Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance

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Summary

Background **In 2000, seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the USA and resulted in dramatic reductions in invasive pneumococcal disease (IPD) and moderate increases in non-PCV7 type IPD. In 2010, PCV13 replaced PCV7 in the US immunisation schedule. We aimed to assess the effect of use of PCV13 in children on IPD in children and adults in the USA.**

Methods **We used laboratory-based and population-based data on incidence of IPD from the Active Bacterial Core surveillance (part of the Centers for Disease Control and Prevention's Emerging Infections Program) in a time-series model to compare rates of IPD before and after the introduction of PCV13. Cases of IPD between July 1, 2004, and June 30, 2013, were classified as being caused by the PCV13 serotypes against which PCV7 has no effect (PCV13 minus PCV7). In a time-series model, we used an expected outcomes approach to compare the reported incidence of IPD to that which would have been expected if PCV13 had not replaced PCV7.**

Findings **Compared with incidence expected among children younger than 5 years if PCV7 alone had been continued, incidence of IPD overall declined by 64% (95% interval estimate [95% IE] 59–68) and IPD caused by PCV13 minus PCV7 serotypes declined by 93% (91–94), by July, 2012, to June, 2013. Among adults, incidence of IPD overall also declined by 12–32% and IPD caused by PCV13 minus PCV7 type IPD declined by 58–72%, depending on age. We estimated that over 30 000 cases of IPD and 3000 deaths were averted in the first 3 years after the introduction of PCV13.**

Interpretation **PCV13 reduced IPD across all age groups when used routinely in children in the USA. These findings provide reassurance that, similar to PCV7, PCVs with additional serotypes can also prevent transmission to unvaccinated populations.**

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Introduction

Streptococcus pneumoniae, or pneumococcus, is a major cause of morbidity and mortality worldwide. In 2000, a seven-valent pneumococcal conjugate vaccine (PCV7, Prevnar, Wyeth [Collegeville, PA, USA]) was introduced into the routine infant immunisation programme in the USA, with a schedule of doses at 2, 4, 6, and 12–15 months of age.[1] After the introduction of the vaccine, rates of invasive pneumococcal disease (IPD) caused by PCV7 serotypes declined substantially among children.[2] 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 outpatient visits[3] and pneumonia hospital admissions.[4] During subsequent years, serotype replacement resulted in increases in non-PCV7 type IPD that were moderate compared with the reductions in PCV7 type IPD.[5] Despite these reductions, pneumococcus caused about 4 million episodes of disease in the USA in 2004, resulting in US$7·7 billion in direct and indirect costs.[6]

In 2010, a 13-valent conjugate vaccine (PCV13 (Prevnar-13, Pfizer, New York, NY, USA) replaced PCV7.[7,8] PCV13 included serotypes that caused replacement disease in the USA and was licensed without a randomised clinical trial. Therefore, after-licensure assessment was the first opportunity to measure the effects of PCV13 on prevention of IPD. In this study, we aimed to assess the population-level effect of PCV13 on incidence of IPD across all age groups and whether the introduction of PCV13 was associated with serotype replacement.

Methods

Study design

We used a long-standing surveillance system to compare rates of IPD before and after the introduction of PCV13. We identified IPD cases through Active Bacterial Core surveillance (ABCs), an active population-based and

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laboratory-based surveillance system that is part of the Centers for Disease Control and Prevention's (CDC's) Emerging Infections Program. ABCs methods are described in full elsewhere.[9] We included cases identified from July 1, 2004, to June 30, 2013, in ten continuously participating ABCs sites in the USA: 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.

ABCs case reporting and isolate collection were regarded as 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.

Procedures

We defined IPD cases as isolation of *S pneumoniae* from normally sterile sites (eg, blood and cerebrospinal fluid). We undertook laboratory audits at least every 6 months to ensure completeness of reporting. PCR for diagnosis of IPD is not uniformly available in the USA and such cases are not captured by ABCs. We reviewed medical records to obtain demographic and clinical information. Isolates were serotyped by Quellung at the CDC's Streptococcus Laboratory (Atlanta, GA, USA) or the Minnesota Department of Health Laboratory (St Paul, MN, USA). We assigned serotypes to the following categories: (1) PCV7 types (4, 6B, 9V,.0.0...0.... 14, 18C, 19F, 23F, and 6A); (2) PCV13 minus PCV7 types (serotypes 19A, 7F, 5, 3, and 1, which are included in PCV13 but are not affected by PCV7); (3) 23-valent penumococcal polysaccharide vaccine (PPV23) minus PCV13 types (serotypes included in PPV23 [Pneumovax 23, Merck, Whitehouse Station, NJ, USA], 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 PCV7.[10] We did antimicrobial susceptibility testing against penicillin, erythromycin, clindamycin, sulfamethoxazole-trimethoprim, tetracycline, chloramphenicol, levofloxacin, and vancomycin using broth microdilution, and we classified isolates as susceptible, intermediate, or resistant according to published guidelines.[11] We used meningitis breakpoints for penicillin for meningitis cases; non-meningitis breakpoints were used for all other cases. For all antibiotics, we combined intermediate and fully resistant strains into a non-susceptible category. Any isolate non-susceptible to three or more classes was deemed multiply non-susceptible.

