Review of Serotype Replacement in the Setting of PCV7 Use and Implications for the PCV10/PCV13 Era

Background

Seven-valent pneumococcal conjugate vaccine (PCV7) was first introduced in the United States in the year 2000. Over the subsequent 5-10 years, PCV7 was introduced in numerous other countries, mostly in the developed world. In 2007, WHO issued recommendations on the use of PCV7 among countries with high rates of childhood mortality. Specifically, countries where mortality among children <5 years old was >50 per 1000 live births or where >50,000 children die annually were recommended to prioritize inclusion of PCV7 in national immunization programs (1). In countries that have introduced PCV7, reductions in PCV7-type invasive pneumococcal disease (IPD) have been well documented, especially in the age group targeted for vaccination (direct effects), but also, in some countries, among groups too young or too old to be vaccinated (indirect effects). Simultaneously, while rates of PCV7-type IPD have declined, in many settings rates of IPD caused by non-PCV7 serotypes have increased. While several causes may affect the magnitude of this observed increase, the increased incidence of non-PCV7-type IPD is likely, in part, caused by vaccination; such increases that result directly from vaccination are referred to as “serotype replacement”. (2) These increases in non-PCV7 serotypes, whether causally associated with PCV7 or not, have partially eroded some of the benefits of vaccination, but only in certain locations and in certain age groups, raising the question of the extent to which increases in non-PCV7 serotypes can be attributed to vaccination (i.e., serotype replacement).

To quantify the extent of increases in non-PCV7-type IPD following vaccination and place it in the context of overall changes in IPD rates, WHO hosted the First Expert Consultation on the Epidemiology of Changing Pneumococcal Serotypes Following Conjugate Vaccine Introduction in July 2010. Experts in epidemiology, immunization programs, surveillance, and microbiology reviewed data from nine settings around the world (3). Evidence of reductions in PCV7-type IPD was consistent across all nine sites. However, increases in non-PCV7 serotypes were clear in some sites but nearly absent in others. In certain instances, issues related to surveillance methodologies could partially explain the differences in observed findings. This lack of consistency and the potential relationship to surveillance methods led to the recommendation that a systematic review should be performed, that inclusion of data from a broader range of settings might shed light on the phenomenon of serotype replacement, and that conclusions might be drawn which could inform vaccine recommendations. A study team and Technical Advisory group were formed, funding was obtained from The Bill and Melinda Gates Foundation, and a protocol was developed.

Methods

Stage 1. Data collection and preliminary analysis

Data collection. The following inclusion and exclusion criteria were developed to identify datasets that could potentially inform the analysis of trends in IPD.

Inclusion criteria:
1. Data published or collected from 2000-present.
2. Populations where at least some children <15 years of age have received PCV7.
3. At least 25 percent PCV7 coverage among those recommended to receive PCV7.
4. IPD surveillance data collected in the setting of any PCV7 schedule with at least one year of data before and one year of data after PCV7 introduction. The year of introduction was identified as
the first year in which PCV7 was recommended and introduced for any segment of the population.

5. Serotype information for at least 50 percent of all reported IPD cases.

6. Measurement of direct or indirect effects of PCV7 (i.e. can include data on the age group targeted for vaccination or age groups not targeted for vaccination).

7. Availability of population denominator data (e.g., number of children <5 years old)

Exclusion criteria: Case-control studies (4), indirect cohort studies (5), or studies that use the screening method (6).

Datasets were identified using two approaches. The first leveraged the comprehensive literature review done as part of a separate study, the PCV Dosing Landscape Analysis undertaken by the GAVI Accelerated Vaccine Introduction-Technical Advisory Consortium (AVI-TAC). The Dosing Landscape Analysis Team developed inclusion and exclusion criteria for assessing the suitability of datasets for that project. When those criteria were applied, 162 articles were identified and reviewed and, ultimately, 39 were determined to represent distinct datasets that potentially met the inclusion criteria for the Serotype Replacement analysis. In the second approach, the study team solicited recommendations from pneumococcal experts, WHO headquarters and regional offices, multinational surveillance networks (e.g., European Centres for Disease Control), and ad hoc reviews of published literature. An additional 31 datasets were identified that met the criteria of the Serotype Replacement analysis but did not meet the Dosing Landscape criteria. Therefore, in total, investigators responsible for 71 sites were contacted for potential participation. Of these 71 potential datasets, data were ultimately received from 31 sites. Of these, 29 were received in time for analysis and discussion at the Second Expert Consultation on Pneumococcal Epidemiology following Conjugate Vaccine Introduction (see Stage 2 below) (Figure 1).

