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# Cost-Effectiveness of Using 2 vs 3 Primary Doses of 13-Valent Pneumococcal Conjugate Vaccine

**AUTHORS:** Charles Stoecker, PhD,<sup>a</sup> Lee M. Hampton, MD, MSc,<sup>a,b</sup> Ruth Link-Gelles, MPH,<sup>a</sup> Mark L. Messonnier, PhD,<sup>a</sup> Fangjun Zhou, PhD,<sup>a</sup> and Matthew R. Moore, MD, MPH<sup>a</sup>

<sup>a</sup>National Center for Immunization and Respiratory Diseases, and <sup>b</sup>Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia

## KEY WORDS

PCV13, decremental cost effectiveness

## ABBREVIATIONS

IPD—invasive pneumococcal disease

OM—otitis media

PCV7—7-valent pneumococcal conjugate vaccine

PCV13—13-valent pneumococcal conjugate vaccine

QALY—quality adjusted life-year

Dr Stoecker conceptualized and designed the study, carried out the analysis, and drafted the initial manuscript; Dr Hampton conceptualized and designed the study, carried out the analysis on disease serotype data, and reviewed and revised the manuscript; Ms Link-Gelles carried out the analysis of Active Bacterial Core surveillance data and reviewed and revised the manuscript; Dr Messonnier conceptualized the study, designed the model, and reviewed and revised the manuscript; Dr Zhou refined the model and reviewed and revised the manuscript; Dr Moore conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Address correspondence to Charles Stoecker, PhD, Centers for Disease Control and Prevention, 1600 Clifton Road, MS A-19, Atlanta, GA 30329. E-mail: [cstoecker@cdc.gov](mailto:cstoecker@cdc.gov)

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**WHAT'S KNOWN ON THIS SUBJECT:** Pneumococcal conjugate vaccines are effective in preventing pneumococcal disease but are also costly. Although the current US immunization schedule recommends 4 doses, many countries have adopted 3-dose schedules that have worked well, but may provide less protection against pneumococcal disease.



**WHAT THIS STUDY ADDS:** Changing the US 13-valent pneumococcal conjugate vaccine schedule from 3 to 2 primary doses while keeping a booster dose would save \$412 million annually but might lead to moderate increases in pneumococcal disease, especially otitis media and pneumonia.

## abstract



**BACKGROUND AND OBJECTIVE:** Although effective in preventing pneumococcal disease, 13-valent pneumococcal conjugate vaccine (PCV13) is the most expensive vaccine on the routinely recommended pediatric schedule in the United States. We examined the cost-effectiveness of switching from 4 total doses to 3 total doses by removing the third dose in the primary series in the United States.

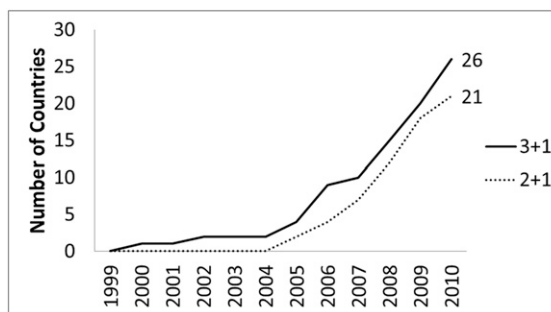
**METHODS:** We used a probabilistic model following a single birth cohort of 4.3 million to calculate societal cost savings and increased disease burden from removing the 6-month dose of PCV13. Based on modified estimates of 7-valent pneumococcal conjugate vaccine from randomized trials and observational studies, we assumed that vaccine effectiveness under the 2 schedules is identical for the first 6 months of life and largely similar after administration of the 12- to 15-month booster dose.

**RESULTS:** Removing the third dose of PCV13 would annually save \$500 million (in 2011\$) but would also result in an estimated 2.5 additional deaths among inpatients with pneumonia or invasive pneumococcal disease. Such dose removal would also result in 261 000 estimated otitis media and 12 000 estimated pneumonia cases annually. These additional illnesses could be prevented through modest increases in coverage. Overall, societal savings per additional life-year lost would be ~\$6 million. When nonfatal outcomes are also considered, savings would range from \$143 000 to \$4 million per additional quality adjusted life-year lost, depending on the assumptions used for otitis media.

**CONCLUSIONS:** Sizable societal cost savings and a moderate pneumococcal disease increase could be expected from removing the PCV13 primary series' third dose. *Pediatrics* 2013;132:1–9

*Streptococcus pneumoniae* (pneumococcus) is a major cause of morbidity and mortality in the United States.<sup>1</sup> Introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in 2000 led to substantial reductions in invasive pneumococcal disease (IPD),<sup>2,3</sup> pneumonia,<sup>4</sup> and otitis media (OM).<sup>5–7</sup> Associated mortality reductions cost between \$7500<sup>8</sup> and \$10 400<sup>7</sup> per life-year saved. The US introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 holds promise for further reductions of pneumococcal disease<sup>9</sup> through a program that is expected to be cost-saving compared with PCV7 immunization efforts.<sup>10</sup> More data on vaccine performance are available for PCV7 than for PCV13, but the 2 vaccines are similar enough that the experience with PCV7 guided both the licensure of and policy for the use of PCV13.<sup>9,11,12</sup>

