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Impact of 13-Valent Pneumococcal Conjugate Vaccine Used in Children on Invasive Pneumococcal Disease in Children and Adults in the United States: Analysis of Multisite, Population-based Surveillance

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Contributors

MRM proposed the initial study idea, drafted the analysis plan, and wrote the main manuscript. RLG worked with ABCs surveillance sites to collect and manage data on cases. WS, RL, CL, NMB, SP, SMZ, LHH, AR, LM, KS, AT, and MMF were the site primary investigators. ERZ, TT, and TP conceptualized and conducted the statistical analyses. LR provided input into the appropriate measures of vaccine coverage and provided data on the introduction and coverage of PCV13 in the United States. LM, BB, and JJ conducted serotyping and antimicrobial resistance testing of case isolates. CW provided input into the analysis plan and the interpretation of the data. All authors contributed to the interpretation of the findings as well as the final manuscript.

Conflicts of Interest

For all other authors, we declare that we have no conflicts of interest.

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SUMMARY

Background—In 2000, 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the U.S. and resulted in dramatic reductions in invasive pneumococcal disease (IPD) and modest increases in non-PCV7-type IPD. In 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the U.S. immunization schedule. We evaluated the effect of PCV13 use in children on IPD in children and adults in the U.S.

Methods—We used laboratory- and population-based data on incidence of IPD from CDC's Emerging Infections Program / Active Bacterial Core surveillance in a time-series model to estimate the impact of vaccination. Cases of IPD during July 2004–June 2013 were classified as being caused by the PCV13 serotypes against which PCV7 has no effect (PCV13/nonPCV7).

Findings—Compared with incidence expected among children <5 years old if PCV7 alone had been continued, incidence of IPD overall and IPD caused by PCV13/nonPCV7 serotypes declined by 64% (95% interval estimate [IE] 59–68 %) and 93% (95%IE 91–94), respectively, by July 2012–June 2013. Among adults, incidence of IPD overall and PCV13/nonPCV7-type IPD also declined by 12–32% and 58–72%, respectively, depending on age. In all age groups, reductions were driven principally by changes in incidence of serotypes 19A and 7F. We estimate that over 30,000 cases of IPD and 3,000 deaths were averted in the first 3 years following PCV13 introduction.

Interpretation—PCV13 has reduced IPD among all ages when used routinely in children in the U.S. Serotypes 19A and 7F, which emerged after PCV7 introduction, have been effectively controlled.

Keywords

invasive pneumococcal infections; pneumococcal conjugate vaccine; pneumococcal serotypes

Background

Streptococcus pneumoniae, or pneumococcus, is a major cause of morbidity and mortality globally. In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7, Prevnar®, Wyeth) was introduced into the routine infant immunization program in the U.S., using a schedule of doses at 2, 4, 6, and 12–15 months of age.¹ Rates of invasive pneumococcal disease (IPD) caused by PCV7 serotypes declined dramatically among children. Because PCV7 also prevented transmission of PCV7 serotypes, rates of IPD among unvaccinated groups also declined.² PCV7 was also linked to reductions in otitis media visits³ and pneumonia hospitalizations.⁴ During subsequent years, serotype replacement resulted in increases in non-PCV7-type IPD that were modest relative to reductions in PCV7-type IPD.⁵ Despite

these reductions, pneumococcus caused about 4 million episodes of disease in the U.S. resulting in \$7.7 billion in direct and indirect costs in 2004.⁶

In 2010, a 13-valent conjugate vaccine (PCV13, Prevnar-13®, Pfizer) replaced PCV7.^{7,8} PCV13 included serotypes causing replacement disease in the U.S. and was licensed without a randomized clinical trial. Post-licensure evaluation was, thus, the first opportunity to evaluate the effects of PCV13 on prevention of IPD. Our objectives were to evaluate the population-level impact of PCV13 on incidence of IPD among all ages and to assess whether PCV13 introduction was associated with serotype replacement.

Methods

We used a long-standing surveillance system to compare rates of IPD before and after PCV13 introduction. We identified IPD cases through Active Bacterial Core surveillance (ABCs), an active population- and laboratory-based surveillance system that is part of CDC's Emerging Infections Program. The methodology used by ABCs is described in full at <http://www.cdc.gov/abcs/index.html>. We included cases identified from July 1, 2004 through June 30, 2013 in ten continuously participating ABCs sites: selected counties in California, Colorado, Georgia, Maryland, New York, Oregon, and Tennessee, and the states of Connecticut, Minnesota, and New Mexico. The total population under surveillance was nearly 30 million.

We defined IPD cases as isolation of *S. pneumoniae* from normally sterile sites (e.g., blood, cerebrospinal fluid). Laboratory audits ensured completeness of reporting. PCR for diagnosis of IPD is not uniformly available in the U.S. and such cases are not captured by ABCs. Medical records were reviewed to obtain demographic and clinical information. Isolates were serotyped by Quellung at CDC's Streptococcus Laboratory or the Minnesota Department of Health Laboratory. For our analysis, we assigned serotypes to the following categories: 1) PCV7-types (4, 6B, 9V, 14, 18C, 19F, 23F, and 6A), 2) PCV13/nonPCV7-types (serotypes 19A, 7F, 5, 3, and 1, which are included in PCV13 but are not affected by PCV7), 3) PPV11 types (serotypes included in 23-valent pneumococcal polysaccharide vaccine [PPV23, PNEUMOVAX 23®, Merck] but not in PCV13: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F) and 4) non-PCV13-types (types not included in PCV13). Note that categories 3 and 4 overlap. Although serotype 6A is included in PCV13 and not in PCV7, we treated it as a PCV7 serotype because of documented cross-reactivity and disease reduction associated with the 6B antigen in PCV7⁹. Antimicrobial susceptibility testing against penicillin, erythromycin, clindamycin, trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol, levofloxacin, and vancomycin was performed using broth microdilution and isolates were classified as susceptible, intermediate, or resistant according to published guidelines¹⁰. Meningitis breakpoints for penicillin were used for meningitis cases; non-meningitis breakpoints were used for all other cases. For all antibiotics, we combined intermediate and fully resistant strains into a "nonsusceptible" category. Any isolate nonsusceptible to three or more classes was considered "multiply nonsusceptible".