Data were collected in standardized tables stratified by serotype, age groups, clinical syndrome, and hospitalization status. Denominators were collected to calculate rates of IPD. In addition, investigators from each site completed a survey requesting information on the characteristics of their surveillance system and the PCV7 vaccination program. Annual incidence rates of IPD due to PCV7 and non-PCV7 serotypes among children <5 years of age and persons ≥5 years of age were calculated. Isolates with unknown serotypes were redistributed according to the distribution of those with known serotypes for each year and within each age group. Because previous analyses have shown that serotype-specific changes after PCV7 introduction vary by hospitalization status and because surveillance sites differ in their inclusion of non-hospitalized children, analyses of data from children <5 years of age were limited to hospitalized cases. Summary measures of changes in serotype-specific IPD rates were calculated as rate ratios by dividing the rates of overall, PCV7 serotype, and non-PCV7 serotype IPD in the intervals 1-2, 3-4 and ≥5 years after PCV7 introduction by the average pre-PCV7 incidence of overall, PCV7 serotype, and non-PCV7 serotype IPD, respectively. For example, consider a site where children <5 years old had pre-PCV7 average baseline rates of 80 cases per 100,000 for all IPD, 60 cases per 100,000 for PCV7-type IPD, and 20 cases per 100,000 for non-PCV7 types. If the rates of IPD for all serotypes, PCV7 types, and non-PCV7 types were 40, 15, and 25 cases per 100,000 at 3-4 years post-introduction, then the corresponding rate ratios would be 0.50, 0.25, and 1.25. Because rate ratios are not normally distributed, summary estimates of rate ratios were expressed as median and interquartile ranges.

Stage 2. Expert review of preliminary data analysis

Preliminary results of this analysis were presented at the WHO-sponsored Second Expert Consultation on the Changing Epidemiology of Pneumococcal Serotypes following Conjugate Vaccine Introduction on
September 15-16, 2011. Data from 29 sites were presented to study co-investigators, experts in the field, Technical Advisory Group (TAG) members and WHO representatives. Wide variability in results was found across sites. Some of this variability was thought to be due to low vaccine coverage, insufficient time before or after PCV7 introduction to have a stable assessment of IPD trends, or surveillance artifacts identified by the co-investigators who provided data. Given this heterogeneity, the meeting participants (including the Technical Advisory Group,) felt that it was inappropriate to infer the magnitude of serotype replacement from the presented datasets. They recommended a re-analysis of the data using a more limited number of sites. The following set of criteria were proposed, and accepted, as those that datasets must meet to be included in the re-analysis to be presented to SAGE:

1. ≥2 years of surveillance before PCV7 introduction. Fewer years of data limit the ability to establish stable baseline rates.
2. ≥3 years of surveillance after PCV7 introduction. Meeting participants agreed that this is the minimum number of years of data needed post-introduction to interpret increases in non-PCV7-serotype IPD.
3. Vaccine coverage of 70% for the primary series (without booster) by age 12 months in the surveillance population. Seventy percent was selected as that is the minimum coverage with DTP3 used by GAVI for financing new vaccine introductions, including PCV.
4. Absence of major surveillance artifacts that would affect estimates of serotype-specific rates or, if such artifacts are present, an ability to adjust for them.

In addition to the methods used in Stage 1, two additional analytic methods were used in Stage 2. In Stage 1, serotypes 6A and 6C were assigned as non-PCV7 serotypes because of the inability to distinguish the two in some sites. In Stage 2, undistinguished 6A/6C isolates were redistributed according to their known distribution in the region and 6A isolates were included as PCV7 types and 6C as non-PCV7 types. Second, the data from England and Wales were adjusted for increasing rates of IPD prior to vaccine introduction (7).

Results

Site characteristics.