Although pneumococcal conjugate vaccines are highly effective, they are also expensive. At ~\$100 per dose<sup>13</sup> and \$400 per completed vaccination series (ie, 3 primary doses during ages 2–6 months and 1 booster dose at ≥12 months of age: a 3+1 schedule), PCV13 was the most costly vaccine on the routine US pediatric schedule in 2011.<sup>13</sup> This expense, and the similar expense of other pneumococcal conjugate vaccines, including PCV7, has led many countries to adopt schedules with only 3 doses instead of the 4 doses currently used in the United States (with some countries using a 4-dose schedule for children at high risk of IPD), and no consensus has emerged about which strategy is best (Fig 1).<sup>14</sup> The attractiveness of 2 primary doses 2 to 6 months after birth and 1 booster dose ≥12 months after birth (a 2+1 schedule) is based, in part, on evidence of nearly identical effectiveness in preventing IPD to that of 4-dose PCV7 schedules.<sup>2</sup> Similarly, the 9-valent PCV formulation prompted similar immune responses when used in



**FIGURE 1**

Number of World Health Organization member states providing universal access to 2+1 or 3+1 dosage regimens of PCV7 and PCV13 in their National Immunization Programs by year. We count Canada as 3+1 even though 8 of 13 provinces and territories recommend 2+1 for the general population. France switched from 3+1 to 2+1 in 2008. Data are from Rozenbaum et al,<sup>14</sup> the World Health Organization Vaccine Preventable Diseases Monitoring System,<sup>15</sup> and the Vaccine Information Management System.<sup>16</sup> Countries are categorized according to their recommendation for the general population, and some countries that use 2+1 for the general population use 3+1 for high-risk groups.

3- and 4-dose schedules,<sup>17</sup> and the 10-valent vaccine has been shown to provide similar protection against IPD when given using 2+1 or 3+1 schedules.<sup>18</sup> Subsequent studies have confirmed that 2+1 PCV7 schedules can be highly effective at a population level in preventing IPD,<sup>19–22</sup> pneumonia,<sup>23,24</sup> and OM.<sup>25</sup>

Early data on the impact of a 2+1 schedule of PCV13 are available,<sup>26</sup> and the effects of 2+1 schedules have been sufficiently encouraging for the World Health Organization<sup>12</sup> and national governments<sup>11,26</sup> to support use of a 2+1 schedule for PCV13. However, other studies have indicated that 2+1 PCV7 schedules may confer reduced immunogenicity<sup>27</sup> and somewhat less protection against lower respiratory tract infections<sup>28</sup> and OM.<sup>6</sup> To inform vaccine policy making in light of the potential trade-offs between vaccine expenses and benefits, we aimed to evaluate the cost-effectiveness of using a 2+1 schedule instead of a 3+1 schedule for PCV13 in the United States.

## METHODS

### Overview

We developed a probabilistic model to estimate the cost-effectiveness of removing the third dose of PCV13 in

a hypothetical cohort of children. We used Monte Carlo simulation in spreadsheet-based software (@Risk 5.7; Palisade Corporation, Newfield, NY) to predict incremental cases of pneumococcal disease and costs per life-year and quality adjusted life-year (QALY) saved, hospitalizations averted, and deaths averted under 2+1 vs 3+1 schedules.

### Model

Our model tracked disease incidence until age 10 years, although costs of sequelae and lost life were tracked through life expectancy. We examined a birth cohort equal in size to the 2010 US birth cohort (4 312 097)<sup>29</sup> and used the most recently available life expectancy and background mortality estimates by age from 2007.<sup>30</sup> The population was stratified by year of age, except in the first year of life, where we looked separately at those younger than 6 months and those between 6 and 12 months. We did not model differential disease incidence after age 10, because cross-country comparisons indicated similar effects under both schedules.<sup>3,20,21</sup>

We modeled the effects of PCV13 on PCV13-serotype IPD, all-cause pneumonia, and all-cause OM separately for 2+1 and 3+1 schedules. Figure 2 presents the outcomes calculated.

We classified serotypes as (1) serotypes in PCV7 (4 6B, 9V, 14, 18C, 19F, 23F), (2) serotypes in PCV13 (PCV7 serotypes plus serotypes 1, 3, 5, 6A, 7F, 19A), and (3) serotypes not found in PCV13, including the newly identified 6C.<sup>31</sup> Because substantial protection against serotype 6A has been documented for PCV7,<sup>2,31</sup> we categorized serotype 6A as a PCV7 serotype for the purposes of estimating the additional protective effect of PCV13 against all-cause pneumonia and OM.

Because the booster dose is critical for reduction of nasopharyngeal colonization by vaccine-type pneumococci<sup>32</sup> and because a randomized control trial found that a 2+1 schedule did not result in significantly more pneumococcal carriage acquisition after booster dose receipt,<sup>33</sup> we assumed that replacement disease would be identical between the 2+1 and 3+1 schedules.

