In the Netherlands, the national immunization program includes 7-valent pneumococcal conjugate vaccine (PCV7) for all newborns born after April 1, 2006. We compared the incidence of invasive pneumococcal disease (IPD) and patient and disease characteristics before PCV7 introduction (June 2004–June 2006) with those after PCV7 introduction (June 2008–June 2010). Culture-confirmed IPD cases were identified by 9 sentinel laboratories covering ≈25% of the Dutch population. Significant declines in overall IPD incidence were observed in children <2 (60%) and in persons

Invasive Pneumococcal Disease and 7-Valent Pneumococcal Conjugate Vaccine, the Netherlands

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Learning Objectives
Upon completion of this activity, participants will be able to:
• Analyze previous research into the effects of 7-valent pneumococcal conjugate vaccine (PCV7)
• Compare the effects of PCV7 on different continents
• Distinguish age groups most affected by PCV7
• Evaluate the clinical presentation and outcomes of IPD after introduction of PCV7.

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covered by the vaccine (also caused differences in the relative proportion of IPD serotypes before the implementation of routine vaccination serotypes. Geographic variations in circulation of PCV7 age; catch-up programs speed up eradication of vaccine implemented a catch-up program for children <5 years of experienced less protection from indirect herd protection PCV7 in 2000, but many European countries did not be- and older adults (PCV7-serotype by non–PCV7 serotype IPD in children in PCV7-serotype IPD in adults and less replacement of reduction in the United States is a result of a decrease and the maturity of vaccination programs (haps as a result of differences in surveillance methods IPD increased (PCV7-serotype IPD in) 1730 Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 11, November 2012 Wales (and by enhanced surveillance, as reported for England and Europe, particularly Dutch surveillance studies, have focused almost exclusively on patients requiring hospitalization for severe IPD and who often had other underlying illnesses (11,12). This difference in reporting leads to different baseline incidence rates and may affect the observed net benefit of vaccination (13). For example, compared with healthy persons of the same age, US adults with co-morbid conditions benefited less from the indirect effects of PCV7 because of an increase in non–PCV7 serotype IPD after introduction of the vaccine (14). Differences in the directive for blood culture and patient populations under surveillance can partly explain the differences in results from use of PCV7.

The invasive disease potential of S. pneumoniae and the population at risk for IPD differs by serotype (12,13,15). Therefore, shifts in circulating serotypes may change the clinical manifestations of IPD, the population segment most at risk for infection, and the disease course and outcome. We investigated these issues and changes in IPD incidence in the Netherlands 4 years after a PCV7 vaccine program was implemented and compared our findings with those from the years just before introduction of the vaccine.

Methods

Pneumococcal Vaccination in the Netherlands

PCV7 was introduced into the Dutch national immunization program in June 2006 and was recommended for children born after April 1, 2006, at 2, 3, 4, and 11 months of age (16). Vaccination uptake is 94%–95% among Dutch infants (17). Use of the 23-valent pneumococcal polysaccharide vaccine is restricted to persons at high-risk for IPD (e.g., persons with asplenia or Hodgkin lymphoma); uptake in elderly persons is negligible (<1%) (18).

Surveillance Data

For this study, we registered all persons with a diagnosis of culture-confirmed IPD during June 1, 2008–May 31, 2010 (late post-implementation period) and all case-patients from previous Dutch IPD surveillance studies during June 1, 2004–May 31, 2006 (pre-implementation period) (1) and June 1, 2006–May 31, 2008 (post-implementation period) (11). All study procedures were the same as those used in the previous studies (11).

Nine sentinel laboratories identified IPD case-patients, which were defined as patients for whom S. pneumoniae was isolated from blood or cerebrospinal fluid (CSF) samples. The laboratories submitted all invasive pneumococcal isolates to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM, Academic Medical Center, Amsterdam, the Netherlands) for typing and characterization. We selected the laboratories on the basis of their geographic distribution throughout the country and their reliability for submitting isolates (1,11). The laboratories were estimated to cover a representative cohort of ≈25% of the Dutch population (=4.1 million inhabitants, including =0.6 million adults ≥65 years of age). In addition, ≈25% of the other meningitis-causing bacterial isolates that were sub-
mitted to NRLBM during the study period were submitted by the 9 sentinel laboratories.

At the NRLBM, co-agglutination was used to type the pneumococcal isolates and the capsular swelling method (Quellung reaction), using antisera (Statens Serum Institute, Copenhagen, Denmark), including serotype 6C, was used for serotyping. For isolates collected before June 2008, serotype 6C was determined by using PCR and antiserum. The serotypes were grouped in either PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) or non–PCV7 serotypes (all other serotypes, including 6A).