We calculated case-fatality ratios (CFR) as the proportion of cases with fatal outcomes among those with known outcomes (>99% of all cases). Comorbid conditions were collected

as per the ABCs protocol¹¹ and classified according to recommendations of the Advisory Committee on Immunization Practices (ACIP).^{12,13}

ABCs case reporting and isolate collection were considered to be surveillance activities and were exempt from CDC institutional review. The protocol was also assessed for review at each site and, when necessary, institutional review board approval was obtained. Informed consent was not required.

We estimated vaccination coverage using immunization information systems (IIS) which are confidential, population-based systems that consolidate data from vaccine providers. As a proxy for coverage in ABCs areas, we used IIS sentinel sites located in Michigan, Minnesota, North Dakota, New York City, Oregon, and Wisconsin that collectively include approximately 2.0 million children aged <5 years. We used SAS® (version 9.3, SAS Institute, Inc., Cary, NC) and Excel® 2010 (Microsoft Corp., Redmond, Washington) to calculate unweighted intra-site mean PCV13 coverage based on 2011 post-Censal population estimates and vaccination records from IIS sentinel sites (queried 2 February 2013). PCV13 primary series coverage estimates included doses of PCV13 administered before 12 months of age to children born during 1 July 2010 through 1 July 2011. Post-primary PCV13 booster dose coverage estimates include doses of PCV13 administered before 19 months of age to children born during 1 July 2010 through 1 December 2010. PCV13 supplemental dose estimates include PCV13 doses administered to children aged 14–59 months born 1 July 2007 through 1 May 2009 who previously completed a routine or catch-up schedule recommended by the ACIP.^{14,11}

Statistical Methods

We fit the monthly case counts, during the pre-PCV13 period from 1 July 2004 through 30 June 2010, to time-series models. Separate models were developed for each age group, <5, 5–17, 18–49, 50–64, 65 and each group of serotypes. We modeled the following 10 serotype groupings: all serotypes; PCV13/nonPCV7 serotypes; non-PCV13 serotypes; and, separately serotypes 19A, 7F, 3, 6C, penicillin non-susceptible, erythromycin non-susceptible, and multiply non-susceptible. The only independent covariates in the models were the calendar month and year, although time series models implicitly include all time-varying effects, including changes in population size. Our nonlinear time series models with sinusoidal seasonality terms fit the pattern of higher disease incidence in early winter and lower disease incidence in late summer. The general form of the models was:

$$\text{cases} = \beta_0 + \beta_1 * \text{year} + \beta_2 * \sin(\text{month} + k) + \beta_3 * \cos(\text{month} + k) + \beta_4 * \text{outlier_indicator}$$

The outlier indicator flagged a total of six unusual events, including five associated with the influenza pandemic of 2009. The parameter estimates from the pre-vaccine time-series model and their variance provided a predictive distribution for post-PCV13 time series model parameters. At each month, from July 2010 through June 2013, we calculated 1000 predicted case counts based on 1000 random draws from the predictive distribution of the model parameters. The median number of cases derived from those simulations represented the number of IPD cases expected in the presence of PCV7 but absence of PCV13. The 2.5th

and 97.5th percentiles of those simulations represented the upper and lower 95 percent interval estimates (95% IE) around the point estimates. We then estimated PCV13 impact as the relative difference between expected and actual case counts.

To estimate the number of cases nationally that would have occurred in the absence of PCV13 introduction, we standardized expected cases of IPD to the age and race distribution of the U.S. population.¹⁵ The proportion of expected cases assigned to each race category (white, black, or other) was based on the racial distribution, in each age group, of the observed surveillance cases from 2004–2009. Race data were imputed for about 15% of cases with missing values. We estimated the numbers of cases prevented nationally as the difference between observed surveillance cases standardized to the age and race distribution of the U.S. population and the national estimates of cases in the absence of PCV13 introduction. To estimate total IPD cases prevented during the combined periods of PCV7 and PCV13 use, we used methods previously described.² Briefly, we assumed that rates of IPD during 1998–1999 would have continued through 2012 and applied these rates to population denominators during each year from 2000–2012. We subtracted from those estimates the estimated number of IPD cases occurring nationally during that same period. Deaths averted were calculated by multiplying the median pre-PCV13 age-specific case-fatality rates by the estimated cases prevented nationally.

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Results

During July 2004 through June 2013, we identified 33,688 IPD cases; 89% had serotyping results. The prevalence of at least one underlying condition (apart from age) that is an indication for PCV13 or PPV23^{12,16} increased slightly among children and adults with IPD (Table 1) after the time of PCV13 introduction. The proportions of cases resulting in hospitalization were also marginally higher in the latter period in both groups while case-fatality rates did not change. Finally, the proportions of cases caused by specific clinical syndromes changed modestly in each age group.

During July 2010 through June 2012, mean coverage with 3 PCV13 doses administered before 12 months of age was 76% (range 67%–90%) among age-eligible children; 65% (range 55%–83%) of all age-eligible children received 3 doses of PCV13 administered before 12 months and a booster dose of PCV13 during ages 12 through 18 months. Among children 14–59 months who had received a complete schedule of PCV7, a mean of 63% (range 40%–88%) received the ACIP-recommended supplemental dose of PCV13 during July 2010 through June 2012.

Trends in incidence of IPD

During July 2004 through June 2010, incidence (numbers of cases) of IPD caused by PCV13/nonPCV7 serotypes increased steadily among both children and adults (Figure 1). However, reductions in incidence of PCV13/nonPCV7-serotype IPD among children <5

years old were already evident by the fourth quarter of 2010 and incidence continued to decline through June 2013 (Figure 1). By July 2012–June 2013, overall incidence of IPD declined by 64% (95% interval estimate [IE], 59–68%) in this group while rates of PCV13/nonPCV7-type IPD declined by 93% (95%IE 91–94) (Table 2). Reductions in PCV13/nonPCV7-type IPD became evident among all adult age groups by the fourth quarter of 2011, with the earliest sign of reductions in incidence evident among 18–49 year-olds (Figure 1). Furthermore, we observed reductions in PCV13/nonPCV7-type incidence among 5–17 year-olds (75%, 95%IE 67–80%), the age group with the lowest rate of disease before PCV13 introduction. In all age groups, changes in incidence were driven principally by declines in IPD caused by serotypes 19A and 7F (Supplemental Table and Figure).