### Parameters: Baseline Disease Incidence and Case-Fatality Rates

IPD disease burden, the proportion of IPD due to PCV13 and non-PCV13 serotypes, and IPD case-fatality rates came from the Active Bacterial Core surveillance system (Centers for Disease Control and Prevention, unpublished data, September 2011). We averaged data from 2006 to 2008 and excluded data from 2009 because of increased rates of IPD caused by the H1N1 pandemic.<sup>34</sup> Estimates of pre-PCV7 incidence of all-cause OM, tympanostomy tube placement, all-cause pneumonia hospitalizations, and all-cause outpatient pneumonia were taken from Ray et al,<sup>7</sup> who in turn based values on data from the National Ambulatory Medical Care Survey, National Hospital Discharge Summary, and National Inpatient Survey, respectively. We used pre-PCV7 incidence data for these syndromes because of unavailability of nationally representative data on the

distribution of serotypes that cause OM and on the proportion of all-cause pneumonia caused by pneumococcus after the introduction of PCV7. Grijalva et al<sup>35</sup> provided case-fatality rates for hospitalized all-cause pneumonia, and we assumed no mortality from outpatient pneumonia and OM (Table 1).

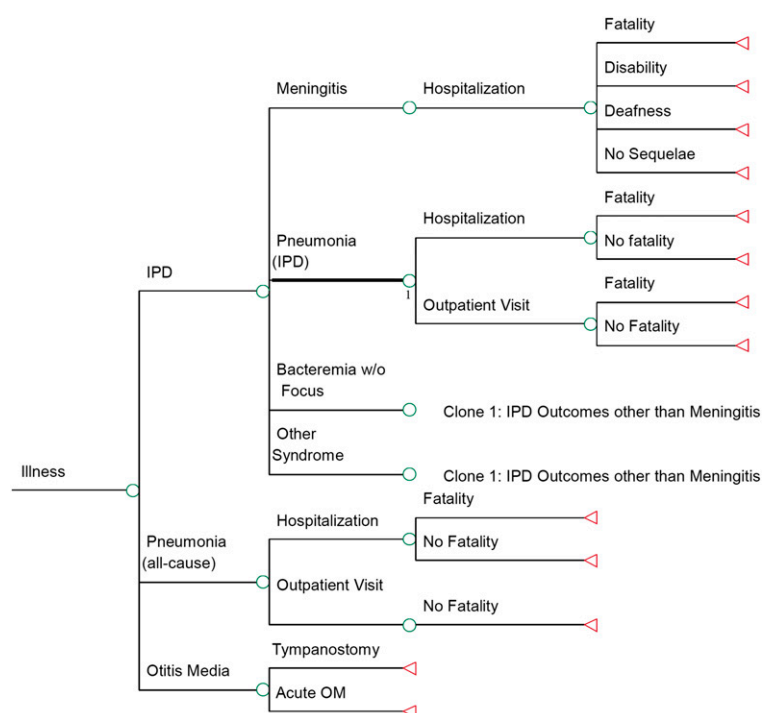
### Parameters: Vaccination With PCV13

In 2010, 83.3% of children aged 19 to 35 months had received at least 4 doses of PCV7.<sup>36</sup> We use this coverage rate for both the 2+1 and 3+1 model scenarios.

Because the immunogenicity of PCV13 against the serotypes it covers is similar to the immunogenicity of PCV7,<sup>9,10</sup> we assumed that the effectiveness of PCV13 against PCV13-serotype pneumococcal disease was the same as the effectiveness of PCV7 against PCV7-serotype pneumococcal disease (Table 2).

To estimate the amount of PCV13-serotype IPD prevented under the 2 schedules at steady state, we directly applied the effectiveness of PCV7 in preventing PCV7-serotype disease from Whitney et al<sup>2</sup> to the 2006–2008 incidence of PCV13-serotype IPD.

Because the case-control study comparing the 2+1 and 3+1 schedules<sup>2</sup> necessarily only estimates direct effects against IPD, we calculated indirect effects against IPD. We did so by tabulating the percentage decline in IPD in Active Bacterial Core surveillance data (Centers for Disease Control and Prevention, unpublished data, September 2011) unexplained by increases in coverage from National Immunization Survey data<sup>36</sup> for 3-year-olds between 1998 and 2009 after deducting the direct protection from PCV7 estimated in Whitney et al.<sup>2</sup> We then assumed the same indirect effects, proportionate to the serotype distribution, applied to PCV13. This estimated indirect effect was used in the model as a percentage



**FIGURE 2**

Health outcomes. Nodes in the IPD branch following “Bacteremia w/o Focus” and “Other Syndrome” are identical in structure to nodes following “Pneumonia.” Examples of IPD “Other Syndromes” include osteomyelitis, endocarditis, pericarditis, and peritonitis.