**Clinical Characteristics**

Trained medical students, using a standardized data collection form, retrospectively extracted the following information for all case-patients from hospital records, as described (1,11): patient characteristics, clinical syndrome, comorbidity, and disease course and outcome. We subdivided comorbid conditions as immunocompromising or nonimmunocompromising and categorized clinical syndromes as meningitis, invasive pneumonia, bacteremia with other focus, and bacteremia without focus, as described (I). Information on disease course and outcome included the length of hospital stay, admission to an intensive care unit, and death (i.e., in-hospital death and/or death within 30 days after first reported blood/CSF culture positive for *S. pneumoniae*). Cases without clinical information were excluded from all analyses.

**Statistical Analyses**

National population coverage was ≥25% by the sentinel laboratories; thus, we estimated annual IPD incidence rates per 100,000 inhabitants by dividing the total number of IPD cases in a specific epidemiologic year by 25% of the total Dutch population. Epidemiologic years were defined as June 1st–May 31 of the succeeding year. We used the population on January 1 of each consecutive year as the population at risk for infection (StatLine, www.cbs.nl/en-GB/menu/cijfers/statline/zelf-tabellen-maken/default.htm), assuming a stable population throughout the year.

We assessed the effect of vaccination by determining the incidence rate ratio. The assessment was done by comparing incidences in the late post-implementation period (2008–2010) with those in the pre-implementation period (2004–2006); we also determined 95% CIs.

To evaluate any changes in population at risk, we compared the proportion of patients with comorbid conditions in the pre- and late post-implementation periods. We also determined changes in disease course (intensive care unit admission, median length of hospital stay, and death). Differences in percentages were compared by using the χ² test, and differences in median length of hospital stay were compared by using the Mann-Whitney U test.

All analyses were stratified by age group (<2, 2–4, 5–17, 18–50, 50–64, and ≥65 years) and by serotype group (PCV7/non–PCV7). All p values <0.05 were considered statistically significant.

**Results**

**Overview**

In the late post-implementation period (June 1, 2008–May 31, 2010), a total of 1,196 pneumococcal isolates from CSF and blood samples were submitted to the NRLBM by the 9 sentinel laboratories; this number compares with 1,297 and 1,352 isolates submitted during the pre- and early post-implementation periods, respectively. In the late post-implementation period, clinical characteristics were available for 1,144 (96%) case-patients, compared with 1,216 (94%) in the pre-implementation period and 1,304 (96%) in the early post-implementation period (Table 1).

**IPD Incidence and Serotype Distribution**

The overall incidence of IPD declined from 14.9 to 13.8 cases/100,000 persons during the pre- and late post-implementation periods, respectively (Table 1). A 60% decline in overall IPD incidence (from 35.0 to 14.1 cases/100,000 persons) was observed in children <2 years of age (i.e., children age-eligible for PCV7 vaccination). A similar but nonsignificant decline was seen in children 2–4 years of age. In the age group with the highest incidence rate, i.e., persons ≥65 years of age, the overall IPD incidence had a significant decline of 13% (from 57.7 to 49.9 cases/100,000 persons). IPD incidence rates remained unchanged in persons 5–64 years of age.

The overall decline of IPD incidences seen among persons <2 and ≥65 years of age from the pre- to the late post-implementation period resulted from declines in the incidence of PCV7-serotype IPD of 100% and 55%, respectively (Table 1); in children <2 years of age, no PCV7-serotype IPD cases were reported after June 1, 2008. Of 3 children (2–4 years of age) with PCV7-serotype IPD after June 1, 2008, 2 were born before April 1, 2006 and had not received PCV7. The third patient (2 years of age) experienced a vaccine failure; PCV7–serotype 19F IPD developed even though the child was fully vaccinated with 4 doses of PCV7. The child was previously healthy, without any comorbidity. Overall, infections with all PCV7 serotypes declined significantly, except for infection with serotype 18C, which was already low (Figure).

However, from the pre- to the late post-implementation period, the overall incidence of non–PCV7 serotype IPD increased by 33% (from 8.0 to 10.6 cases/100,000 persons) (Table 1). IPD incidence due to non–PCV7 serotypes showed an increasing trend in all age groups, and the increase was significant in patients 50–64 and ≥65 years of age.
reasearch.

Non–PCV7 serotypes 1, 19A, 22F, and 23B increased significantly (Figure), although absolute numbers remained relatively small.

Clinical Characteristics

During all 3 study periods, surveillance data were primarily (97%–98%) for hospitalized IPD patients; the few exceptions were data for patients who visited a hospital emergency department and went home the same day. The distribution of clinical IPD manifestations among patients in different age groups did not change between the pre- and late post-implementation period (Table 2). In children <5 years of age, there was no decline in the incidence of meningitis because of an increase in non–PCV7 serotype meningitis in the late post-implementation period. In older children and adults, invasive pneumonia remained the most prevalent manifestation. The incidence of invasive pneumonia declined in the late post-implementation period in persons >65 years of age despite a significant increase in invasive pneumonia caused by non–PCV7 serotypes (Table 2).