IPD caused by serotypes 3 (included in PCV13) and 6C (cross-reactive with 6A antigen of PCV13¹⁷) represented special cases. Serotype 3 caused only 4% of pediatric cases and 9% of adult cases before PCV13 introduction. Incidence of serotype 3 among children was too low and too unstable to develop an adequate time-series model. Among adults 18–49 years old, we identified a 38% (95%IE 15–53%) reduction in serotype 3 IPD during 2011–2012 but this reduction was not sustained in 2012–2013 (2% decline, 95% IE –28, 46). No significant reductions of serotype 3 were observed in any other adult age groups or in any other years (Supplemental Table and Figure). Similarly, we were unable to model serotype 6C among children and we were unable to identify any reductions in serotype 6C among adults (data not shown).

No reductions in serotypes 6A, 1, or 5 were identified as these serotypes were rare, causing only 1.7%, 1.4%, and 0.2%, respectively, of IPD in all age groups before PCV13 introduction. By 2012–2013, the most common serotypes causing IPD among children <5 years old were, in decreasing order, 22F (11%), 33F (10%), 38 (9%), 35B (8%), 15B (7%), 19A (7%), 15C (7%), 3 (6%), 23B (5%), and 12F (4%). Among adults 18 years old, the most common serotypes were 22F (13%), 3 (11%), 7F (6%), 19A (6%), 6C (6%), 12F (5%), 33F (5%), 35B (4%), 16F (4%), and 9N (4%) (Supplemental Table).

With respect to serotype replacement, we did not identify a significant increase in incidence of disease caused by non-PCV13 serotypes, as a group, among children <5 years old (Table 2). Similarly, in most adult age groups, we observed no evidence of serotype replacement. However, among adults 50–64 years-old we detected a 26% increase in non-PCV13-type IPD during 2012–13 compared to what we would have expected in the absence of PCV13 (Table 2, Figure 2). Overall IPD rates among this age group during July 2010 through June 2013 remained 18% (95% IE 11–24%) below those expected in the absence of PCV13. In contrast to the PCV7 experience, no one serotype stood out as causing substantially more disease than any other (Supplemental Table).

Incidence of antibiotic resistant IPD (especially caused by serotype 19A) increased before PCV13 introduction.² In contrast, after PCV13, we identified reductions in penicillin-non-susceptible IPD, erythromycin-non-susceptible IPD, and multiply non-susceptible IPD of 78–96% among children <5 years old. Among adults, penicillin non-susceptible IPD was 50–69% lower than expected during 2012–13, depending on age, while IPD caused by multiply non-susceptible IPD was 50–62% lower (data not shown).

Estimates of cases of disease and deaths prevented in the U.S

We estimated that approximately 10,000 and 20,000 IPD cases may have been prevented among children and adults, respectively, in the first three years of PCV13 introduction. Using a similar approach, we estimated that approximately 3,000 fewer deaths occurred, 97% of these among adults. After incorporating the effects of both PCV7 and PCV13 from 2001 through 2012, we estimate nearly 400,000 cases of IPD and about 30,000 deaths have been prevented with more than half of the cases prevented and nearly 90 percent of the deaths prevented among persons older than 5 years of age (Figure 3).

Discussion

Our analysis demonstrates substantial and rapid reductions in IPD within three years of the introduction of PCV13 in the U.S. The serotypes most affected were those most common before PCV13 introduction, particularly serotypes 19A and 7F, and the age groups that experienced the earliest reductions in PCV13/nonPCV7-type IPD were the groups targeted for vaccination: children less than five years old. These reductions became evident rapidly—within six months of PCV13 introduction—possibly because PCV13 was introduced into the routine infant immunization schedule as a simple replacement for PCV7, a vaccine with over 80 percent coverage by 2008, along with substantial use of the supplemental dose of PCV13 among toddlers and other children <5 years old.¹⁸

We found a reduction in IPD in adults associated with PCV13 introduction in children. In all adult age groups, PCV13/nonPCV7-type IPD (especially serotypes 19A and 7F) declined by 58–72% (comparable to that observed early after PCV7 introduction), leading to overall reductions of IPD of 12–32%. These findings are consistent with the hypothesis that PCV13 prevents nasopharyngeal colonization with serotypes 19A and 7F among children, and therefore, transmission of these types between children and adults.¹⁹ Similar to the experience with PCV7, the reductions we observed among adults became evident very soon—by January 2011 in 18–49 year-olds—after vaccine introduction for children. For these reductions to be attributed to PCV13 use among adults, PCV13 would have to be licensed, recommended, and implemented by early 2011. PCV13 was not licensed for adults until December 2011 and ACIP refrained from recommending its use for adults until October 2012 and, even then, only for adults with immunocompromising conditions.¹² Therefore, we believe that PCV13 use among adults cannot explain our findings. In September 2014, ACIP recommended use of PCV13 for all adults 65 years of age and older but with the caveat that this recommendation should be revisited in 2018,¹³ primarily because of the large indirect effects demonstrated here. Continued monitoring of disease among adults will assist in determining whether this recommendation should be continued.

Comparing the period after PCV13 introduction to the period before, we observed modest increases in case-fatality ratios and in the proportion of cases with underlying conditions. Among pediatric cases, we observed a trend toward reduced prevalence of pneumonia²⁰ compared to other syndromes. Among adults, the proportion of cases resulting in bacteremia declined after PCV13 introduction compared to before. Potential explanations for these changes include differential effects on individual serotypes that may predispose to certain

syndromes and differential effectiveness among children with and without underlying conditions.