Seventeen datasets (mostly from North America and Europe) met the inclusion criteria for Stage 2 (Active Bacterial Core surveillance (ABCs, U.S.); Alaska, Native & Non-Native combined (U.S.); Australia, Indigenous; Australia, Non-indigenous; Bilbao (Spain); Calgary, Alberta (Canada); Denmark; England & Wales; France; Greece; Navajo (U.S.); Northern California Kaiser Permanente (U.S); Netherlands; Norway; Scotland; Switzerland; Utah (U.S.)). Of note, data from Australian Indigenous and non-Indigenous populations, which were not available for presentation at the Second Expert Consultation in September 2010, are included in the Stage 2 analysis. The following datasets from Stage 1 were excluded from Stage 2 for the following reasons: <2 years pre-PCV 7 data: Belgium, German Pediatric Surveillance Unit (ESPED), Quebec; <3 years post-PCV7 data: Czech Republic, Ireland, Israel, New Zealand, South Africa, Uruguay; <70% PCV7 coverage: Austria, Barcelona, Singapore; denominators unavailable: provinces of Canada other than Alberta and Quebec; unclear population base: Dallas, U.S.; changes to surveillance methods: German National Reference Center for Streptococci. All sites except Bilbao introduced PCV7 into their national immunization program as a universal recommendation for children. All included sites introduced PCV7 using one of four schedules: 2 primary doses with a booster (“2+1”, 6 sites, 35%); 3 primary doses with a booster (“3+1”, 9 sites, 53%); 3 primary doses without a booster (“3+0”, Australian non-Indigenous); and 3 primary doses with a dose of 23-valent pneumococcal polysaccharide vaccine (PPV23) given in the second year of life (“3+PPV23”, Australian Indigenous).
Vaccine coverage for the primary series of PCV7 ranged from 70-97%. Vaccine coverage increased with subsequent years after introduction in most sites. The majority of surveillance systems captured data at a national level, although some were regional in scale (Table 1). Most sites relied on passively reported cases while a minority used active systems where regular communication with reporting entities (e.g., clinical microbiology laboratories) aimed to ensure complete case ascertainment. A smaller minority performed audits of clinical microbiology laboratories to document complete case reporting. The number of years of surveillance pre- and post-PCV7 introduction varied by site (Figure 2).

Children <5 years of age.
The average number of isolates per year before PCV7 introduction varied from 2 in Greece to 690 in England and Wales (Figure 3a). Of the 9 sites with surveillance for 5 or more years post-PCV7 introduction, 6 had ≤20 cases per year. Pre-PCV7 rates of overall hospitalized IPD varied from 4 per 100,000 persons in Greece to 283 per 100,000 persons among Australian Indigenous (Figure 4a). The percentage of pre-PCV7 IPD cases caused by PCV7 serotypes also varied by site, ranging from 51% among the Navajo to 88% among Australian non-Indigenous (Figure 5a).

Decreases in PCV7-type IPD were observed in all 17 sites after vaccine introduction (Figure 6). Rates of PCV7-type IPD declined consistently with each successive year of the vaccination program: at 5 or more years after PCV7 introduction the median rate ratio for PCV7 serotypes was 0.058. Increases in IPD caused by non-PCV7 serotypes were observed after PCV7 introduction in all sites (Figure 7). Rates of non-PCV7–type IPD increased consistently with each successive year of the vaccination program: at 5 or more years after PCV7 introduction, the median rate ratio for non-PCV7 serotypes was 2.77. Reductions in overall IPD were evident after PCV7 introduction in all 17 sites (Figure 8). Reductions in overall IPD were generally greatest at 3-4 years post-introduction and mostly maintained at 5 or more years when the median rate ratio for overall IPD was 0.83 (range 0.30-0.95). Of note, the 9 sites with surveillance data extending 5 or more years post-PCV7 introduction appeared to segregate into two groups, i.e., those with rate ratios of 0.30-0.40 (Calgary, Australia non-Indigenous, ABCs) and those with rate ratios from 0.80-0.95 (Australia Indigenous, Navajo, Bilbao, France, Utah, Alaska).

Because indigenous populations are typically at higher risk of IPD and because their socioeconomic status and living conditions are substantially different from non-Indigenous populations, we also evaluated changes in non-PCV7 serotype IPD among two indigenous populations: the Navajo in the U.S. and Indigenous Australians. We found that rate ratios for non-PCV7-type IPD at 5 or more years in these two groups (1.91, Navajo; 1.96 Australia Indigenous) were below the median (2.77). The rate ratio for Australian non-Indigenous was actually higher than for the Australian Indigenous (2.77). At 5 or more years, the rate ratios for overall IPD in these two groups was 0.83 for the Navajo and 0.79 for the Australian Indigenous, very similar to the median rate ratio of 0.83.

