in children between 19 and 35 months of age and between 2011 and 2020, vaccine coverage rate was the estimated coverage of 4 or more doses of PCV by age 24 months by birth year.
Calculation of PCV13 Impact on IPD

The impact of PCV13 on IPD burden in Massachusetts children was evaluated by fitting a negative binomial regression model to the pre-vaccine IPD data and extrapolating the model to the post-vaccine period and predicting the number of IPD cases that would have occurred had PCV13 not been implemented. The outcome variable was pre-vaccine weekly IPD case counts, the predictor variables were time and a weekly dummy variable to control for seasonality, and the offset term was the population of children aged 5 and younger in Massachusetts.

The pre-vaccine period was defined as January 2003 to February 24, 2010, the date that PCV13 was licensed for use in children. The vaccine evaluation period began 1 year after PCV13 introduction on February 24, 2011, and commenced in December 2022. The percent decline in observed number of weekly IPD cases compared to the predicted number of weekly IPD cases had PCV13 not been introduced was calculated by taking an average of the weekly estimates of the rate ratio during the evaluation period. The number of IPD cases averted by PCV13 during the vaccine evaluation period was calculated by taking the sum of the difference between the observed and predicted number of weekly IPD cases at each time point.

Temporal Relationship between IPD, Influenza, and COVID-19

The temporal relationship between IPD, influenza, and COVID-19 was illustrated by overlaying the time series of weekly IPD cases with weekly cases of influenza or COVID-19. Due to the change in the influenza surveillance system in October 2018, the time series were separated from January 2003-September 2018 and October 2018-December 2022.

Calculation of COVID-19 Interventions Impact on IPD

The change in the number of IPD cases in Massachusetts children aged 5 and younger after the introduction of COVID-19 in March 2020 was visualized using a time series of number of IPD cases by period. The average number of IPD cases per period pre-PCV13 (2003-2010), the average number of IPD cases per period post-PCV13 (2011-2019), and the number of IPD cases per period for 2020, 2021, and 2022 were plotted. Period 1 includes MMWR weeks 1-4, period 2 includes MMWR weeks 5-8, period 3 includes MMWR weeks 9-12, period 4 includes MMWR weeks 13-16, period 5 includes MMWR weeks 17-20, period 6 includes MMWR weeks 21-24, period 7 includes MMWR weeks 25-28, period 8 includes MMWR weeks 29-32, period 9 includes MMWR weeks 33-36, period 10 includes MMWR weeks 37-40, period 11 includes MMWR weeks 41-44, period 12 includes MMWR weeks 45-48, and period 13 includes MMWR weeks 49-53.
The decline in the number of IPD cases in Massachusetts children during the period of NPIs and the COVID-19 pandemic was determined by fitting a Poisson regression model to the pre-NPI/COVID period and extrapolating the model to the NPI/COVID period to determine the predicted number of IPD cases had the NPIs not been implemented. The outcome variable was pre-NPI/COVID weekly IPD case counts, the predictor variables were time and a weekly dummy variable to control for seasonality, and the offset term was the population of children aged 5 and younger in Massachusetts.

The pre-NPI/COVID period was defined as January 2013 to March 1, 2020. The NPI/COVID period was defined as March 1, 2020 to June 15, 2021, the day that the state of emergency and all Emergency and Public Health Orders issued for the COVID-19 pandemic were ended in Massachusetts. The percent decline in the observed number of IPD cases during the evaluation period compared to the predicted number of cases had NPIs not been implemented was calculated by taking the average of the weekly estimates of the rate ratio during the NPI/COVID period. The number of IPD cases averted during through the NPI/COVID period was calculated by taking the sum of the difference between the observed and predicted number of weekly IPD cases for each time point.

Results

Annual IPD Incidence and Vaccination Rates

Between January 2023 and December 2022, a total of 945 IPD cases occurred in Massachusetts children aged and younger. In 2003, the incidence of IPD in children under 5 years old in the United States was approximately 6.5 times the incidence of IPD in children aged 5 and younger in Massachusetts with annual incidences of 90.1 cases per 100,000 children and 13.7 cases per 100,000 children, respectively (Fig.1). By 2021, the disparity between the incidence of IPD in children in Massachusetts compared to the United States narrowed but United States children still had approximately 4 times the incidence of IPD compared to Massachusetts children with annual incidences of 19.2 cases per 100,000 children and 4.6 cases per 100,000 children (Fig.1). Between 2003 and 2021, the incidence of IPD in US children declined by 79% and the incidence of IPD in MA children declined by 66% (Fig.1). Children in both the United States and Massachusetts experienced a marked decline in IPD incidence following the introduction of the PCV13 vaccine in 2010 (Fig.1). A portion of the disparity in IPD incidence between children in Massachusetts...
compared to children in the United States is associated with differences in PCV coverage rates. Between 2007 and 2021, Massachusetts children had higher rates of at least 4 doses of PCV compared to US children (Fig.1).