We were unable to assess a reduction in IPD caused by serotype 3 (included in PCV13 but not PCV7). One recent publication suggests a reduction in serotype 3 IPD cases seen in 8 pediatric hospitals²¹ while data from a large, national surveillance program in England and Wales suggest no evidence of effectiveness of PCV13 against serotype 3.^{19,20} A recent randomized controlled trial comparing immunogenicity and efficacy of PCV13 and PCV7 against nasopharyngeal colonization suggests no effect of PCV13 on nasopharyngeal colonization with serotype 3.¹⁷ Definitive evidence of effectiveness of PCV13 against serotype 3 colonization and IPD requires more study.

Serotype replacement has been documented since PCV7 introduction.²² A recent review of serotype replacement disease following pneumococcal conjugate vaccine introduction from multiple surveillance programs around the world indicated that serotype replacement would not be expected within two years of PCV13 introduction^{21, 22} Indeed, we observed some evidence of serotype replacement but only among adults 50–64 years of age and only during the third year after PCV13 introduction (Table 2). Early evidence of serotype replacement may be emerging in Europe.²³ Importantly, we did observe reductions in antibiotic nonsusceptible IPD that are largely attributable to reductions in IPD caused by serotype 19A, the serotype associated with increased antibiotic nonsusceptibility before PCV13 introduction^{24, 24} Vaccination is an important tool in combatting antimicrobial resistance.

To quantify the effect of PCV13 introduction, we used a potential outcomes modeling approach^{25,26} with advantages over “before-after” comparisons.² First, rates of serotypes 19A and 7F were increasing in ABCs areas before PCV13 introduction. Therefore, estimates of PCV13 impact would depend, in part, on the arbitrary selection of baseline incidence. A high baseline incidence rate would lead to an overestimate of effect while a low baseline rate would underestimate the effect. Second, our method takes into consideration all data points during the period of observation, not just those chosen as the “before-after” comparison points. Finally, this method leads directly to an estimate of cases prevented, an estimate previously derived indirectly.²

Our analysis does have certain limitations. For children who had already received a full series of PCV7, a single supplemental dose of PCV13 was recommended^{27, 27} We are unable to assess the relative contributions of the full 4-dose series vs. the supplemental dose. Our model assumed that the incidence of IPD caused by PCV13/nonPCV7 serotypes would have continued increasing after PCV13 introduction. While this assumption is reasonable for the first 2–3 years after introduction, experience with epidemics of serotype 1 suggests that some population-level immunity is achieved within a few years after the epidemic starts. Thus, we cannot expect that rates of PCV13/nonPCV7-type IPD would have continued to increase indefinitely. Additionally, as with any national estimates from limited geographical surveillance, it is possible the ABCs areas are not fully representative of the entire country. However, given the high variability in ABCs areas with respect to geography, socio-economic status, and urbanicity, this is unlikely to change our conclusions substantially.

In summary, PCV13 has already demonstrated dramatic reductions in IPD among children and, through herd protection, adults. In the first three years alone, an estimated 30,000 cases of invasive disease and 3,000 deaths have been prevented. The continued success of the pediatric PCV13 program will be critical for policy-making related to the recently adopted age-based recommendations for PCV13 in adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel: Research in Context

Systematic Review

We searched PubMed using the search terms “13-valent pneumococcal conjugate vaccine” and “invasive pneumococcal”. We identified 138 papers published from 1 January 2012 (two years after PCV13 became available) through 8 October 2014. Of these, two^{23,28} described stable, population-based surveillance programs with high proportions of isolates collected from all ages captured. Both reports described substantial PCV13 impact using two doses in the first year of life and a booster dose in the second year of life. An additional publication demonstrates impact of PCV13 in the U.S. during the first two years²⁰. However, these findings are based on medical claims data without the additional support of serotype data to confirm serotype-specific effects. None of these reports present findings beyond two years post-PCV13 introduction.