We calculated case-fatality rates as the proportion of cases with fatal outcomes among those with known outcomes (>99% of all cases). Comorbid disorders were collected as per the ABCs protocol[12] and classified according to recommendations of the Advisory Committee on Immunization Practices (ACIP).[13,14]

We estimated vaccination coverage using immunisation information systems, which are confidential, population-based systems that consolidate data from vaccine providers. As a proxy for coverage in ABCs areas, we used immunisation information system sentinel sites located in Michigan, Minnesota, North Dakota, New York, Oregon, and Wisconsin, which collectively include about 2·0 million children younger than 5 years. We used SAS (version 9.3, SAS Institute, Cary, NC, USA) and Excel 2010 (Microsoft, Redmond, WA, USA) to calculate unweighted intra-site mean PCV13 coverage on the basis of 2011 post-census population estimates and vaccination records from immunisation information system sentinel sites (queried Feb 2, 2013). PCV13 primary series coverage estimates included doses of PCV13 administered before age 12 months to children born between July 1, 2010, and July 1, 2011. Coverage estimates of PCV13 booster doses after primary vaccination included doses of PCV13 administered before age 19 months to children born between July 1, 2010, and Dec 1, 2010. PCV13 supplemental dose estimates included PCV13 doses administered to children aged 14–59 months born July 1, 2007, to May 1, 2009, who previously completed a routine or catch-up schedule recommended by the ACIP.[15]

Statistical analysis

We fitted the monthly case counts, during the period before introduction of PCV13, from July 1, 2004, to June 30, 2010, to time-series models. We developed separate models for each age group (<5, 5–17, 18–49, 50–64, and ≥65 years) and for ten serotype groups (all serotypes; PCV13 minus PCV7 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 non-linear 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:

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

The outlier indicator flagged six unusual events, including five associated with the influenza pandemic of 2009. The parameter estimates from the before vaccine time-series model and their variance provided a predictive distribution for time-series model parameters for after the introduction of PCV13. Each month, from July, 2010, to 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 these 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% interval estimates (95% IEs) around the point estimates. We then estimated PCV13 effect as the difference between expected and actual case counts.

To estimate the number of cases nationally that would have occurred without the introduction of PCV13, we standardised expected cases of IPD to the age and race distribution of the US population.[16] 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 recorded surveillance cases from 2004 to 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 reported surveillance cases standardised to the age and race distribution of the US population and the national estimates of cases in the absence of introduction of PCV13. To estimate total IPD cases prevented during the combined periods of PCV7 and PCV13 use, we used previously described methods.[2] Briefly, we assumed that rates of IPD during 1998–99 would have continued until 2012 and applied these rates to population denominators during each year from 2000 to 2012. We subtracted from those estimates the estimated number of IPD cases occurring nationally during the same period. We calculated deaths averted by multiplying the median age-specific case-fatality rates before the introduction of PCV13 by the estimated cases prevented nationally.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 1, 2004, and June 30, 2013, we identified 33 688 people with IPD, 30 014 (89%) of whom had serotyping results. The prevalence of at least one risk factor (apart from age) that is an indication for PCV13 or PPV23[7,13] increased among children (p=0·009) and adults (p<0·0001) with IPD after the introduction of PCV13 (table 1). The proportions of cases resulting in hospital admission were also higher in the latter period in both groups (both p<0·0001), whereas case-fatality rates did not change (children p=0·04 and adults p=0·69). Finally, the proportion of cases caused by specific clinical syndromes changed in both age groups (children p=0·005 and adults p<0·0001).