**Figure 1.** Annual incidence of IPD in children 5 years of age and younger in Massachusetts (solid purple line) compared with the annual incidence of IPD in children 4 years of age and younger in the United States (solid green line). The annual vaccination coverage rate estimates for 4 doses of PCV in children aged between 19 and 35 months from 2007-2010 and the vaccination coverage rate estimate for 4 doses of PCV in children aged 24 months by birth year cohort from 2011-2021 for Massachusetts (dashed, light purple line) and the United States (dashed, light green line). PCV13 introduction in 2010 is indicated by the dashed gray line.

**Impact of PCV13 on IPD in Massachusetts Children**

Using a negative binomial regression model controlling for time, seasonality, and offset for population size, we evaluated the impact of PCV13 on number of IPD cases in Massachusetts children aged 5 and younger. The model was fit to the pre-PCV13 period, from January 2003 to February 2010, and extrapolated to the post-PCV13 period (Fig.2). The impact of PCV13 was evaluated from February 2011 to December 2022 by comparing the predicted number of IPD cases to the observed number of IPD cases. During this time there was a 78% decline in the observed IPD cases counts compared to the predicted number of IPD cases if PCV13 has not been implemented and approximately 1,135 cases of IPD averted in children aged 5 and younger (Fig.2).
Figure 2. The weekly number of confirmed IPD cases in Massachusetts children 5 years of age and younger between 2003 and 2022 is shown with the gray line. The blue line shows the estimated number of weekly IPD cases in Massachusetts children using a negative binomial regression model fitted to the pre-vaccine period and extrapolated to the post-vaccine period. The first, dashed black line indicates the date of vaccine introduction and the end of the pre-vaccine period on February 24, 2010, and the second dashed, black line indicates the beginning of the vaccine evaluation period on February 24, 2011.

Assessing the Temporal Association between Respiratory Viruses and IPD

The temporal relationship between IPD, influenza, and COVID-19 was evaluated from 2003 to 2018 and from 2019 to 2022. Both IPD and influenza show seasonal variations in the number of weekly cases, with the peak number of cases occurring in the winter (Fig.3A-B). The first wave of COVID-19 seen in Massachusetts children was between Autumn 2020 and the first half of 2021. During this first peak of COVID-19, there were very few IPD and influenza cases compared to previous years (Fig.3). In 2020, the number of IPD cases per 4 week period was consistently lower than the average number of IPD cases per 4 week period from 2003-2010 and from 2011-2019, suggesting that the emergence of COVID-19 in 2020 corresponded to the decline of average weekly IPD cases (Fig.4).
Figure 3. Time series of weekly IPD cases and A) weekly influenza cases from 2003-2018, B) weekly influenza cases from 2019-2022, and C) weekly COVID-19 cases from 2019-2022 in Massachusetts children 5 years of age and younger.
Figure 4. The number of confirmed IPD cases in children 5 years of age and younger in Massachusetts by period. Period 1 includes MMWR weeks 1-4, period 2 includes MMWR weeks 5-8, period 3 includes MMWR weeks 9-12, period 4 includes MMWR weeks 13-16, period 5 includes MMWR weeks 17-20, period 6 includes MMWR weeks 21-24, period 7 includes MMWR weeks 25-28, period 8 includes MMWR weeks 29-32, period 9 includes MMWR weeks 33-36, period 10 includes MMWR weeks 37-40, period 11 includes MMWR weeks 41-44, period 12 includes MMWR weeks 45-48, and period 13 includes MMWR weeks 49-53.

Impact of COVID-19 Interventions on IPD in Massachusetts Children

Using a Poisson regression model controlling for time, seasonality, and offset for population size, we evaluated the impact of COVID-19 (NPIs) on the number of IPD cases in Massachusetts children aged 5 years of age and younger. The model was fit to a pre-COVID/NPIs period from January 2013 to March 2020 and extrapolated to the COVID/NPIs period from March 2020 to June 2021, when NPIs, like limiting the number of people allowed at both indoor and outdoor gatherings and mask mandates, were ended (Fig. 5). During the COVID/NPIs period, a 62% decrease in the observed number of IPD cases compared to the predicted number of IPD cases had no NPIs been implemented was ascertained and approximately 18 IPD cases were averted in children aged 5 and younger in Massachusetts (Fig. 5).
Figure 5. The weekly number of confirmed IPD cases in Massachusetts children 5 years of age and younger between 2013 and 2022 is shown with the gray line. The blue line shows the estimated number of weekly IPD cases in Massachusetts children using a Poisson regression model fitted to the pre-COVID-19 intervention period and extrapolated forward to the COVID-19 intervention period and the post-COVID-19 intervention period. The first dashed, black line indicates the beginning of the COVID-19 intervention period on March 1, 2020, and the second dashed, black line indicates the end of the COVID-19 intervention period on June 15, 2021.