Interpretation

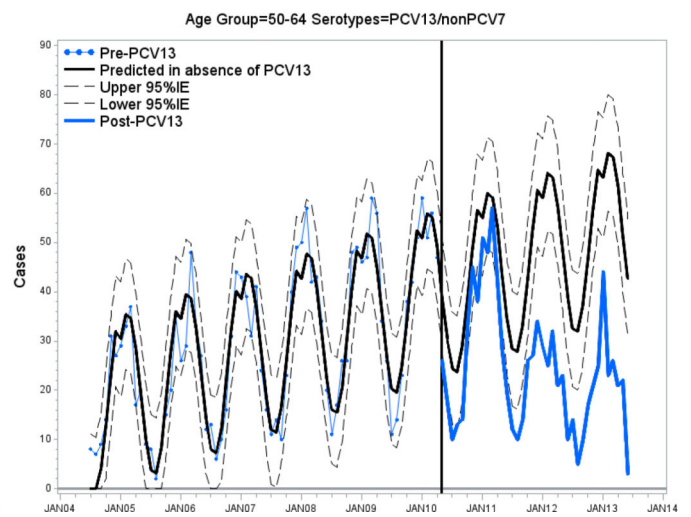
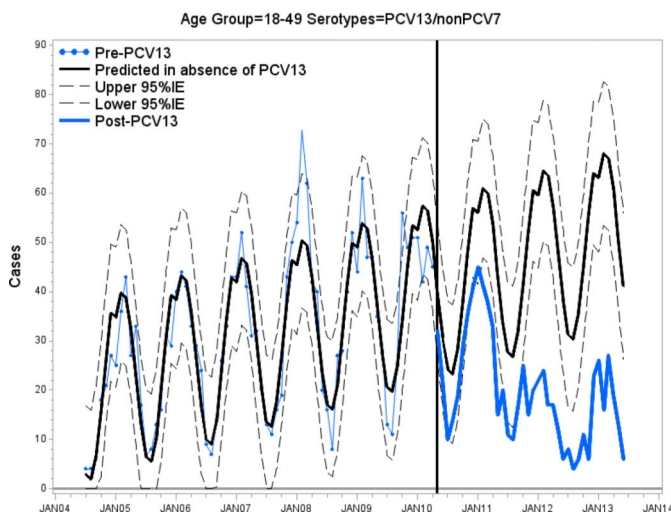
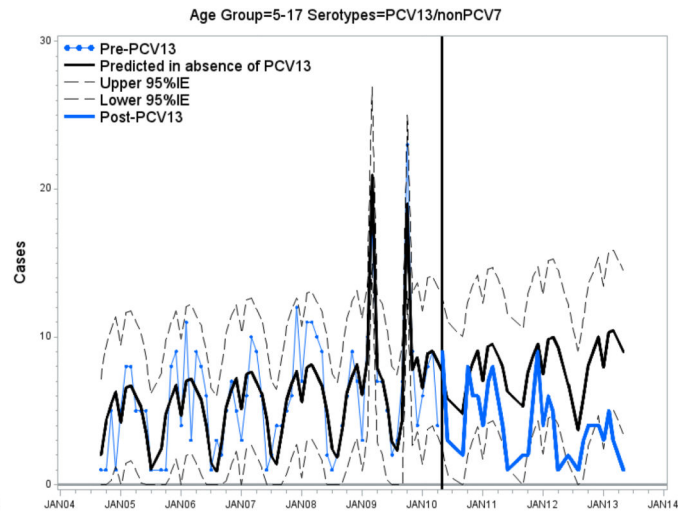
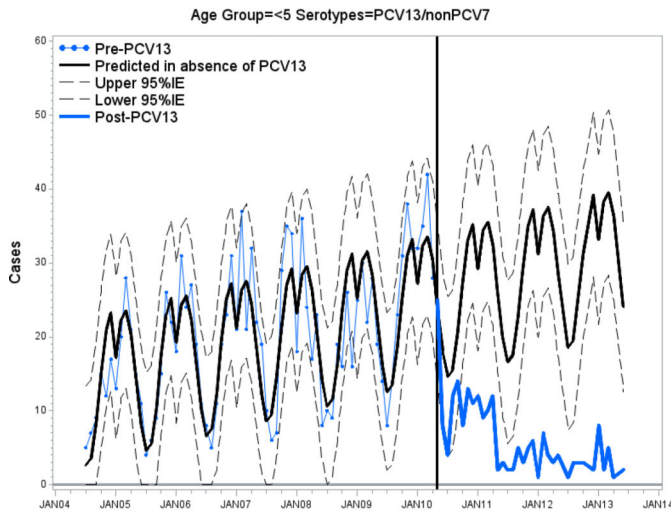
Our study adds key findings related to the introduction of PCV13 using the four-dose schedule licensed in the U.S. and many other countries. Because rates of IPD caused by the PCV13/nonPCV7 serotypes were increasing in the U.S. before PCV13 introduction, our study shows how introduction of an expanded valency vaccine can reverse increases associated with serotype replacement and ultimately reduce further the incidence of IPD. Our findings among unvaccinated persons also serves to inform national immunization policy, especially the potential short-term use of PCV13 among older adults.