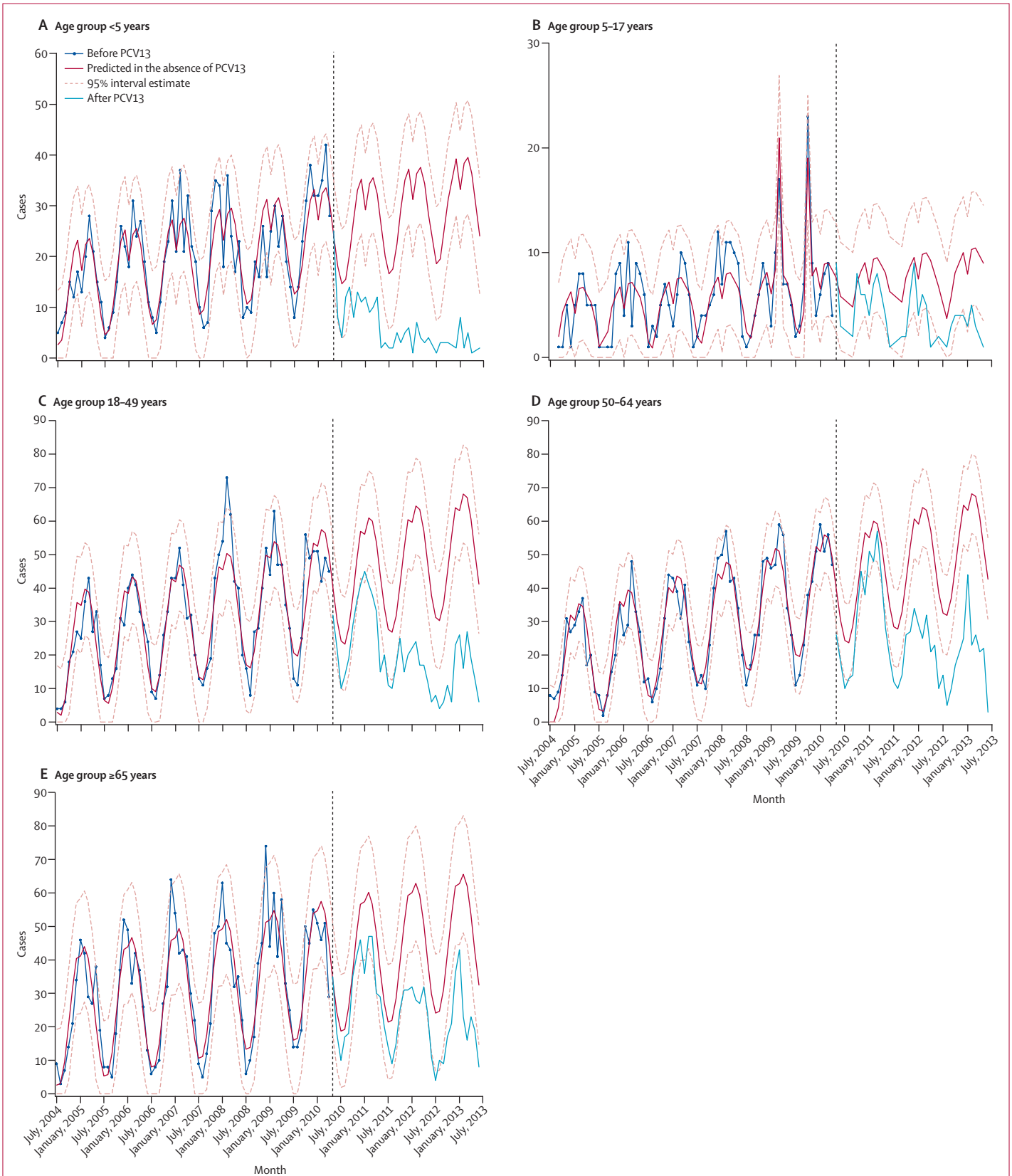
Between July 1, 2010, and June 30, 2012, mean coverage with at least three PCV13 doses administered before age 12 months was 76% (range 67–90) among age-eligible children; 65% (55–83) of all age-eligible children received at least three doses of PCV13 before age 12 months and a booster dose of PCV13 during ages 12–18 months. Among children aged 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 between July, 2010, and June, 2012.