**TABLE 1** Pneumococcal Disease Incidence by Indicated Age Used in the Cost-Effectiveness Model (per 100 000)

|   | Age, y    |           |         |        |        |        |      |      |      |      |      |
|---|-----------|-----------|---------|--------|--------|--------|------|------|------|------|------|
|   | 0 to <0.5 | 0.5 to <1 | 1       | 2      | 3      | 4      | 5    | 6    | 7    | 8    | 9    |
| All-cause OM visits <sup>a,b</sup>                                | 32 264    | 92 086    | 124 350 | 80 475 | 36 600 | 36 600 |      |      |      |      |      |
| Tympanostomy tube placements <sup>a,b</sup>                       | 121       | 477       | 4680    | 2370   | 1130   | 1020   |      |      |      |      |      |
| All-cause outpatient pneumonia <sup>a,b</sup>                     | 4500      | 4500      | 9000    | 6500   | 4000   | 4000   |      |      |      |      |      |
| All-cause inpatient pneumonia <sup>a,c</sup>                      | 649       | 649       | 1297    | 418    | 418    | 418    | 74   | 74   | 74   | 74   | 74   |
| % of all-cause pneumonia cases resulting in fatality <sup>d</sup> | 0.13      | 0.13      | 0.13    | 0.13   | 0.19   | 0.19   | 0.19 | 0.19 | 0.19 | 0.19 | 0.19 |
| IPD incidence <sup>e</sup>  | 34.3      | 41.6      | 32.6    | 15.9   | 10.1   | 9.5    | 4.5  | 4.5  | 4.5  | 4.5  | 4.5  |
| % of IPD due to PCV13 serotypes <sup>e</sup>                      | 62.6      | 61.1      | 56.7    | 66.5   | 66.1   | 75.2   | 64.1 | 64.1 | 64.1 | 64.1 | 64.1 |
| % IPD cases resulting in meningitis <sup>e</sup>                  | 24.9      | 8.4       | 4.1     | 5.1    | 2.9    | 4.8    | 7.7  | 7.7  | 7.7  | 7.7  | 7.7  |
| % of meningitis cases resulting in disability <sup>f</sup>        | 6.7       | 6.7       | 6.7     | 6.7    | 6.7    | 6.7    |      |      |      |      |      |
| % of meningitis cases resulting in deafness <sup>f</sup>          | 13        | 13        | 13      | 13     | 13     | 13     |      |      |      |      |      |
| % of meningitis cases resulting in fatality <sup>e</sup>          | 5.4       | 13.0      | 5.6     | 9.1    | 25.0   | 16.7   | 5.0  | 5.0  | 5.0  | 5.0  | 5.0  |
| % of IPD cases resulting in pneumonia <sup>e</sup>                | 13.8      | 19.8      | 36.9    | 48.8   | 51.5   | 54.4   | 42.7 | 42.7 | 42.7 | 42.7 | 42.7 |
| % of pneumonia cases resulting in fatality <sup>e</sup>           | 0.0       | 0.0       | 0.0     | 0.0    | 1.4    | 1.5    | 0.9  | 0.9  | 0.9  | 0.9  | 0.9  |
| % of pneumonia cases hospitalized <sup>e</sup>                    | 77.4      | 70.4      | 70.4    | 76.2   | 82.9   | 77.9   | 77.5 | 77.5 | 77.5 | 77.5 | 77.5 |
| % of IPD cases resulting in bacteremia <sup>e</sup>               | 52.9      | 53.1      | 44.7    | 38.6   | 33.8   | 36.8   | 40.1 | 40.1 | 40.1 | 40.1 | 40.1 |
| % of bacteremia resulting in fatality <sup>e</sup>                | 2.9       | 0.0       | 0.4     | 2.0    | 0.0    | 0.0    | 2.3  | 2.3  | 2.3  | 2.3  | 2.3  |
| % of bacteremia cases hospitalized <sup>e</sup>                   | 58.8      | 44.1      | 39.9    | 37.8   | 42.6   | 52.9   | 57.5 | 57.5 | 57.5 | 57.5 | 57.5 |
| % of IPD cases resulting in all other syndromes <sup>e</sup>      | 8.4       | 18.7      | 14.4    | 7.4    | 11.8   | 4.0    | 9.2  | 9.2  | 9.2  | 9.2  | 9.2  |
| % of other cases resulting in fatality <sup>e</sup>               | 2.9       | 0.0       | 0.4     | 2.0    | 0.0    | 0.0    | 2.3  | 2.3  | 2.3  | 2.3  | 2.3  |
| % of other cases hospitalized <sup>e</sup>                        | 58.8      | 44.1      | 39.9    | 37.8   | 42.6   | 52.9   | 57.5 | 57.5 | 57.5 | 57.5 | 57.5 |

Empty cells were not used in the model.

<sup>a</sup> Non-IPD rates for children younger than 5 are adapted from Ray et al 2009.<sup>7</sup> Incidence rates in the first year of life are broken into 6-month categories by the proportions reported in Ray et al 2006.<sup>8</sup>

<sup>b</sup> OM visits (on which tympanostomy tube placement estimates are based) and outpatient pneumonia visits are averages from 1994–1999.

<sup>c</sup> Pneumonia hospitalizations after age 5 are from Grijalva et al<sup>35</sup> from 1997–1999 averages.

<sup>d</sup> Pneumonia case-fatality rates were computed by Carlos Grijalva from 2006–2008 averages in the Nationwide Inpatient Sample.

<sup>e</sup> IPD incidence, syndrome distribution, case fatality rates, and hospitalization rates are averages from 2006–2008 Active Bacterial Core surveillance data (Centers for Disease Control and Prevention, unpublished data, September 2011).