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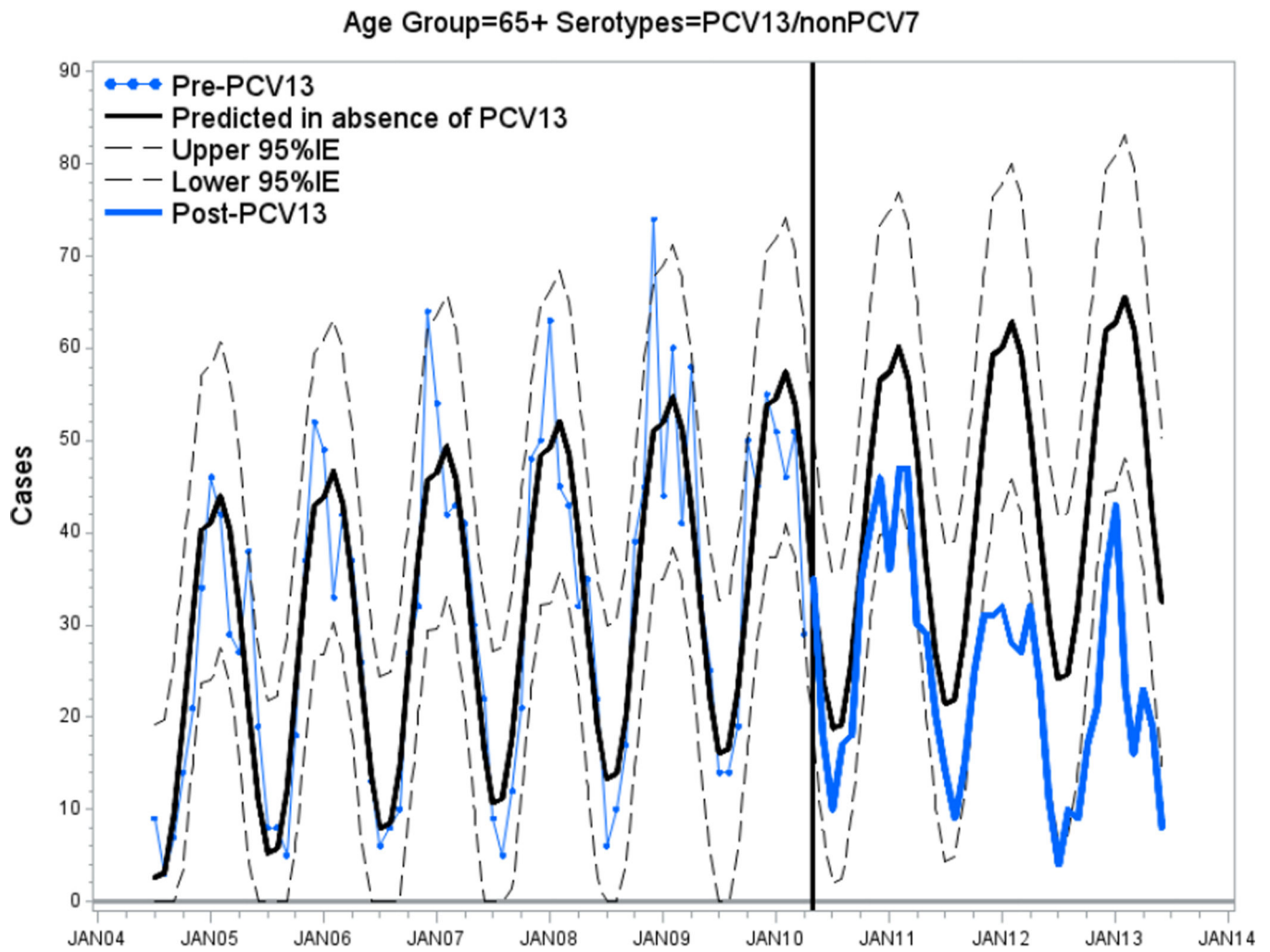
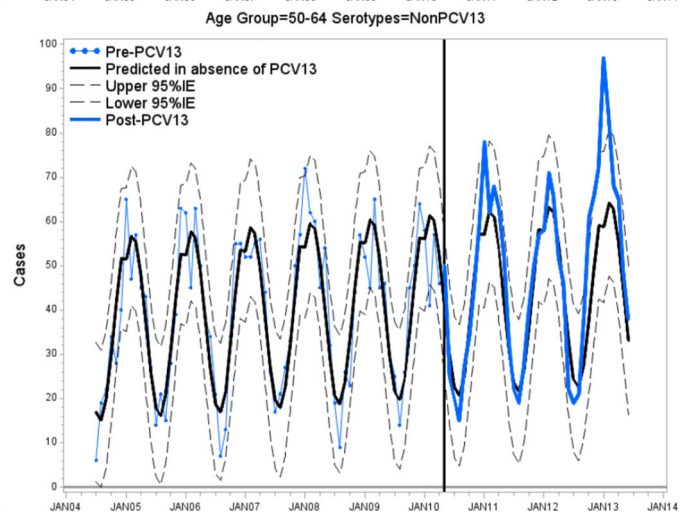
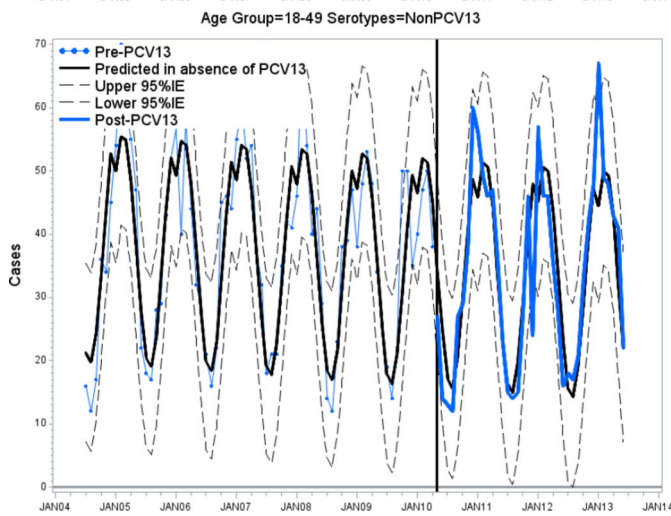
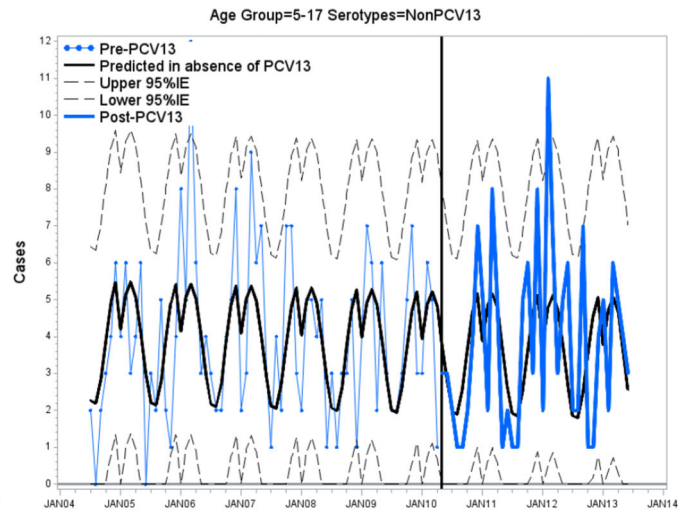
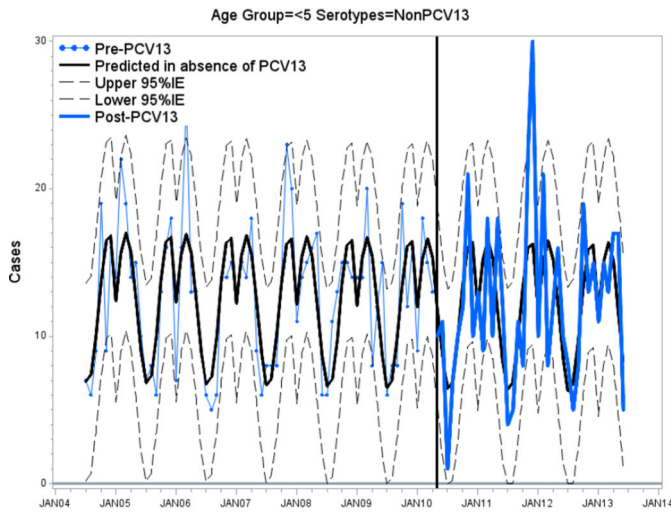


Figure 1. Modeled and observed cases of PCV13/nonPCV7-type IPD, by age and date of culture, July 2004 through June 2013. Vertical black line indicates introduction of PCV13 for children.