Between July 1, 2004, and June 30, 2010, incidence of IPD caused by PCV13 minus PCV7 serotypes increased steadily across all age groups (figure 1). However, reductions in incidence of PCV13 minus PCV7 serotype

	Before the introduction of PCV13 (n=23 858)	After the introduction of PCV13 (n=9830)	p value
Age (years)			
<2	1833 (8%)	426 (4%)	<0·0001
2–4	995 (4%)	285 (3%)	..
5–17	875 (4%)	273 (3%)	..
18–49	6274 (26%)	2234 (23%)	..
50–64	6284 (26%)	2994 (30%)	..
≥65	7597 (32%)	3618 (37%)	..
Sex			
Male	12 513/23 831 (53%)	5092/9820 (52%)	0·28
Female	11 318/23 831 (47%)	4728/9820 (48%)	..
Any risk factor (apart from age) that is an indication for PPV23*			
<18 years	620/3703 (17%)	200/984 (20%)	0·009
≥18 years	14 656/20 155 (73%)	6766/8846 (76%)	<0·0001
Cases resulting in hospital admission			
<18 years	2313/3683 (63%)	692/974 (71%)	<0·0001
≥18 years	18 593/20 100 (93%)	8319/8785 (95%)	<0·0001
Case-fatality rate			
<18 years	61/3698 (2%)	26/971 (3%)	0·04
≥18 years	2383/20 145 (12%)	1023/8771 (12%)	0·69
Cases of IPD caused by groups of or individual pneumococcal serotypes in children <5 years old†			
PCV7 types	102/2438 (4%)	17/638 (3%)	<0·0001
PCV13 minus PCV7 types	1427/2438 (59%)	179/638 (28%)	..
PPV23 minus PCV13 types	460/2438 (19%)	235/638 (37%)	..
Non-PCV13 and non-PPV23 types	449/2438 (18%)	207/638 (32%)	..
Cases of IPD associated with specified clinical syndromes			
<18 years			
Bacteraemia	1558/3283 (47%)	404/844 (48%)	0·005
Pneumonia	1417/3283 (43%)	331/844 (39%)	..
Meningitis	308/3283 (9%)	109/844 (13%)	..
≥18 years			
Bacteraemia	3446/19 222 (18%)	1155/8188 (14%)	<0·0001
Pneumonia	14 698/19 222 (76%)	6500/8188 (79%)	..
Meningitis	1078/19 222 (6%)	533/8188 (7%)	..

Data are number (%) or n/N (%). Some percentages do not total 100 because of rounding. IPD=invasive pneumococcal disease. PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine. PPV23=23-valent pneumococcal polysaccharide vaccine. *Based on Advisory Committee on Immunization Practices recommendations for children[7,8] and adults.[13,14] †PCV7 types consist of 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A. PCV13 minus PCV7 types consist of 1, 3, 5, 7F, and 19A. PPV23 minus PCV13 types consist of 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F.

Table 1: **Epidemiological features of cases of invasive pneumococcal disease before versus after introduction of 13-valent pneumococcal conjugate vaccine**



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IPD among children younger than 5 years were already evident by the fourth quarter of 2010 and incidence continued to decline to June, 2013 (figure 1). Compared with what would have been predicted in the absence of PCV13, overall incidence of IPD in June, 2013, was 64% (95% IE 59–68) lower in this group, whereas incidence of PCV13 minus PCV7 type IPD was 93% (91–94) lower (table 2). Reductions in PCV13 minus PCV7 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, between July, 2012, and June, 2013, we noted a 75% (95% IE 67–80) reduction in incidence of PCV13 minus PCV7 type IPD among 5–17-year-olds—the age group with the lowest rate of disease before introduction of PCV13. In all age groups, changes in incidence were driven principally by declines in IPD caused by serotypes 19A and 7F (appendix).

IPD caused by serotypes 3 (included in PCV13) and 6C (cross-reactive with the 6A antigen of PCV13)[17] represented special cases. Serotype 3 caused only 133 (4%) of 3025 paediatric cases and 1552 (9%) of 17 844 adult cases before the introduction of PCV13. Incidence of serotype 3 among children before the introduction of PCV13 was too low and too inconsistent to develop an adequate time-series model. Among adults aged 18–49 years, we identified a 38% (95% IE 15–53) reduction in serotype 3 IPD during 2011–12, but this reduction was not sustained in 2012–13 (2% decline, 95% IE –28 to 46). No significant reductions of serotype 3 were noted in any other adult age groups or in any other years (appendix). 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 because these serotypes were rare, causing only 365 of 21 049 (1·7%), 294 of 21 049 (1·4%), and 33 of 21 049 (0·2%), respectively, of IPD in all age groups before the introduction of PCV13. By 2012–13, the most common serotypes causing IPD among children younger than 5 years were, in decreasing order, 22F (20 of 177 [11%]), 33F (17 [10%]), 38 (16 [9%]), 35B (14 [8%]), 15B (13 [7%]), 19A (13 [7%]), 15C (12 [7%]), 3 (ten [6%]), 23B (nine [5%]), and 12F (seven [4%]). Among adults aged at least 18 years, the most common serotypes were 22F (339 of 2672 [13%]), 3 (288 [11%]), 7F (165 [6%]), 19A (161 [6%]), 6C (152 [6%]), 12F (124 [5%]), 33F (121 [5%]), 35B (113 [4%]), 16F (111 [4%]), and 9N (110 [4%]; appendix).