Although the overall number of IPD cases declined from 1,216 in the pre-implementation period to 1,144 in the late post-implementation period, the number of IPD patients (all ages) with an immunocompromising condition increased from 216 to 255 (Table 3). This increase mainly occurred among persons >5 years of age, particularly among those ≥65 years of age. The number of PCV7-serotype IPD cases declined from 565 in the pre-implementation period to 268 in the late post-implementation period (all ages), and the number of patients with any comorbidity also showed a clear reduction. However, the number of immunocompromised persons with PCV7-serotype IPD declined only marginally (Table 3), indicating that persons with immunocompromising conditions may benefit less than others from herd immunity against PCV7-serotype IPD. This relatively marginal decline was seen for all PCV7 serotypes (data not shown). For non–PCV7 serotype IPD cases, there were similar increases in the number of infected immunocompromised patients and patients with any comorbidity. Moreover, at baseline a smaller proportion of immunocompromised (41%) than nonimmunocompromised (47%) persons had PCV7-serotype IPD (Table 4). Before and after introduction of PCV7, few children <5 years of age had a comorbid condition along with IPD (online Technical Appendix Table, wwwnc.cdc.gov/EID/pdfs/12-0329-Techapp.pdf).

Despite the relative increase in immunocompromised patients with IPD, the overall death rate for IPD decreased

Table 1. Incidence of invasive pneumococcal disease before and after implementation of a PCV7 vaccination program, the Netherlands, June 2004–May 2010*

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>Pre-implementation</th>
<th>Early post-implementation</th>
<th>Late post-implementation</th>
<th>Late post- vs. pre-implementation period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>Incidence</td>
<td>No. cases</td>
<td>Incidence</td>
</tr>
<tr>
<td>All serotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>1,216</td>
<td>14.9</td>
<td>1,304</td>
<td>15.9</td>
</tr>
<tr>
<td>&lt;2</td>
<td>68</td>
<td>35.0</td>
<td>42</td>
<td>22.8</td>
</tr>
<tr>
<td>2–4</td>
<td>24</td>
<td>8.2</td>
<td>26</td>
<td>8.9</td>
</tr>
<tr>
<td>5–17</td>
<td>23</td>
<td>1.8</td>
<td>22</td>
<td>1.7</td>
</tr>
<tr>
<td>18–49</td>
<td>181</td>
<td>4.9</td>
<td>209</td>
<td>5.8</td>
</tr>
<tr>
<td>50–64</td>
<td>253</td>
<td>16.4</td>
<td>292</td>
<td>18.3</td>
</tr>
<tr>
<td>&gt;65</td>
<td>666</td>
<td>57.7</td>
<td>713</td>
<td>59.6</td>
</tr>
<tr>
<td>PCV7 serotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>565</td>
<td>6.9</td>
<td>561</td>
<td>6.9</td>
</tr>
<tr>
<td>&lt;2</td>
<td>48</td>
<td>24.7</td>
<td>15</td>
<td>8.1</td>
</tr>
<tr>
<td>2–4</td>
<td>17</td>
<td>5.6</td>
<td>17</td>
<td>5.8</td>
</tr>
<tr>
<td>5–17</td>
<td>11</td>
<td>0.9</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>18–49</td>
<td>56</td>
<td>1.5</td>
<td>66</td>
<td>1.8</td>
</tr>
<tr>
<td>50–64</td>
<td>114</td>
<td>7.4</td>
<td>129</td>
<td>8.1</td>
</tr>
<tr>
<td>&gt;65</td>
<td>319</td>
<td>27.6</td>
<td>330</td>
<td>27.6</td>
</tr>
<tr>
<td>Non–PCV7 serotypes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>650</td>
<td>8.0</td>
<td>741</td>
<td>9.1</td>
</tr>
<tr>
<td>&lt;2</td>
<td>20</td>
<td>10.3</td>
<td>27</td>
<td>14.7</td>
</tr>
<tr>
<td>2–4</td>
<td>8</td>
<td>2.6</td>
<td>9</td>
<td>3.1</td>
</tr>
<tr>
<td>5–17</td>
<td>12</td>
<td>0.9</td>
<td>18</td>
<td>1.4</td>
</tr>
<tr>
<td>18–49</td>
<td>125</td>
<td>3.4</td>
<td>142</td>
<td>3.9</td>
</tr>
<tr>
<td>50–64</td>
<td>139</td>
<td>9.0</td>
<td>163</td>
<td>10.2</td>
</tr>
<tr>
<td>&gt;65</td>
<td>346</td>
<td>30.0</td>
<td>382</td>
<td>32.0</td>
</tr>
</tbody>
</table>