<sup>f</sup> Ray et al 2006.

**TABLE 2** Vaccine Effectiveness Assumptions, by Schedule, Outcome, and Age (%)

| Parameter  | 0 to <0.5 y | 0.5 to <1 y       | 1 to <10 y |
|--|-------------|-------------------|------------|
| <b>3+1 schedule</b>                                    |             |                   |            |
| IPD, vaccine serotypes, direct effect <sup>a</sup>     | 96          | 96                | 100        |
| IPD, vaccine serotypes, indirect effect <sup>a,b</sup> | 7.8         | 7.8               | 7.8        |
| All-cause OM <sup>c</sup>                              | 14.6        | 14.6              | 14.6       |
| All-cause tympanostomy tube placement <sup>c</sup>     | 25.1        | 25.1              | 25.1       |
| All-cause outpatient pneumonia <sup>d</sup>            | 6.3         | 6.3               | 6.3        |
| All-cause hospitalized pneumonia <sup>d</sup>          | 13.8        | 13.8              | 13.8       |
| <b>2+1 schedule</b>                                    |             |                   |            |
| IPD vaccine serotypes direct effect <sup>a</sup>       | 96          | 96                | 98         |
| IPD vaccine serotypes indirect effect <sup>a,b</sup>   | 7.8         | 7.8               | 7.8        |
| All-cause OM <sup>c</sup>                              | 14.6        | 6.7 <sup>e</sup>  | 14.6       |
| All-cause tympanostomy tube placement <sup>c</sup>     | 25.1        | 11.5 <sup>e</sup> | 25.1       |
| All-cause outpatient pneumonia <sup>d</sup>            | 6.3         | 0 <sup>f</sup>    | 6.3        |
| All-cause hospitalized pneumonia <sup>d</sup>          | 13.8        | 7.5 <sup>f</sup>  | 13.8       |

<sup>a</sup> Vaccine serotype effectiveness is adapted from effectiveness of PCV7 from Whitney et al<sup>2</sup> then multiplied by the age and syndrome-specific serotype rates for those covered by PCV13 from Active Bacterial Core surveillance data (Centers for Disease Control and Prevention, unpublished data, September 2011).

<sup>b</sup> Authors' calculation based on observed declines in IPD (Centers for Disease Control and Prevention, unpublished data, September 2011), increases in immunization,<sup>36</sup> and estimates of direct protection.<sup>2</sup> See text.

<sup>c</sup> Total effects of PCV7 against OM and tympanostomy tube placements were adapted from those calculated in Ray et al<sup>7</sup> and then inflated by the relative proportions of PCV13 serotypes and serotypes covered by PCV7 that were present in the pre-PCV7 population distribution of OM from Wald et al.<sup>37</sup>

<sup>d</sup> Inflating total effects on pneumonia from Ray et al<sup>7</sup> by serotype incidence rates (approximated with serotype incidence rates from invasive disease) in Active Bacterial Core surveillance data (Centers for Disease Control and Prevention, unpublished data, September 2011). We assumed no direct effects of the 2+1 schedule for children 6 to 11 months old,<sup>28</sup> thus only indirect effects affected this group.

<sup>e</sup> Children 6 to 11 months old are assigned no direct protection against OM or tympanostomy tube placements in the 2+1 schedule<sup>6</sup> and are affected by only the indirect effect calculated in Ray et al<sup>7</sup> for PCV7 then inflated by PCV13 serotype coverage from Wald et al.<sup>38</sup>

<sup>f</sup> Derived from Pelton et al<sup>28</sup> see text for details.

increase applied to the product of coverage and protection provided against IPD by the vaccine's direct effects. Because we assumed identical coverage levels with both schedules, a slightly smaller direct effect against IPD under the 2+1 schedule, and that indirect effects would be proportionate to direct effects, we effectively assumed fewer cases would be prevented indirectly under the 2+1 schedule.

Because estimates of the effectiveness of PCV13 against OM and all-cause pneumonia hospitalizations are not available, we inflated PCV7 effectiveness against these syndromes by the ratios of the proportions of pneumococcal OM or pneumonia cases caused by PCV13 serotypes and the proportions of pneumococcal OM or pneumonia cases caused by serotypes covered by PCV7 before the introduction of PCV7. This approach is similar to the one used by Rubin et al,<sup>10</sup> but differs in that we

considered serotype 6A as 1 of the serotypes affected by PCV7 instead of PCV13.<sup>3,5</sup> We calculated the proportions of pneumococcal OM that were due to PCV13 serotypes and serotypes covered by PCV7 using the US 1994–1997 pneumococcal OM serotype distribution reported by Wald et al.<sup>37</sup> We assumed that the ratio of the proportion of all-cause pneumonia due to PCV13 serotypes and the proportion of all-cause pneumonia due to serotypes covered by PCV7 was similar to the ratio of the proportion of IPD due to PCV13 serotypes and the proportion of IPD due to serotypes covered by PCV7 in 1998–1999 (Centers for Disease Control and Prevention, unpublished data, September 2011). We then assumed that the 2+1 schedule was as protective as a 3+1 schedule for all ages against OM, tympanostomy tube placements, and all-cause pneumonia except for children 6 to 12 months old, where we assumed that 2+1 provided no direct protection against OM,<sup>6</sup> tympanostomy tube placements, or all-cause pneumonia.<sup>28</sup> We note that these assumptions strongly favor the 3+1 strategy, particularly in light of some data suggesting no difference between the 2 schedules.<sup>28,38</sup> For children 6 to 12 months old, we assigned indirect protection, likely provided by population-wide reductions in vaccine-type pneumococcal carriage,<sup>59</sup> which we derived from Ray et al.<sup>7</sup>