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 younger than 5 years (table 2). Similarly, in most adult age groups, we noted no evidence of serotype replacement. However, among adults 50–64 years old, we detected a 26% increase (95% IE 13–44) in non-PCV13 type IPD during 2012–13 compared with what we would have been expected in the absence of PCV13 (table 2; figure 2). Overall IPD rates among this age group for the same period were 18% (95% IE 10–26) below those expected in the absence of PCV13. By contrast with the PCV7 findings, no non-PCV13 serotype stood out as causing substantially more disease than any other (appendix).

Incidence of antibiotic-resistant IPD (especially caused by serotype 19A) increased before the introduction of PCV13.[2] By 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 younger than 5 years. Among adults, penicillin non-susceptible IPD was 50–69% lower than expected during 2012–13, depending on age, whereas IPD caused by multiply non-susceptible IPD was 50–62% lower (data not shown).

We estimated that about 10 000 IPD cases among children and 20 000 cases among adults were probably prevented in the first 3 years after introduction of PCV13. We also estimated that about 3000 fewer deaths occurred, an estimated 97% of which were among adults. After incorporating the effects of both PCV7 and PCV13 from 2001 to 2012, we estimate that nearly 400 000 cases of IPD and about 30 000 deaths were probably prevented, with more than half of the cases prevented and nearly 90% of