We stratified the analysis by vaccine schedule and syndrome. Reductions in overall IPD were very similar among sites with and without catch-up programs. Only one site with a 2+1 schedule had ≥5 years of data post-introduction, precluding comparison of schedule at that time point. The two Australian sites had slightly different schedules (Indigenous, 3+PPV23; non-Indigenous, 3+0). Although the number of meningitis cases was small in many datasets, we found that most trends in serotype-specific IPD were similar among meningitis cases to those among all hospitalized cases.

To identify which serotypes were contributing most to increases in non-PCV7 serotypes, we evaluated separately the additional serotypes in PCV10 (1, 5, 7F), in PCV13 (1, 5, 7F, 3, 19A, but not 6A, which was grouped with PCV7 serotypes as described in methods), and all other serotypes not included in any of
the three conjugate vaccine formulations. Rates of IPD caused by all three of these groups of non-PCV7 serotypes increased after PCV7 introduction (Figure 9). The rate of IPD caused by serotypes 1, 3, 5, 7F, and 19A (as a group) was higher than the rate of IPD caused by the other two groups in all time periods. By 5 or more years post-introduction, the absolute rate of IPD caused by serotypes 1, 3, 5, 7F, and 19A increased by 7.4 per 100,000 from the baseline rate (median RR 3.7), compared to an increase of 4.3 per 100,000 from the baseline rate (median RR 2.9) for serotypes 1, 5, and 7F and an increase of 3.8 per 100,000 from the baseline rate (median RR 1.9) for all other non-PCV7 serotypes. The serotypes with the most consistent increases across sites included serotypes 19A, 7F and 3, all serotypes included in PCV13. Although the numbers were small, the non-PCV13 serotypes with the most consistent increases included serotypes 22F, 12F and 33F.

**Persons >5 years of age**

Among the 15 sites conducting surveillance for IPD among persons >5 years of age, all observed decreases in PCV7-type IPD after PCV7 introduction (Figure 10). Similar to the observations among young children, reductions in PCV7-type IPD progressed with the number of years since vaccine introduction: by 5 or more years post-introduction, the median rate ratio for PCV7-type IPD was 0.17. The one site that observed an increase in PCV7-type IPD was Bilbao, Spain, a site that averaged only three isolates per year in the post-PCV period among persons >5 years old. All 15 sites observed increases in non-PCV7 types after PCV7 introduction (Figure 11). Again, similar to the observations among young children, these increases became progressively greater with the number of years since vaccine introduction: 5 or more years post-introduction, the median rate ratio for non-PCV7-type IPD was 1.98. Similar to our observations for children <5 years old, rate ratios for non-PCV7-type IPD at 5 years post-introduction among the Navajo (1.11) and Australian Indigenous (1.48) populations >5 years old were below the median for all sites (1.98). There was a spectrum of changes in overall IPD, with some sites showing an increase, others showing a decrease, and many having little change post-introduction (Figure 12). In terms of overall rates of IPD, rate ratios ranged from 0.66 to 2.18 at 3-4 years post-introduction with a median of 0.93. At 5 or more years post-introduction, rate ratios for overall IPD among persons >5 years old ranged from 0.69 to 1.66 with a median of 1.15.

A summary of findings for both age groups is shown in Table 2.

**Surveillance characteristics.**

Of the 17 sites included for further analysis, 16 sites provided additional information on detailed characteristics of their surveillance system. Specifically, questions were asked regarding possible changes in blood culturing practices, laboratory practices (e.g., percentage of isolates serotyped), referral and care seeking practices, outbreaks of IPD caused by individual serotypes, and changes in surveillance methodology or programs (addition/subtraction of sites, case definition, enhanced surveillance).