For children younger than 6 months, we assumed that the 2+1 and 3+1 schedules would provide equivalent protection against all syndromes of pneumococcal disease because the third primary dose is not usually given before 6 months of age.<sup>9</sup> Finally, we assumed no waning immunity of PCV13 until age 10, at which point direct immunity vanished. Elevated antibody levels beyond 6 years have been observed<sup>40</sup> and each of the 2000–2003 birth cohorts in the United States had, on average, fewer than 1 vaccine-type

IPD case detected each year during 2008 to 2010 (Centers for Disease Control and Prevention, unpublished data, September 2011).

### Parameters: Costs

We performed our analysis from the societal perspective and thus included both medical and nonmedical costs. Costs were converted to 2011 dollars using the Consumer Price Index for all items for nonmedical costs or the Consumer Price Index for medical care for medical costs.<sup>41</sup> All outcomes were discounted by 3%.

The public (\$97.21) and private (\$120.95) price of a dose of PCV13 vaccine came from the Centers for Disease Control and Prevention vaccine price list<sup>13</sup> from 2011 and were weighted by public (65%) and private (35%) purchase shares from Centers for Disease Control and Prevention's Biologics Surveillance Data (Centers for Disease Control and Prevention, unpublished data, 2010). These weights were used to calculate the average vaccine administration cost (\$14.57) using public (\$7.67) and private (\$27.36) vaccine administration costs.<sup>42</sup> We assumed vaccine wastage was 5%, consistent with the 1% to 5% wastage

reported by 92% of Vaccines for Children grantees<sup>43</sup> and the 1.5% to 2.6% wastage rates reported for other injectable vaccines for children.<sup>44</sup>

### Parameters: Utilities

To compare mortality outcomes with less severe health outcomes, we applied QALY decrements to each episode of disease. No loss of health was indicated by a decrement of 0, whereas moving from perfect health to death had a decrement of 1. The specific decrements per episode of disease are detailed in Table 3. Although larger quality decrements have been used,<sup>9</sup> we, like others,<sup>10,50</sup> were concerned they did not accurately reflect the quality of life decrement associated with acute illness.

### Sensitivity Analyses

As effectiveness of PCV against OM has been a driver of previous cost-effectiveness studies,<sup>7,8,10</sup> we conducted 1-way sensitivity analyses around the effectiveness against OM and the QALYs lost because of OM. In 1 analysis, we relaxed the base case assumption that the 2+1 schedule provided no direct protection against OM and tympanostomy tube placement in 6- to 11-month-olds and instead assumed that it afforded 6- to

**TABLE 3** Cost Inputs Used in the Cost-Effectiveness Model<sup>a</sup>

|                                    | Medical, \$          | Nonmedical, \$       | QALY Decrement <sup>b</sup> |
|------------------------------------|----------------------|----------------------|-----------------------------|
| Inpatient pneumonia age 0 to <5 y  | 7763                 | 371                  | 0.006                       |
| Inpatient pneumonia age 5 to <10 y | 5329                 | 749 <sup>c</sup>     | 0.006                       |
| Outpatient pneumonia               | 248                  | 371                  | 0.004                       |
| OM                                 | 59                   | 147                  | 0.005                       |
| Tympanostomy tube placement        | 2556                 | 367                  | 0.005 <sup>d</sup>          |
| Nonmeningitis IPD age 0 to <5 y    | 3471                 | 497                  | 0.0079                      |
| Meningitis age 0 to <5 y           | 18 189               | 2603                 | 0.0232                      |
| Nonmeningitis IPD age 5 to <10 y   | 13 591               | 749 <sup>c</sup>     | 0.0079                      |
| Meningitis age 5 to <10 y          | 13 591               | 749 <sup>c</sup>     | 0.0232                      |
| Deafness                           | 34 230 <sup>e</sup>  | 110 240 <sup>e</sup> | 0.73                        |
| Disability                         | 182 700 <sup>e</sup> | 123 107 <sup>e</sup> | 0.68                        |

<sup>a</sup> Unless noted, details of cost computations are found in Ray et al<sup>7</sup> and inflated to 2011 prices using the Bureau of Labor Statistics Consumer Price Index for All Items for nonmedical expenses or Medical Care component of the Consumer Price Index for medical expenses.<sup>41</sup>

<sup>b</sup> Assembled by Rubin et al.<sup>10</sup>

<sup>c</sup> Based on lost wages of \$118 per day in 2004<sup>45</sup> and a hospital stay of 5.5 days from Active Bacterial Core surveillance data (Centers for Disease Control and Prevention, unpublished data, September 2011).