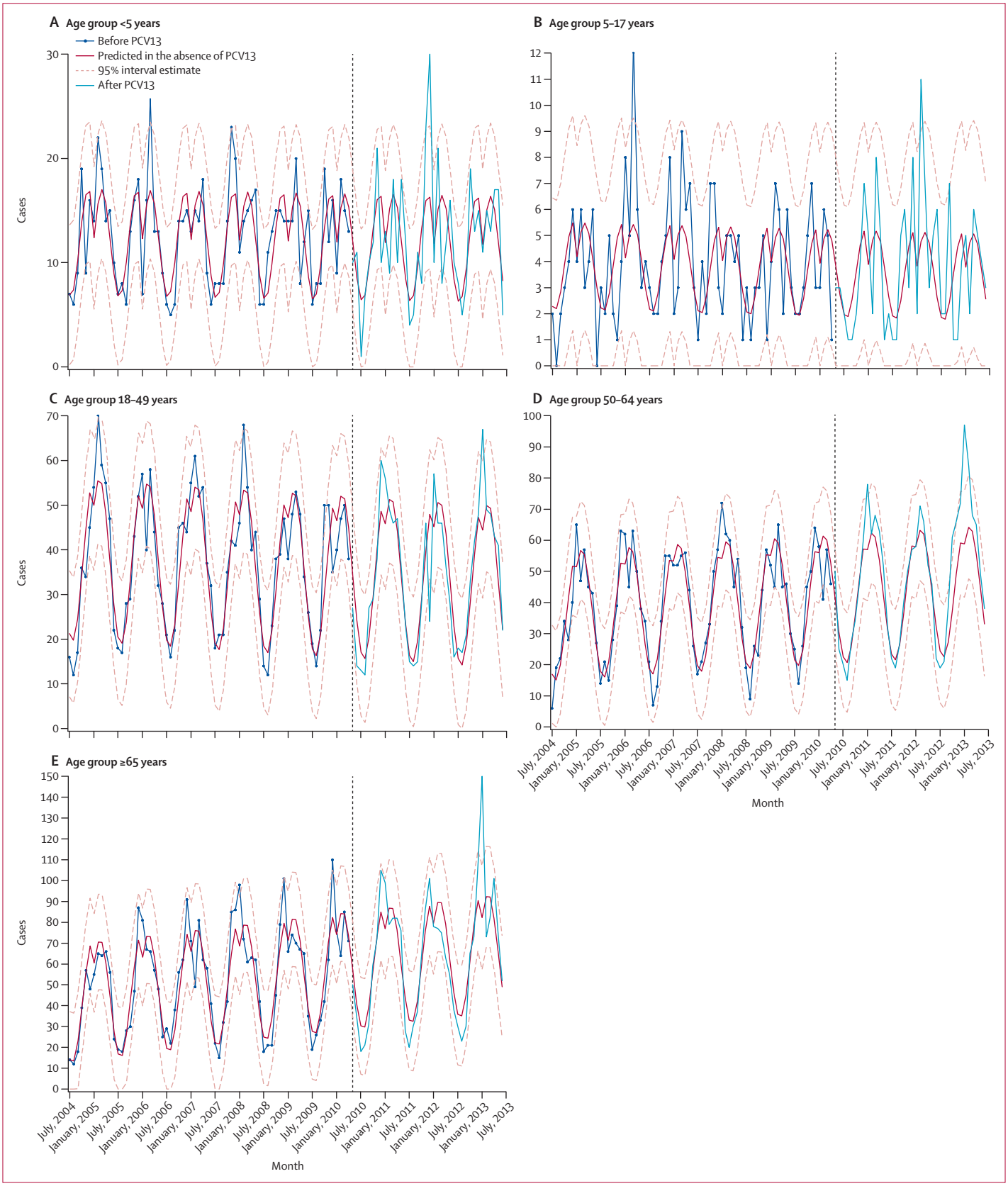
	2010–11*	2011–12*	2012–13*
<5 years			
All	−45% (−50 to −40)	−58% (−63 to −53)	−64% (−68 to −59)
PCV13 minus PCV7	−66% (−70 to −61)	−88% (−89 to −86)	−93% (−94 to −91)
Non-PCV13	−4% (−16 to 12)	7% (−9 to 31)	−2% (−19 to 27)
5–17 years			
All	−33% (−45 to −18)	−36% (−49 to −16)	−53% (−64 to −35)
PCV13 minus PCV7	−33% (−45 to −21)	−59% (−66 to −48)	−75% (−80 to −67)
Non-PCV13	−11% (−31 to 25)	32% (−2 to 110)	−2% (−32 to 80)
18–49 years			
All	−12% (−20 to −5)	−37% (−43 to −30)	−32% (−40 to −22)
PCV13 minus PCV7	−33% (−38 to −26)	−64% (−68 to −60)	−72% (−75 to −69)
Non-PCV13	3% (−6 to 15)	−10% (−20 to 4)	13% (−2 to 34)
50–64 years			
All	−8% (−14 to −2)	−28% (−33 to −22)	−18% (−26 to −10)
PCV13 minus PCV7	−23% (−28 to −18)	−54% (−57 to −50)	−62% (−65 to −59)
Non-PCV13	8% (0 to 18)	0% (−9 to 12)	26% (13 to 44)
≥65 years			
All	−6% (−14 to 3)	−19% (−27 to −9)	−12% (−22 to 1)
PCV13 minus PCV7	−23% (−31 to −13)	−46% (−52 to −39)	−58% (−64 to −52)
Non-PCV13	1% (−6 to 10)	−7% (−15 to 3)	7% (−4 to 20)

Data are difference in incidence (95% interval estimate). PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine. *July 1 to June 30.

***Table 2*: Difference between incidence expected in the absence of 13-valent pneumococcal conjugate vaccine and that noted after introduction of the vaccine**

See Online for appendix

***Figure 1*: Modelled and noted cases of 13-valent minus seven-valent pneumococcal conjugate vaccine type invasive pneumococcal disease**
Vertical black lines show the introduction of PCV13 for children. PCV13=13-valent pneumococcal conjugate vaccine.



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the deaths prevented among people older than 5 years (figure 3).

Discussion

Our analysis shows there were substantial and rapid reductions in IPD within 3 years of the introduction of PCV13 in the USA. The serotypes most affected were those most common before introduction of PCV13, particularly serotypes 19A and 7F. Also, the age groups that experienced the earliest reductions in PCV13 minus PCV7 type IPD were those targeted for vaccination: children younger than 5 years. These reductions became evident rapidly—within 6 months after introduction of PCV13—possibly because PCV13 was introduced into the routine infant immunisation schedule as a replacement for PCV7—a vaccine with over 80% coverage by 2008[18]—and because of substantial use of the supplemental dose of PCV13 among toddlers and other children younger than 5 years.[19]