*Cases are number of patients included in a study covering >25% of the Dutch population; incidence is number of cases/100,000 persons. Three pneumococcal isolates (1 in the pre- and 2 in the early post-implementation period) were either not typeable or typed as a rough strain and, therefore, could not be classified as 7-valent pneumococcal conjugate vaccine (PCV7) or non–PCV7 serotypes. IRR, incidence rate ratio; NS, not significant (p>0.05); NA, not applicable; **boldface**, significant difference (p<0.05).

significantly from 2.4 to 1.6 cases/100,000 persons. This decline in IPD-related deaths appears to be the result of 1) an overall decrease in the incidence of PCV7-serotype IPD and 2) a lower case-fatality rate among persons with non–PCV7 serotype IPD (Table 3). The lower death rate was seen in all age groups, but the decrease was significant only for patients ≥65 years of age. Moreover, a decrease in the case-fatality rate for non–PCV7 serotype cases was seen not only among otherwise healthy persons (decrease from 10% to 4%; p = 0.02), but also among immunocompromised persons (from 27% to 16%; p = 0.03) and/or persons with other comorbidities (from 19% to 14%; p = 0.03). Likewise, the median length of hospital stay for children >5 years of age and adults was significantly lower during the post-implementation period than in the pre-implementation period (online Technical Appendix Table).

Discussion
Our findings show that 4 years after introduction of PCV7 in the Netherlands, the overall annual incidence of IPD decreased by 60% (from 35.0 to 14.1 cases/100,000 persons) among children <2 years of age, the age group targeted for vaccination; the decrease was a result of virtually complete eradication of PCV7 serotypes. In children 2–4 years of age, a 48% reduction was seen in IPD cases overall. A significant decline of 13% was also observed in persons >65 years of age. No significant decline in overall IPD was seen in persons 5–64 years of age because the
Our results for children are in line with those in England and Wales (4). However, among persons 5–65 years of age, the effect of herd immunity was less pronounced in the Netherlands than in England and Wales (4), where PCV7 was introduced around the same time as in the Netherlands (summer 2006), or in the United States 4 years after the introduction of PCV7 in 2000 (4). This difference can be partly explained by the absence of a catch-up campaign for children <2 years of age in the Netherlands. Young children are a primary reservoir for carriage and transmission of pneumococci because of prolonged colonization episodes related to their immature immune systems. Vaccination of toddlers in addition to newborns has a major effect on the speed of onset of herd immunity in the population.

Therefore, by continuing surveillance in the Netherlands, we will likely see more reduction of PCV7-serotype IPD in

decline in PCV7-serotype IPD was offset by a similar increase in non–PCV7 serotype IPD. The proportion of immunocompromised patients within PCV7-serotype IPD also increased. Despite these findings, the length of hospital stay and case-fatality rates declined over the last years. Our findings indicate that use of PCV7 in the Netherlands resulted in a major decrease in PCV7-serotype IPD among all age groups.

Our results for children are in line with those in England and Wales (4). However, among persons 5–65 years of age, the effect of herd immunity was less pronounced in the Netherlands than in England and Wales (4), where PCV7 was introduced around the same time as in the Netherlands (summer 2006), or in the United States 4 years after the introduction of PCV7 in 2000 (4). This difference can be partly explained by the absence of a catch-up campaign for children <2 years of age in the Netherlands. Young children are a primary reservoir for carriage and transmission of pneumococci because of prolonged colonization episodes related to their immature immune systems. Vaccination of toddlers in addition to newborns has a major effect on the speed of onset of herd immunity in the population. Therefore, by continuing surveillance in the Netherlands, we will likely see more reduction of PCV7-serotype IPD in

Table 3. Characteristics for persons with invasive pneumococcal disease before and after implementation of a PCV7 vaccination program, the Netherlands, June 2004–May 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All serotypes</th>
<th>PCV7 serotypes</th>
<th>Non-PCV7 serotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (n = 1,216)</td>
<td>After (n = 1,144)</td>
<td>p value</td>
</tr>
<tr>
<td>Comorbidity Immunocompromising condition†</td>
<td>216 (18)</td>
<td>255 (22)</td>
<td>0.013</td>
</tr>
<tr>
<td>Any comorbidity§</td>
<td>817 (67)</td>
<td>788 (69)</td>
<td>NS</td>
</tr>
<tr>
<td>Disease course/outcome ICU admission</td>
<td>258 (21)</td>
<td>243 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of hospital stay, median (IQR)</td>
<td>11.0 (7.0–18.0)</td>
<td>9.0 (5.0–16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Died</td>
<td>194 (16)</td>
<td>135 (12)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Cases are number of patients included in a study covering ≥25% of the Dutch population. Boldface, significant difference (p<0.05) between pre- and post-implementation period as calculated by \( \chi^2 \) test (% of cases), Mann-Whitney U test (median days of hospitalization), or incidence rate ratio (mortality rate). PCV7, 7-valent pneumococcal conjugate vaccine; NS, not significant (p>0.05).