<sup>d</sup> Following Poirier et al<sup>48</sup> we interpret the quality decrement estimated in Oh et al<sup>49</sup> to apply to either OM or tympanostomy tube placement.

<sup>e</sup> From *Morbidity and Mortality Weekly Report*.<sup>46,47</sup>

11-month-olds both direct and indirect protection. In another, we calculated estimates in which the QALY loss associated with OM and tympanostomy tube placement was 0.005 or 0.011 to span the range of frequently used values in the literature.<sup>49,51</sup>

Additional sensitivity analyses that relax the assumptions about the differences in schedule effectiveness against all-cause pneumonia and IPD are available in the Supplemental Table 9. We also conducted multivariate sensitivity analysis with Monte Carlo simulations until there was a 95% chance that the mean estimate of the cost per QALY was within 3% of its true value. For these simulations, we used 0.005 as the QALY loss per episode of OM, no direct protection against OM for 6- to 11-month-olds under a 2+1 schedule, and all parameters were allowed to vary by 1 SD or 20% if estimates of SDs were unavailable (Supplemental Tables 5–7). We then calculated the percentage of simulations in which the cost per QALY exceeded \$100 000, a possible figure used for evaluating decrementally cost-effective interventions,<sup>52</sup> and \$450 000, an estimate for the statistical value of

a life-year and thus the highest savings that should be demanded from decrementally cost-effective interventions.<sup>53</sup>

To assess how potentially negative health consequences of a change to a 2 +1 schedule could be offset, we examined scenarios in which coverage was expanded in the context of a 2+1 regimen. Specifically, we looked at how far coverage needed to expand to result in either no additional estimated deaths or no QALY loss.

## RESULTS

Under our base case assumptions, IPD cases increased by 44, fatalities (largely due to all-cause pneumonia) increased by 2.5, pneumonia hospitalizations increased by approximately 1500, pneumonia treated in the outpatient setting increased by 10 000, tympanostomy tube placements increased by 2300, and OM cases increased by 261 000 per birth cohort (Table 4). We calculated savings per life-year lost of ~\$6 million and savings per QALY lost of \$300 000. Direct cost savings from removing the third dose in the primary series amounted to \$500 million per birth co-

hort (Table 4). These savings were \$421 million after accounting for increases in medical and nonmedical costs totaling \$79 million per birth cohort.

Univariate sensitivity analyses around the OM parameters are also shown in Table 4. Increasing the QALYs lost due to OM from 0.005 to 0.011 decreased the savings per QALY lost to \$143 000. Assuming that the 2+1 and 3+1 schedules have the same effectiveness against OM increased the savings per QALY lost to ~\$4 000 000.

Our Monte Carlo simulations indicated that 2+1 saved more than \$100 000 per QALY lost in 99% of simulations and saved >\$450 000 per QALY lost in 55% of simulations (Supplemental Table 8).

We also found that when a change to a 2 +1 schedule was combined with a coverage expansion from the current 83.3% to 86.0% there were (on net) no additional deaths. When the schedule switch was combined with a further coverage expansion to 93%, there were no lost QALYs (Table 4).

## DISCUSSION

We found that eliminating the third dose in the primary series of PCV13 saved

**TABLE 4** Net Effects of Switching PCV13 Dosage From 3+1 to 2+1

|  | Base Case | OM QALY = 0.011 | 2+1 Provides Same Protection from OM as 3+1 | Coverage Expanded to 86% | Coverage Expanded to 93% |
|--|-----------|-----------------|---|--------------------------|--------------------------|
| <b>Health outcomes</b>                               |           |                 |   |                          |                          |
| <b>Cases</b>   |           |                 |   |                          |                          |
| IPD  | 44        | 44              | 44  | (82)                     | (410)                    |
| Hospitalized pneumonia                               | 1453      | 1453            | 1453  | 831                      | (780)                    |
| Nonhospitalized pneumonia                            | 10 136    | 10 136          | 10 136                                      | 8091                     | 2790                     |
| Tympanostomy tube placement                          | 2318      | 2318            | 0   | (450)                    | (7624)                   |
| OM   | 261 324   | 261 324         | 0   | 201 596                  | 46 745                   |
| <b>Deaths due to IPD<sup>a</sup></b>                 |           |                 |   |                          |                          |
|  | 0.6       | 0.6             | 0.6   | (1.5)                    | (6.7)                    |
| <b>Deaths due to all-cause pneumonia<sup>a</sup></b> |           |                 |   |                          |                          |
|  | 1.9       | 1.9             | 1.9   | 1.0                      | (1.4)                    |
| <b>Discounted QALYs gained (lost)</b>                |           |                 |   |                          |                          |
|  | (1403)    | (2939)          | (123)                                       | (974)                    | 138                      |
| <b>Discounted life-years gained (lost)</b>           |           |                 |   |                          |                          |
|  | (70)      | (70)            | (70)  | 12                       | 222                      |
| <b>Costs/Savings, \$</b>                             |           |                 |   |                          |                          |
| <b>Total cost (savings) in \$ millions</b>           |           |                 |   |                          |                          |
| Medical  | (421)     | (421)           | (482)                                       | (434)                    | (466)                    |
| Nonmedical   | 35        | 35              | 14  | 19                       | (22)                     |
| Vaccine dose reduction                               | 44        | 44              | 4   | 33                       | 5                        |
|  | (500)     | (500)           | (500)                                       | (486)                    | (450)                    |
| <b>Saving ratios, \$</b>                             |           |                 |   |                          |                          |
| Savings/QALY lost                                    | 300 000   | 143 000         | 3 919 000                                   | 446 000                  | Cost Saving <sup>b</sup> |
| Savings/Life-year lost                               | 6 014 000 | 6 014 000       | 6 886 000                                   | Cost Saving <sup>b</sup> | Cost Saving <sup>b</sup> |