The majority of sites reported no changes in blood culturing practices during the surveillance period. However, some reported increases in the number of blood cultures collected while others (ABCs, Utah) suspected that fewer blood cultures were being collected among ambulatory children with no changes among hospitalized children or adults. Furthermore, three sites indicated other changes in laboratory practices. More specifically, Norway noted that since PCV7 introduction, missing isolates have been requested directly by the laboratory and the proportion of isolates available has increased.
Four sites noted changes in antibiotic prescribing practices. Specifically, both France and ABCs (USA) indicated a decrease in overall use of antibiotics. Two sites indicated changes in host susceptibility. Calgary noted an increase in infections among non-HIV immunocompromised patients; however, this population represents a small proportion of all cases. Switzerland noted an increase in co-morbidities among elderly patients hospitalized for community-acquired pneumonia. There were no major changes to pneumococcal polysaccharide vaccine recommendations during the period of surveillance in any of the sites.

Six sites reported IPD outbreaks that have occurred during their surveillance period. Three sites (Utah, Australia and Norway) reported outbreaks of serotype 1 among their populations. The serotype 1 outbreak in Utah occurred among children during 1993 to 2007, years which spanned the introduction of PCV7. Norway’s serotype 1 outbreak occurred nationwide from 1994-1997, before PCV7 introduction and before the years included in the pre-PCV7 period of this analysis. The serotype 1 outbreak in Australia occurred more recently in 2010-2011 among children in the Northern Territory and Western Australia, during years which would have been included in the post-PCV7 period for this analysis. The Navajo site reported an outbreak of serotype 5 among all ages in 1995 before PCV7 introduction and the Alaska site reported outbreaks of 12F (2003, 2006 among Alaskan Natives) and 8 (2006 among homeless) after PCV7 introduction. Calgary reported an outbreak of serotypes 5 and 8 in middle-aged, homeless, aboriginal males in 2005 and 2007 after PCV7 introduction.

Both Calgary and ABCs (USA) indicated expansion to their surveillance areas during the reported surveillance period. From 1998 to 2009, Calgary surveillance included only the Calgary Health Region; from 2010, the surveillance area was expanded to include surrounding localities and the population increased by 33%. ABCs also added two sites and expanded their catchment area in other sites; however, the data submitted for this analysis only included the original continuously reporting sites. The Navajo site indicated enhanced surveillance during the surveillance period noting an implementation of more systematic processes for identifying cases over years and more systematic audit processes. These enhancements have been accounted for in the data.

Discussion

These data confirm that PCV7 has been successful in dramatically reducing the incidence of the disease it was designed for – vaccine serotype IPD among young children – in many different settings. Moreover, PCV7 has demonstrated indirect (or herd) protection in most of these settings by leading to a decrease in PCV7 serotypes among adult populations. These data also confirm that non-PCV7 serotypes have increased after vaccine introduction in children. Because of the influence of PCV7 on nasopharyngeal colonization with PCV7 and non-PCV7 serotypes, the vaccine has led, simultaneously, to herd protection against PCV7 serotypes and increases in non-PCV7 serotypes among adults. The consistency of this finding across sites suggests that serotype replacement following vaccination is a real phenomenon. This is supported by the similarity of serotypes that appear after vaccination in multiple sites, suggesting that some serotypes have a greater propensity to “replace” PCV7 serotypes in IPD. Importantly, the non-PCV7 serotypes that tend to cause IPD after PCV7 introduction are only a subset of those that replace those found in the nasopharynx following vaccination with PCV7, a phenomenon that occurs quickly among children after they receive PCV7 vaccine. Despite the evidence for serotype replacement, other contributors to observed increases in non-PCV7 serotypes cannot be excluded. These contributors include outbreaks (e.g., serotypes 1 and 8), antibiotic pressure (e.g., serotype 19A), and surveillance artifacts that result in increased intensity of surveillance in the post-PCV7 period. The relative contribution of serotype replacement and these other factors in causing increases in non-PCV7 disease
remains to be determined. Importantly, PCV7 has clearly led to a net benefit in reducing overall IPD among children, despite increases in non-PCV7-type IPD. The same overall reduction in IPD has not been observed consistently among older children and adults. Six of nine sites with ≥5 years of data post-PCV7 introduction showed an increase in overall IPD. Of these 6 sites, two reported outbreaks of non-PCV7 serotypes after vaccine introduction among adults, and two sites were very small, averaging <10 IPD cases per year. The effect of PCV7 on serotype-specific IPD seems to be a dynamic process, with continued changes with time since vaccine introduction. Therefore, it will be important to continue surveillance for many years after PCV introduction in multiple geographic and epidemiologic settings to document the ongoing story of post-PCV serotype-specific epidemiology.