†Data are no. (%) except as indicated in first column. Vaccination periods: before, pre-implementation period (June 2004–May 2006); after, late post-implementation period (June 2008–May 2010).

‡Immunocompromising condition: primary immunodeficiency, HIV/AIDS, lymphoma, leukemia, myeloma, solid organ or stem cell transplant, current immunosuppressive therapy for malignancy or autoimmune disease, asplenia/splenectomy, sickle cell disease, and renal insufficiency (dialysis required and nephrotic syndrome).

§Any comorbidity: malignancies (within previous 5 y) not considered to be immunocompromising; chronic obstructive pulmonary disease; asthma; diabetes mellitus; myocardial infarction; coronary artery condition; stroke/transient ischemic attack; cardiomyopathy; heart failure; heart valve disease; presence of cerebral/abdominal/thoracic aneurysms; thyroid disease; liver disease; intravenous drug use; long-term alcohol abuse; cerebrospinal fluid leak; recent physical trauma/skull fracture; and, for children, premature birth (<37 weeks for children 0–1 y old and <32 weeks for children 0–4 y old).

Table 4. Proportion of vaccine-type and nonvaccine-type invasive pneumococcal disease cases before and after implementation of a PCV7 vaccination program, the Netherlands, June 2004–May 2010

<table>
<thead>
<tr>
<th>Vaccination period and infecting serotype(s)</th>
<th>Otherwise healthy</th>
<th>Immunocompromising condition†</th>
<th>p value</th>
<th>Any comorbidity‡</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-implementation period Total no. cases</td>
<td>399</td>
<td>216</td>
<td>NA</td>
<td>817</td>
<td>NA</td>
</tr>
<tr>
<td>PCV7 cases</td>
<td>319 (47)</td>
<td>88 (14)</td>
<td>NS</td>
<td>76 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-PCV7 cases</td>
<td>209 (52)</td>
<td>129 (59)</td>
<td>NS</td>
<td>44 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>Post-implementation period Total no. cases</td>
<td>356</td>
<td>255</td>
<td>NA</td>
<td>788</td>
<td>NA</td>
</tr>
<tr>
<td>PCV7 cases</td>
<td>189 (22)</td>
<td>73 (29)</td>
<td>NS</td>
<td>190 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Non-PCV7 cases</td>
<td>278 (78)</td>
<td>182 (71)</td>
<td>0.050</td>
<td>598 (76)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Cases are number of patients included in a study covering ≥25% of the Dutch population. Boldface, significant difference (p<0.05) between pre- and post-implementation period, June 2004–May 2010. Pre-implementation period, June 2004–May 2010. Boldface, significant difference (p<0.05, calculated by \( \chi^2 \) test) compared with otherwise healthy patients. PCV7, 7-valent pneumococcal conjugate vaccine; NA, not applicable; NS, not significant (p>0.05).

†Immunocompromising condition: primary immunodeficiency, HIV/AIDS, lymphoma, leukemia, myeloma, solid organ or stem cell transplant, current immunosuppressive therapy for malignancy or autoimmune disease, asplenia/splenectomy, sickle cell disease, and renal insufficiency (dialysis required and nephrotic syndrome).

‡Any comorbidity: malignancies (within previous 5 y) not considered to be immunocompromising; chronic obstructive pulmonary disease and asthma; diabetes mellitus; cardiovascular disease (myocardial infarction, coronary artery condition, stroke/transient ischemic attack, cardiomyopathy, heart failure, heart valve disease, and presence of cerebral/abdominal/thoracic aneurysms); thyroid disease; liver disease; intravenous drug use; long-term alcohol abuse; cerebrospinal fluid leak; recent physical trauma/skull fracture; and, for children, premature birth (<37 weeks for children 0–1 y old and <32 weeks for children 0–4 y old).
the years after 2010. A major issue will be the rise in non-
PCV7 serotypes, which is estimated by Choi et al. (19) to
be ≈90% in England and Wales. Despite this large increase
in non–PCV7 serotype IPD, it is expected that this will not
offset the decrease in PCV7-serotype IPD in infants and
elderly persons.