<sup>a</sup> The decimal of precision is meant to denote uncertainty rather than precision. We felt reporting predicted deaths in whole numbers would give a false sense of the model's accuracy.

<sup>b</sup> Scenarios where health improved.

\$421 million annually but would cause an estimated 2.5 additional deaths for a savings of \$6 million per additional life-year lost. After incorporating nonfatal conditions, we found savings would range between \$143 000 and \$4 million per additional QALY lost. We found that increases in coverage, perhaps funded by savings from the change in schedule, could entirely offset the health losses from the schedule switch.

This is the first study to have explicitly examined the cost-effectiveness of 2 dosage schedules in a US context. Previous US cost-effectiveness studies of PCV compared new vaccines with the previous vaccine.<sup>7,8,10</sup> Previous comparisons of the 2 schedules for PCV13 in the Netherlands<sup>54</sup> and PCV7 in Norway<sup>55</sup> have rested on the assumption that PCV effectiveness against disease was the same for both schedules. Although there is evidence a 2+1 schedule provides as much protection as a 3+1 schedule against OM,<sup>38</sup> pneumonia,<sup>28</sup> and IPD,<sup>18,22</sup> we adopted the cautious assumption that the 2+1 schedule, compared with the 3+1 schedule, provided inferior protection against pneumococcal disease. Nevertheless, we still found considerable savings per QALY lost when switching to the 2+1 schedule. We further made the cautious assumption that the amount of disease prevented by indirect effects against IPD would be smaller under the 2+1 schedule. If the booster dose confers identical indirect effects to each schedule, as suggested by some studies,<sup>11,20,21</sup> then the savings from a 2+1 schedule would be even greater and increases in disease incidence would be even lower than in our base model.

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Our analysis has certain limitations. No randomized controlled trials have compared the effectiveness of 2+1 and 3+1 schedules against outpatient pneumonia, pneumonia hospitalizations, or OM. We extrapolated our estimates of relative effectiveness based on estimates from observational studies<sup>2,28,38</sup> and a group of noncompliers in a clinical trial.<sup>6</sup> If indirect protection or replacement disease differs under the 2 schedules, our results may over- or underestimate the true health effects of switching schedules. Further, our PCV13 effectiveness estimates against OM and all-cause pneumonia were based on PCV7 effectiveness estimates inflated by serotype distributions. If, as a result, we inaccurately estimated the effectiveness of PCV13 on a 3+1 schedule against OM and all-cause pneumonia, then our estimates of the additional disease associated with a 2+1 schedule and the cost-effectiveness of switching to a 2+1 schedule would also be affected.

Conceptually we have attempted to estimate the effect of switching from the current 3+1 schedule to a 2+1 schedule. Our IPD estimates used the most recent US data derived after 8 years of PCV7 usage on a 3+1 schedule. Because of the lack of more recent data on pneumococcal serotype distribution in OM or the proportion of all-cause pneumonia from pneumococcus, our estimates of US noninvasive disease came from data collected before any introduction of PCV. We therefore possibly overstate the negative effects of switching to a 2+1 schedule on noninvasive disease by using baseline epidemiology data from before the reductions of disease that have occurred under PCV7 and then PCV13.

Cost-effectiveness, although important, is not the only consideration when evaluating the appropriateness of any particular immunization schedule. In the United States, the number of injection doses recommended for children younger than 2 increased from 17 to 24 between 2000 and 2010<sup>56,57</sup> (disregarding combination vaccines), which may contribute to vaccine hesitancy among parents.<sup>58</sup> A series with fewer doses may also be more flexible in dealing with temporary vaccine shortages similar to the ones that occurred with PCV7 in 2001–2003 and 2004 in the United States.<sup>59</sup>

## CONCLUSIONS

Switching the PCV13 schedule from 3+1 to 2+1 may merit further consideration, because sizable societal cost savings, albeit with a moderate increase in pneumococcal disease, could be expected from removing a dose from the PCV13 primary series. Disease increases could be more than offset by moderate increases in coverage, although further investigation would be necessary to determine if the savings from removing 1 of the doses would exceed, equal, or fall short of the cost of interventions needed to increase coverage. Examining the cost-effectiveness of alternative dosage regimens of pneumococcal and other new vaccines may be worthwhile for formulations with high costs per dose.

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## Cost-Effectiveness of Using 2 vs 3 Primary Doses of 13-Valent Pneumococcal Conjugate Vaccine

Charles Stoecker, Lee M. Hampton, Ruth Link-Gelles, Mark L. Messonnier, Fangjun Zhou and Matthew R. Moore

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