Discussion

Our analysis found that since 2003, children in the United States have had between 4 and 6.5 times the incidence of IPD compared to Massachusetts children and much of this disparity in IPD incidence is likely due to higher rates of PCV coverage in Massachusetts. Rollout of PCV13 in 2010 addressed serotype replacement following PCV7 and led to a marked decline in IPD incidence. In Massachusetts, PCV13 led to a 78% decline in the predicted number of IPD cases had PCV13 not been implemented compared to observed IPD cases.

A temporal relationship between peak influenza cases and peak IPD cases since 2003 was observed and a drastic decline in influenza and IPD cases was seen between March 2020 and June 2021, when non-pharmaceutical interventions for COVID-19 were enacted in Massachusetts. We estimated that had NPIs not been rolled out, there would have been approximately 62% more IPD cases. Previous studies reported no change the pneumococcal carriage rate, density, and distribution of serotypes in children during the pandemic despite substantial declines in invasive disease.18–19 If this observation holds true for Massachusetts children, then the decline in IPD incidence during the period of NPIs is likely due to the impact that exposure to respiratory viruses has on ability for S. pneumoniae colonizing the respiratory tract to cause invasive disease.
The ability to create the best fitting models, make predictions, and examine patterns in the surveillance data was restricted by the limited, and at times sparse, surveillance data. By using hospital record data for bacterial pneumonia in lieu of the surveillance data for IPD we may be able to create a more comprehensive picture of invasive disease in children. The change in healthcare seeking behavior, healthcare capacity, and testing for infectious diseases due to the COVID-19 pandemic makes it difficult to compare the IPD and influenza data from 2020-2022 to previous years. Additionally, the testing patterns for COVID-19 have changed testing methods evolved and capacity was built. The ability to capture the true number of weekly COVID-19 cases in children 5 and younger is further complicated by the high rate of asymptomatic COVID-19 infections in children.

This study demonstrated how the high PCV coverage rate in Massachusetts relative to the United States dramatically reduced the incidence of IPD of Massachusetts. We would like to repeat this analysis in states with lower PCV coverage rates than Massachusetts to determine how PCV vaccination rates impact incidence of IPD and relationship between IPD and respiratory viruses. In the future we would like to expand of this study to include surveillance data from more childhood respiratory viruses such as RSV. A 2015 study found a strong temporal and spatial relationship between RSV and pneumococcal pneumonia in US children and found that 20.3% and 10.1% of cases of pneumococcal pneumonia could be attributed to RSV in children less than 1 years old and children between 1 and 2 years of age, respectively.21

We would also like the expand the study to include older children and adults to get a more comprehensive picture of the prevalence of IPD, impact of PCVs, temporal relationships between IPD and respiratory viruses, and impact of COVID-19 on IPD in Massachusetts. The Massachusetts Department of Public Health estimates that nearly 90% of IPD cases each year in the United States occur in adults, so it is vital to include adults in our analysis to gain a comprehensive landscape of IPD in Massachusetts.22 Furthermore, incorporating surveillance systems for respiratory viruses in the adult population may provide insights into IPD burden in the population of young children because many of the social contacts of young children are adults such as parents and caregivers.

In conclusion, our study provides evidence of the substantial effectiveness of PCV13 at combatting the burden of IPD in children. Our study estimates that PCV13 saved over a thousand
Massachusetts children from contracting IPD since 2010 and that the enactment of NPIs during the COVID-19 pandemic drastically reduced influenza and IPD burden. This research highlights the considerable impact of respiratory viruses on the prevalence of IPD. Ideally, having robust respiratory virus surveillance data will allow for predictive models that estimate the excess seasonal burden of IPD in target populations due to respiratory virus activity.

References


https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5911a1.htm


19. Rybak, A. *et al.* Association of Nonpharmaceutical Interventions During the COVID-19 Pandemic With Invasive Pneumococcal Disease, Pneumococcal Carriage, and