The decline of IPD cases among persons with immu
nocompromising conditions was limited compared with the
decline among nonimmunocompromised persons. This re
sult may be biased because the number of PCV7-serotype
IPD cases in this group was relatively small before intro
duction of PCV7. However, the case-fatality rate for non–
PCV7 serotype IPD in the post-implementation period de
clined among otherwise healthy persons and among those
with comorbid conditions, suggesting a less severe course
of disease, even in patients with serious immunocompro
mising conditions. Thus, even if the incidence of IPD de
creased less in immunocompromised persons than in the
general population, persons with immunocompromising
conditions still appear to benefit from the vaccination pro
gram because of a reduction in case-fatality rates.

The reduced case-fatality rate for non–PCV7 serotype
IPD since the introduction of PCV7 can be partly explained
by a large increase in serotype 1 IPD. This invasive sero
type is associated with a low case-fatality rate (12,15,20),
which remained low (6%–8%) in the Netherlands during the
study period. Case-fatality rates for the other individual
serotypes also did not change significantly after introduc
tion of PCV7. In line with a lower case-fatality rate, we
also found a reduced length of hospital stay for patients
with PCV7-serotype IPD and those with non–PCV7 sero
type IPD. However, in the Netherlands, there has been a
tendency toward shorter hospital stays, which along with
other factors (e.g., improved hospital efficiency) may affect
the finding of a reduced length of hospital stay for patients
with IPD (21). For example, in 2006 a new financial system
was introduced in the Netherlands that encourages shorten
ing of the length of hospital stay.

In children, the increase in non–PCV7 serotype dis
case was most pronounced among patients with meningitis.
Although the numbers were too small to yield significant
differences, these data indicate that surveillance should be
continued and special attention should be paid to patient
characteristics and the evolution of serotype circulation
over time.

The incidence of IPD caused by nonvaccine–S. pneu
moniae serotypes 1, 19A, 22F, and 23B increased signifi
cantly after introduction of PCV7 in the Netherlands. The
increase in serotype 19A has been consistently reported
worldwide, especially increased carriage among children
(22,23) and increased cases of serotype 19A–associated
invasive disease (24) and otitis media (25–27). The role of
PCV7 in promoting serotype 19A carriage in vaccinated
children compared with unvaccinated controls has been
shown (22,28). In many countries, the increase in serotype
19A disease is associated with high levels of penicillin resi
stance (24). In the Netherlands, only 1.8% of pneumococ
cal strains are reported to be resistant (29). The increase
in serotype 22F was also seen in the United States and in
England and Wales (3,4). The occurrence of serotype 1 was
also shown to fluctuate and decline in presence of PCV7
(4). We did not see an increase in IPD caused by serotypes
6C and 15B/C, although increases have been reported
elsewhere (3,4). On May 1, 2011, the Dutch government
switched from the 7-valent to the 10-valent pneumococcal
conjugate vaccine, which includes serotypes 1, 5, and 7F in
addition to those in PCV7 (30). The 13-valent pneumococ
cal conjugate vaccine, which has not been introduced in
the Netherlands, adds protection against serotypes 3, 6A,
and 19A.

Surveillance artifacts resulting from enhanced sur
veillance and increased awareness after the introduction
of the vaccine should be considered when evaluating the
effects of the PCV7 vaccination program (4). However,
adjustments for these artifacts can introduce new biases
leading to over- and underestimation of the true effects
of the vaccine. We believe there are no indications for
enhanced surveillance and increased awareness in our
study. The laboratory-based surveillance system re
mained unchanged during the study period, 2004–2010.
Unlike the situation in England and Wales (4), the number
of pneumococcal isolates obtained from CSF samples in
the Netherlands remained stable during the years before
PCV7 was introduced (online Technical Appendix Figure
1). Moreover, the incidences of IPD caused by a great ma
jority of non–PCV7 serotypes remained stable during the
entire study period; the exceptions were for IPD caused
by serotypes 1, 19A, 22F, and 23B (online Technical
Appendix Figure 2). If enhanced surveillance had taken
place, one would expect an increase in the reported num
ber of IPD cases caused by any of these serotypes. Thus,
we made no corrections for increased case ascertainment
or awareness in this study.

Our study does have limitations. First, the study pe
riods before and after implementation of the vaccine pro
gram were relatively short; this may have caused an over
estimation or underestimation of our results. To account for
a proper transition period, we did not include June 2006–
May 2008 in our comparisons because no clear conclusions
could be drawn from this period. Second, changes in IPD
epidemiology could have been influenced by variations in
the seasonal influenza and the influenza A(H1N1)pdm09
virus epidemics in 2009 (31,32). Last, no data were avail
able on the national prevalence of comorbiditides/diseases.
Thus, we could not evaluate IPD incidence rate ratios for
the 3 patient groups in our study: otherwise healthy per-
sons, persons with any comorbidity, and persons with immunocompromising conditions.