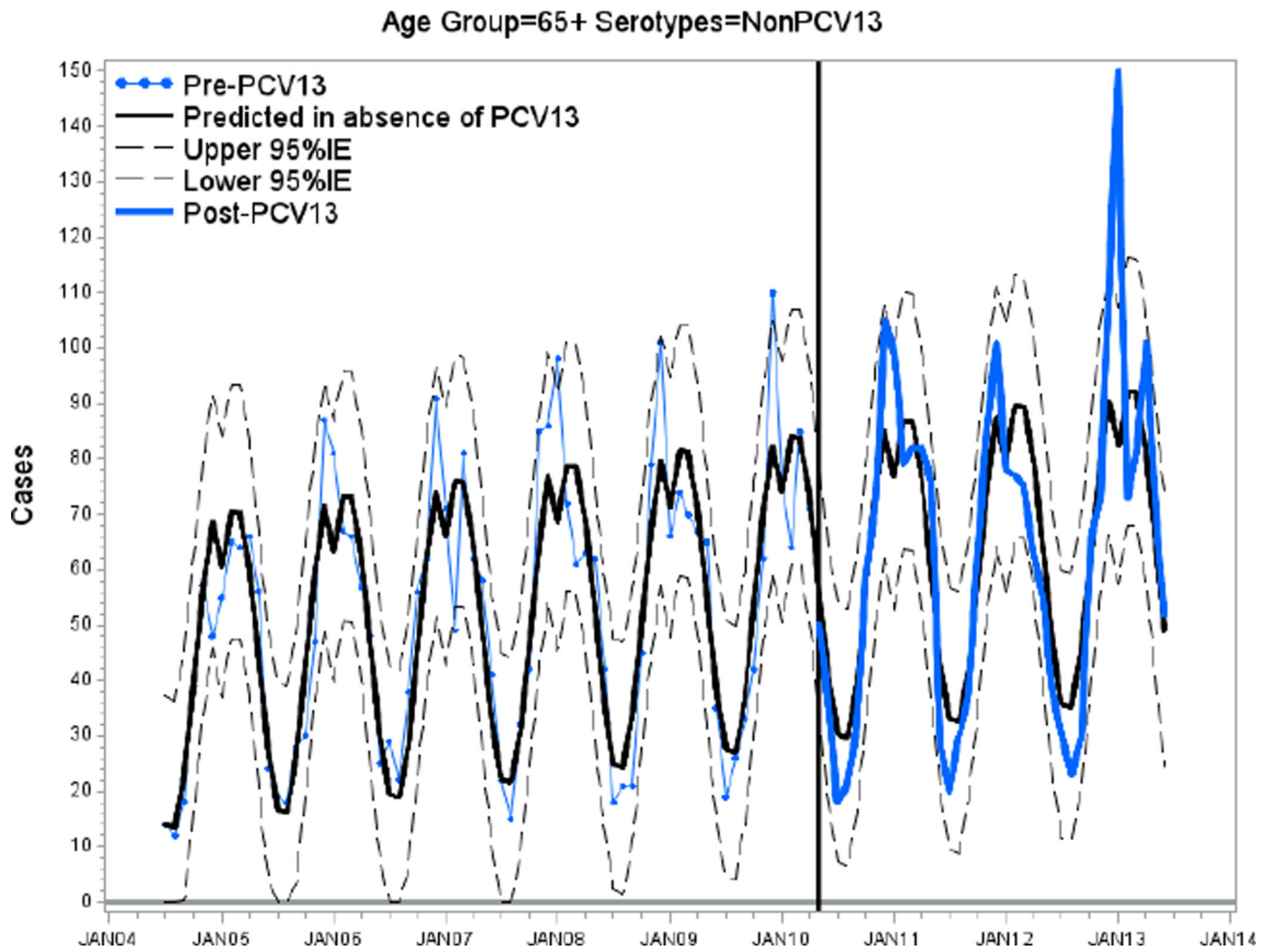
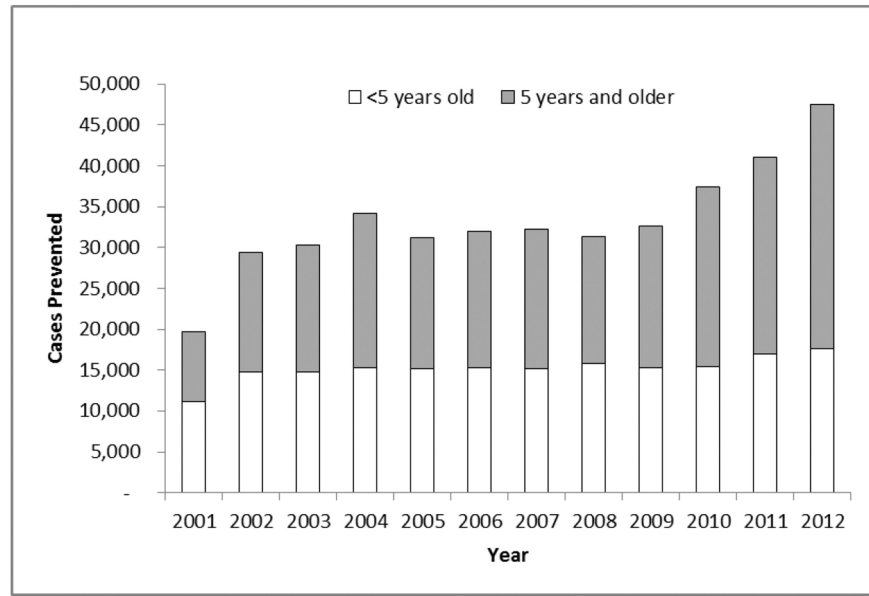


Figure 2. Modeled and observed cases of non-PCV13-type IPD, by age and date of culture, July 2004 through June 2013. Vertical black line indicates introduction of PCV13 for children.