We found a reduction in IPD in adults associated with introduction of PCV13 in children. In all adult age groups, PCV13 minus PCV7 type IPD (especially serotypes 19A and 7F) declined by 58–72%, which is comparable with that reported early after the introduction of PCV7, leading to overall reductions in IPD of 12–32%. These findings are consistent with the hypothesis that PCV13 prevents nasopharyngeal colonisation with serotypes 19A and 7F among children and, therefore, prevents transmission of these types between children and adults.[20] Similar to the experience with PCV7, the reductions that we noted among 18–49-year-olds became evident very soon—by January, 2011—after introduction of the vaccine for children. For these reductions to be attributed to PCV13 use among adults, PCV13 would have to have been 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 disorders.[13] Therefore, we believe that PCV13 use among adults cannot explain our findings. In September, 2014, ACIP recommended use of PCV13 for all adults aged at least 65 years, but with the caveat that this recommendation should be revisited in 2018,[14] primarily because of the large indirect effects reported herein. Continued monitoring of disease among adults will assist in identifying whether this recommendation should be continued.

Comparing the period after introduction of PCV13 to the period before, we noted slight increases in case-fatality rates and in the proportion of cases with underlying disorders. Among paediatric cases, we noted a numerically reduced prevalence of pneumonia[21] compared with other syndromes. Among adults, the proportion of cases resulting in bacteraemia declined after introduction of PCV13 compared with before. Potential explanations for these changes include differential effects on individual serotypes that might predispose to specific syndromes and differential effectiveness among children with and without underlying disorders.

We were unable to identify a reduction in IPD caused by serotype 3 (included in PCV13 but not in PCV7). Findings from another publication suggest that there was a reduction in serotype 3 IPD cases in eight paediatric hospitals,[22] whereas data from a large, national surveillance programme in England and Wales suggested no evidence of effectiveness of PCV13 against serotype 3.[23] Findings from a randomised controlled trial that compared immunogenicity and efficacy of PCV13 and PCV7 against nasopharyngeal colonisation suggest no effect of PCV13 on nasopharyngeal colonisation with serotype 3.[17] Definitive evidence of effectiveness of PCV13 against serotype 3 colonisation and IPD needs more study.

Serotype replacement has been documented since the introduction of PCV7.[24] Findings from a review of

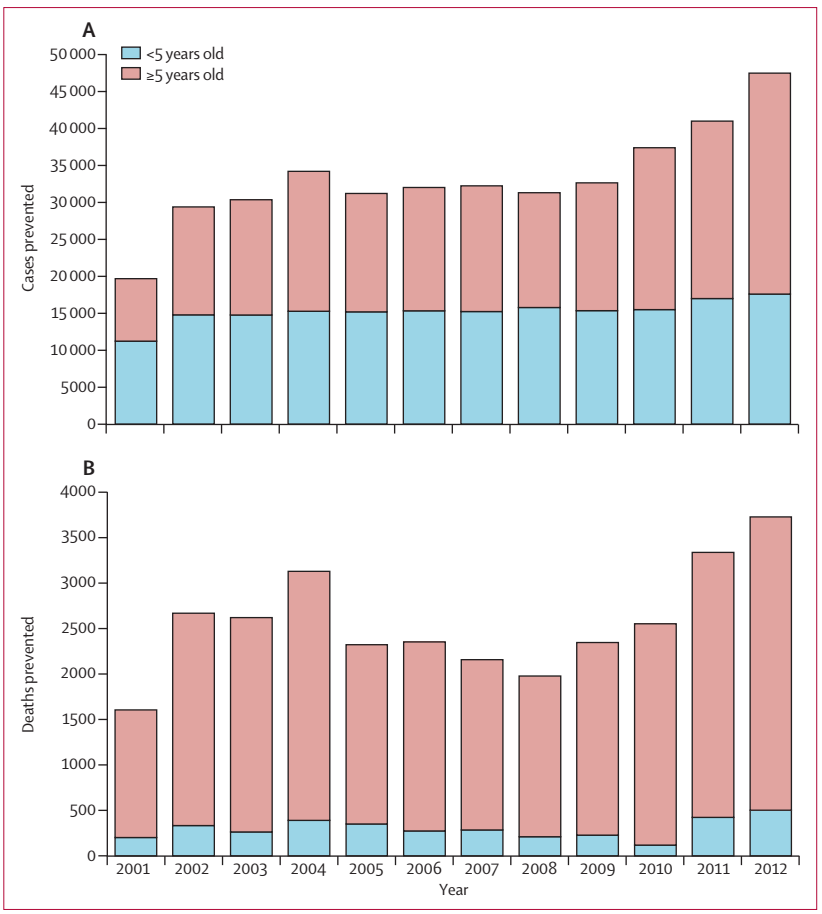

Figure 3: **Estimated numbers of cases of and deaths from invasive pneumococcal disease prevented after introduction of seven-valent and 13-valent pneumococcal conjugate vaccine for children in the USA**
Seven-valent pneumococcal conjugate vaccine was introduced in 2000 and 13-valent pneumococcal conjugate vaccine in 2010.