The results of this study show that PCV7 use has reduced the number of IPD cases and deaths in children <2 years of age (the age group targeted for vaccination) and in persons ≥65 years of age. However, after introduction of PCV7, cases of IPD caused by non-PCV7 serotypes increased significantly among elderly persons, and the proportion of immunocompromised persons with IPD increased. Despite these increases, the overall IPD case-fatality rate among patients ≥65 years of age decreased, which seems to be a positive consequence of shifts in circulating serotypes after introduction of a pneumococcal conjugate vaccine for infants.

Acknowledgments

We thank all involved medical students for making data collection possible and all participating hospitals and sentinel laboratories for their cooperation.

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Ms van Deursen is a doctoral candidate at Utrecht University; this manuscript was part of her doctoral research project. Her research interests include the effectiveness of pneumococcal conjugate vaccinations on invasive pneumococcal disease and more common respiratory infections in vaccinated and unvaccinated populations.

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Invasive Pneumococcal Disease, the Netherlands

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Invasive Pneumococcal Disease and 7-Valent Pneumococcal Conjugate Vaccine, the Netherlands

Technical Appendix

Technical Appendix Table. Clinical characteristics for persons with invasive pneumococcal disease, by age group, before and after introduction of PCV7 vaccine, the Netherlands, June 2004–May 2010.*

<table>
<thead>
<tr>
<th>Age group, y, characteristic</th>
<th>Pre</th>
<th>Post</th>
<th>p value</th>
<th>Pre</th>
<th>Post</th>
<th>p value</th>
<th>Pre</th>
<th>Post</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
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</tr>
<tr>
<td>Cases total, n</td>
<td>93</td>
<td>38</td>
<td>NS</td>
<td>65</td>
<td>3</td>
<td>NS</td>
<td>28</td>
<td>35</td>
<td>NS</td>
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<tr>
<td>Comorbidities</td>
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<tr>
<td>Immunocompromising condition†, n (%)</td>
<td>4 (4)</td>
<td>3 (8)</td>
<td>NS</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>NS</td>
<td>2 (7)</td>
<td>3 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Any comorbidity‡, n (%)</td>
<td>31 (33)</td>
<td>7 (18)</td>
<td>NS</td>
<td>22 (34)</td>
<td>0 (0)</td>
<td>NS</td>
<td>9 (32)</td>
<td>7 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Disease course/outcome</td>
<td></td>
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<tr>
<td>ICU admission, n (%)</td>
<td>15 (16)</td>
<td>5 (13)</td>
<td>NS</td>
<td>11 (17)</td>
<td>0 (0)</td>
<td>NS</td>
<td>4 (14)</td>
<td>5 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay, median (IQR)</td>
<td>8.0 (5.0–12.0)</td>
<td>8.0 (4.0–12.5)</td>
<td>NS</td>
<td>8.0 (4.5–12.5)</td>
<td>10.0 (3.0–14.0)</td>
<td>NS</td>
<td>8.0 (4.8–12.0)</td>
<td>7.5 (4.0–11.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Case-fatality, n (%)</td>
<td>5 (5)</td>
<td>2 (5)</td>
<td>NS</td>
<td>4 (6)</td>
<td>0 (0)</td>
<td>NS</td>
<td>1 (4)</td>
<td>2 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality rate, cases/100,000</td>
<td>1.0</td>
<td>0.4</td>
<td>NS</td>
<td>0.8</td>
<td>0.0</td>
<td>NS</td>
<td>0.2</td>
<td>0.4</td>
<td>NS</td>
</tr>
<tr>
<td>5–64</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Cases total, n</td>
<td>457</td>
<td>481</td>
<td>181</td>
<td>108</td>
<td>276</td>
<td>373</td>
<td></td>
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</tr>
<tr>
<td>Comorbidities</td>
<td></td>
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</tr>
<tr>
<td>Immunocompromising condition†, n (%)</td>
<td>88 (19)</td>
<td>102 (21)</td>
<td>NS</td>
<td>27 (15)</td>
<td>30 (28)</td>
<td>0.008§</td>
<td>61 (22)</td>
<td>72 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Any comorbidity‡, n (%)</td>
<td>257 (56)</td>
<td>272 (57)</td>
<td>NS</td>
<td>106 (59)</td>
<td>63 (58)</td>
<td>NS</td>
<td>151 (55)</td>
<td>209 (56)</td>
<td>NS</td>
</tr>
<tr>
<td>Disease course/outcome</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>106 (23)</td>
<td>120 (25)</td>
<td>NS</td>
<td>46 (25)</td>
<td>27 (25)</td>
<td>NS</td>
<td>60 (22)</td>
<td>93 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay, median (IQR)</td>
<td>10.0 (6.0–17.0)</td>
<td>8.0 (5.0–15.0)</td>
<td>&lt;0.001§</td>
<td>10.0 (6.0–17.0)</td>
<td>8.0 (5.0–14.0)</td>
<td>0.027§</td>
<td>10.0 (6.0–17.0)</td>
<td>8.0 (5.0–15.0)</td>
<td>0.006§</td>
</tr>
<tr>
<td>Case-fatality, n (%)</td>
<td>41 (9)</td>
<td>31 (6)</td>
<td>NS</td>
<td>18 (10)</td>
<td>9 (8)</td>
<td>NS</td>
<td>23 (8)</td>
<td>22 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality rate, cases/100,000</td>
<td>0.6</td>
<td>0.5</td>
<td>NS</td>
<td>0.3</td>
<td>0.1</td>
<td>NS</td>
<td>0.4</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;65</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cases total, n</td>
<td>666</td>
<td>625</td>
<td>319</td>
<td>157</td>
<td>346</td>
<td>468</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompromising condition†, n (%)</td>
<td>124 (19)</td>
<td>150 (24)</td>
<td>0.018§</td>
<td>59 (18)</td>
<td>43 (27)</td>
<td>0.026§</td>
<td>65 (19)</td>
<td>107 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>Any comorbidity‡, n (%)</td>
<td>529 (79)</td>
<td>509 (81)</td>
<td>NS</td>
<td>248 (78)</td>
<td>127 (81)</td>
<td>NS</td>
<td>281 (81)</td>
<td>382 (82)</td>
<td>NS</td>
</tr>
<tr>
<td>Disease course/outcome</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission, n (%)</td>
<td>137 (21)</td>
<td>118 (19)</td>
<td>NS</td>
<td>58 (18)</td>
<td>33 (21)</td>
<td>NS</td>
<td>79 (23)</td>
<td>85 (18)</td>
<td>NS</td>
</tr>
</tbody>
</table>
### Length of hospital stay, median (IQR)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (IQR)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-implementation</td>
<td>13.0 (8.0–20.0)</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Post-implementation</td>
<td>13.0 (8.0–20.0)</td>
<td>0.001§</td>
</tr>
</tbody>
</table>