A



B

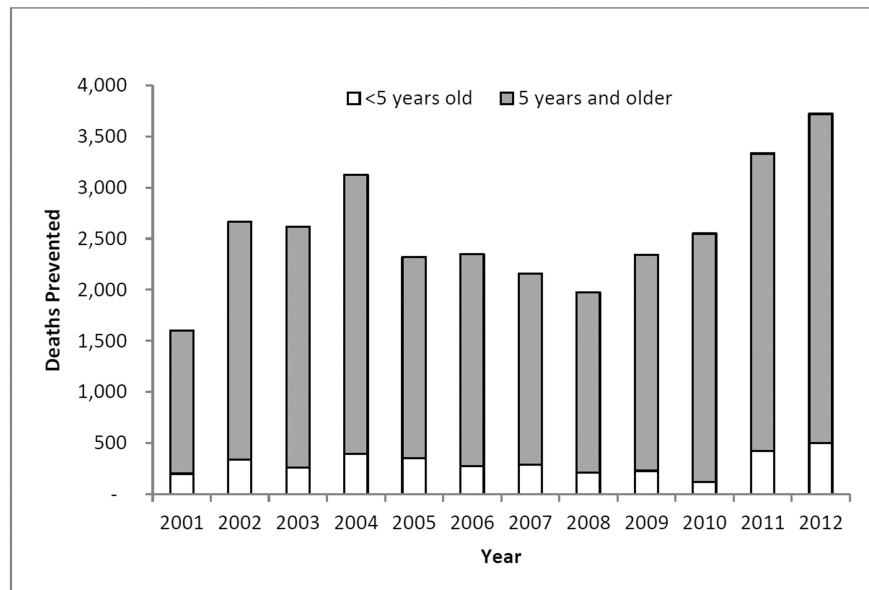


Figure 3. Estimated national cases of IPD (Panel A) and deaths (Panel B) prevented following introduction of PCV7 (2000) and PCV13 (2010) for children in the U.S.

Table 1

Descriptive Epidemiologic Features of Cases of Invasive Pneumococcal Disease, 1 July 2010 through 30 June 2013 vs. 1 July 2004 through 30 June 2010, ABCs sites.

Characteristic	1 July 2004 – 30 June 2010 Pre-PCV13 Introduction	1 July 2010 – 30 June 2013 Post-PCV13 Introduction	P-value
Age, years	N (%)	N (%)	
<2	1833 (7.7)	426 (4.3)	<0.0001
2–4	995 (4.2)	285 (2.9)	
5–17	875 (3.7)	273 (2.8)	
18–49	6,274 (26.3)	2,234 (22.7)	
50–64	6,284 (26.3)	2,994 (30.5)	
65+	7,596 (31.8)	3,618 (36.8)	
Total	23,858 (100)	9,830 (100)	
Male, Cases / Total (%)	12,513/23,831 (52.5)	5,092/9,820 (51.9)	0.28
Prevalence of any underlying condition that is an indication for PPV23 [*] , by age in years, Cases / Total (%)			
<18	620/3,703 (16.7)	200/894 (20.3)	0.009
18	14,656/20,155 (72.7)	6,766/8,846 (76.5)	<0.0001
Cases resulting in hospitalization, by age in years, Cases / Total (%)			
<18	2,313/3,683 (62.8)	692/974 (71.0)	<0.0001
18	18,593/20,100 (92.5)	8,319/8,785 (94.7)	<0.0001
Fatal cases, by age in years, Cases / Total (%)			
<18	61/3,698 (1.7)	26/971 (2.7)	0.04
18	2,383/20,145 (11.8)	1,023/8,771 (11.7)	0.69
Cases of IPD caused by groups of or individual pneumococcal serotypes, children <5 years old, Cases (%) [†]			
PCV7 types	102 (4.2)	17 (2.7)	<0.0001
PCV13/nonPCV7 types	1,427 (58.5)	179 (28.1)	
PPV11 types	460 (18.9)	235 (36.8)	
Non-PCV13, Non-PPV23 types	449 (18.4)	207 (32.5)	
Total	2,438 (100)	638 (100)	
Cases of IPD associated with specified clinical syndromes, by age, Cases / Total (%)			
<18			
Bacteremia	1,558 / 3,283 (47.5)	404 / 844 (47.9)	P=0.005
Pneumonia	1,417 / 3,283 (43.2)	331 / 844 (39.2)	
Meningitis	308 / 3,283 (9.4)	109 / 844 (12.9)	
18			
Bacteremia	3,446 / 19,222 (17.9)	1,155 / 8,188 (14.1)	P<0.0001

Characteristic	1 July 2004 – 30 June 2010 Pre-PCV13 Introduction	1 July 2010 – 30 June 2013 Post-PCV13 Introduction	P-value
Pneumonia	14,698 / 19,222 (76.5)	6,500 / 8,188 (79.4)	
Meningitis	1,078 / 19,222 (5.6)	533 / 8,188 (6.5)	

* Based on ACIP recommendations for children^{7,8} and adults.^{12,13}

[†] PCV7 types include 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A. PCV13/nonPCV7 types include 1, 3, 5, 7F, and 19A. PPV11 types include 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F.

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Table 2

Percent difference between incidence expected in the absence of PCV13 and incidence observed in the indicated year, by Age, ABCs sites.

Age group, years	Serotypes	Percent difference in incidence (95% IE)		
		2010–11	2011–12	2012–13
<5	All	-45 (-50, -40)	-58 (-63, -53)	-64 (-68, -59)
	PCV13/nonPCV7	-66 (-70, -61)	-88 (-89, -86)	-93 (-94, -91)
	Non-PCV13	-4 (-16, 12)	7 (-9, 31)	-2 (-19, 27)
5–17	All	-33 (-45, -18)	-36 (-49, -16)	-53 (-64, -35)
	PCV13/nonPCV7	-33 (-45, -21)	-59 (-66, -48)	-75 (-80, -67)
	Non-PCV13	-11 (-31, 25)	32 (-2, 110)	-2 (-32, 80)
18–49	All	-12 (-20, -5)	-37 (-43, -30)	-32 (-40, -22)
	PCV13/nonPCV7	-33 (-38, -26)	-64 (-68, -60)	-72 (-75, -69)
	Non-PCV13	3 (-6, 15)	-10 (-20, 4)	13 (-2, 34)
50–64	All	-8 (-14, -2)	-28 (-33, -22)	-18 (-26, -10)
	PCV13/nonPCV7	-23 (-28, -18)	-54 (-57, -50)	-62 (-65, -59)
	Non-PCV13	8 (0, 18)	0 (-9, 12)	26 (13, 44)
65	All	-6 (-14, 3)	-19 (-27, -9)	-12 (-22, 1)
	PCV13/nonPCV7	-23 (-31, -13)	-46 (-52, -39)	-58 (-64, -52)
	Non-PCV13	1 (-6, 10)	-7 (-15, 3)	7 (-4, 20)