Figure 2: **Modelled and noted cases of non-13-valent pneumococcal vaccine type invasive pneumococcal disease**
Vertical black lines show the introduction of PCV13 for children. PCV13=13-valent pneumococcal conjugate vaccine.

Panel: Research in context

Systematic review

We searched PubMed using the search terms "13-valent pneumococcal conjugate vaccine" and "invasive pneumococcal", with no language limits set. We identified 138 papers published between Jan 1, 2012 (2 years after PCV13 became available), and Oct 8, 2014. Of these, two[25,30] described stable, population-based surveillance programmes with high proportions of isolates collected from all ages assessed. Both reports described a substantial effect of PCV13 using two doses in the first year of life and a booster dose in the second year of life. An additional publication showed the effect of PCV13 in the USA during the first 2 years after the introduction of PCV13.[21] 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 presented findings beyond 2 years after the introduction of PCV13.

Interpretation

Our study adds key findings related to the introduction of PCV13 using the four-dose schedule licensed in the USA and many other countries. Because rates of IPD caused by the PCV13 minus PCV7 serotypes were increasing in the USA before the introduction of PCV13, our study shows how introduction of a vaccine with a greater number of serotypes than a previously introduced vaccine can reverse increases associated with serotype replacement and ultimately reduce further the incidence of IPD. Our findings among unvaccinated people can be used to determine whether national immunisation policy should change, especially the potential short-term use of PCV13 among older adults.

serotype replacement disease after the introduction of PCV from several surveillance programmes around the world suggested that serotype replacement would not be expected within 2 years after introduction of PCV13.[5] We noted some evidence of serotype replacement, but only among adults aged 50–64 years and only during the third year after introduction of PCV13. Early evidence of serotype replacement seems to be emerging in Europe.[25] We noted reductions in antibiotic non-susceptible IPD that were largely attributable to reductions in IPD caused by serotype 19A—the serotype associated with increased antibiotic non-susceptibility before the introduction of PCV13.[26] Vaccination is an important way of combatting antimicrobial resistance.

To quantify the effect of the introduction of PCV13, we used a potential outcomes modelling approach,[27,28] which has advantages over before–after comparisons.[2] First, rates of serotypes 19A and 7F were increasing in ABCs areas before the introduction of PCV13. Therefore, estimates of the effect of PCV13 would depend, in part, on the arbitrary selection of baseline incidence. A high baseline incidence rate would lead to an overestimate of effect, whereas a low baseline rate would underestimate the effect. Second, our method takes into consideration all datapoints during the period of assessment, 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 has some limitations. For children who had already received a full series of PCV7, a supplemental dose of PCV13 was recommended.[7] We were unable to assess the contributions of the full four-dose series versus the supplemental dose. Our model assumed that the incidence of IPD caused by PCV13 minus PCV7 serotypes would have continued increasing after introduction of PCV13. Although 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.[29] Thus, we cannot expect that rates of PCV13 minus PCV7 type IPD would have continued to increase indefinitely. Additionally, as with any national estimates from limited geographical surveillance, ABCs areas might not be fully representative of the entire country. However, in view of the high variability in ABCs areas with respect to geography, socioeconomic status, and urbanicity, this limitation is unlikely to change our conclusions substantially.

PCV13 has already shown dramatic reductions in IPD among children and, through herd protection, adults. The continued success of the paediatric PCV13 programme will be crucial for policy making related to the recently adopted age-based recommendations for PCV13 in adults (panel).

Contributors

MRM proposed the initial study idea, drafted the analysis plan, and wrote the main manuscript. RL-G worked with ABCs 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, THTJr, and TP conceptualised and did 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 USA. LMG, BB, and JHJ did serotyping and antimicrobial resistance testing of case isolates. CGW provided input into the analysis plan and the interpretation of the data. All authors contributed to the interpretation of the findings and the writing of the final manuscript draft.

Declaration of interests

WS has received personal fees from Merck, Pfizer, the Cleveland Clinic, and Sanofi Pasteur. LHH has received grants and personal fees from Sanofi Pasteur and personal fees from GlaxoSmithKline, Merck, Novartis, and Pfizer. All relationships with industry were terminated before he became a voting member of the ACIP on July 1, 2012. JHJ has received grants from Merck and personal fees from Accelerate Diagnostics. All other authors declare no competing interests.

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