### Case-fatality, n (%) case/100,000

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (IQR)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-implementation</td>
<td>148 (22)</td>
<td>0.007§</td>
</tr>
<tr>
<td>Post-implementation</td>
<td>70 (22)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Mortality rate, cases/100,000

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (IQR)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-implementation</td>
<td>12.8</td>
<td>0.001§</td>
</tr>
<tr>
<td>Post-implementation</td>
<td>6.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Significant difference (p < 0.05) between pre- and post-implementation period calculated by χ² test (% of cases), Mann-Whitney U (median length hospital of stay) or incidence rate ratio (mortality rate).

---

Technical Appendix Figure 1.

Nationwide collection of pneumococcal isolates (from cerebrospinal fluid), the Netherlands, 2001–02 through 2008–09. Epidemiologic years, June 1–May 31 of the succeeding year.

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*Cases = number of cases included in the surveillance study (covering ≥25% of the Dutch population); Pre = pre-implementation period (June 2004–May 2006); Post = late post-implementation period (June 2008–May 2010). PCV7, 7-valent pneumococcal conjugate vaccine; ICU, intensive care unit; IQR, interquartile range; NS, not significant.

†Immunocompromising condition: primary immunodeficiency, HIV/AIDS, lymphoma, leukemia, myeloma, solid organ or stem cell transplantation, current immunosuppressive therapy for malignancy or autoimmune disease, asplenia/splenectomy, sickle cell disease and renal insufficiency (need for dialysis and nephrotic syndrome).

‡Any comorbidity: malignancies (within the previous 5 y) not considered to be immunocompromising, chronic pulmonary disease (chronic obstructive pulmonary disease and asthma), diabetes mellitus, cardiovascular disease (myocardial infarction, coronary artery condition, stroke/transient ischemic attack (TIA), cardiomyopathy, heart failure, heart valve disease, and/or presence of cerebral/abdominal/thoracic aneurysms), thyroid disease, liver disease, intravenous drug use, long-term alcohol abuse, cerebrospinal fluid leak, recent physical trauma/skull fracture and for children premature birth (<37 weeks for children 0–1 y old and <32 for children 0–4 y old).

§Significant difference (p < 0.05) between pre- and post-implementation period calculated by χ² test (% of cases), Mann-Whitney U (median length hospital of stay) or incidence rate ratio (mortality rate).
Technical Appendix Figure 2.
Incidence rate ratio of serotype-specific invasive pneumococcal disease among patients ≥65 years of age, the Netherlands, 2004-2010.
Epidemiologic years, June 1–May 31 of the succeeding year. Incidence rate ratios (IRRs) calculated by using 2004-2006 as reference period (IRR=1.00).

- 1
- 19A
- 3
- 22F
- 7F
- 8
- PCV7
- Non-PCV7