All countries, whether they have introduced PCV or are planning to do so, should exercise great care in their approach to performing surveillance for IPD. Virtually all surveillance systems require several years to mature as clinicians become familiar with reporting requirements, as laboratories collect, store and ship isolates, and as system investigators consider the most useful ways to analyze the data. Several factors can lead to erroneous interpretations of surveillance data. If the proportion of all cases for which isolates are available for serotyping increases over time, then the observed reductions in PCV7-type disease will be underestimated while increases in non-PCV7-type IPD will be overestimated. Similarly, if the proportion of all cases that are captured by the surveillance system increases after PCV7 introduction, then increases in non-PCV7-type IPD (whether caused by vaccination or not) will appear more pronounced than if case ascertainment were consistent over time. Finally, if only certain cases (e.g., the severest or those who have been vaccinated) are selected for serotyping, then inferences about the extent of serotype replacement will not represent that of the target population for vaccination.

A comparison of findings from two surveillance systems can serve as an instructive example. In England and Wales, baseline rates of IPD were increasing before PCV7 introduction, which amplified further the increases in post-PCV7 introduction rates of non-PCV7-type IPD. After controlling for this increasing baseline, rates of non-PCV7-type IPD increased less dramatically. In the United States, it was standard practice before PCV7 introduction to collect blood for culture from ambulatory children with febrile illnesses and no clear source of infection. There is some evidence to suggest that this practice became less common after PCV7 introduction. When rates of IPD among all children are examined in the U.S., increases in non-PCV7-type IPD are less evident than when cases are limited to those who have been hospitalized. Indeed, when these types of surveillance issues are taken into account, overall trends in IPD in England and Wales as compared to the United States appear much more similar (7).

This analysis has certain limitations. First, all data were from sites that had introduced PCV7, which has now been replaced by PCV10 and PCV13. The greatest increases in non-PCV7 types after PCV7 introduction were among serotypes included in the higher valency vaccines. Therefore, replacement disease (as a result of PCV7 use) caused by PCV10 or PCV13 serotypes is unlikely to continue. Although there were also increases among serotypes not included in PCV13, the increases were smaller, both in absolute number of cases and proportionately, than the increases in IPD caused by serotypes in PCV13. Despite this observation, the magnitude of serotype replacement following introduction of PCV10 or PCV13 could be different from that observed with PCV7, and cannot be fully predicted by this analysis. Second, we identified evidence of surveillance artifacts in certain datasets but we cannot be sure that we have identified—let alone controlled for—artifacts that may remain in the existing datasets. The third limitation was that this analysis was undertaken in mostly high-income countries. While South Africa was included in our initial analysis, we excluded it from the final analysis because it only had one year of post-introduction data. Findings from the two indigenous populations among our datasets did
not diverge substantially from the findings of the overall analysis. Nonetheless, the results of this analysis might differ in developed countries, where the pressure of pneumococcal carriage, serotype distributions, pneumococcal epidemiology, and presence of underlying conditions differ from high-income countries. A fourth limitation is that all sites, regardless of population size or numbers of cases, received equal weight and therefore contributed equally to estimates of median rate ratios. We hope to address this issue in future modeling efforts. Fifth, none of the countries included in this analysis had high prevalence of HIV, a condition known to markedly increase risk of IPD and to modestly decrease the efficacy of PCVs. Finally, these conclusions apply only to IPD and may not be representative of serotype replacement in the context of non-bacteremic pneumococcal pneumonia, an important cause of morbidity and mortality worldwide.

Recommendations

Recommendation #1. The results of this analysis of serotype replacement suggest that no changes are needed to the current SAGE recommendation for introduction of pneumococcal conjugate vaccines into developing countries. Indeed, the benefits of PCV use in preventing IPD among children are clear. Countries planning to introduce PCV should continue their plans. Countries that are considering introduction of PCV should view serotype replacement as just one of many considerations and not as an impediment to introduction.

Recommendation #2. Surveillance for IPD should be performed in a way that maximizes the interpretability of the results. Based on the datasets reviewed, the co-investigators arrived at several recommendations regarding the approach to surveillance for IPD in the context of identifying and characterizing the magnitude of PCV-induced serotype replacement, apart from other factors that can influence serotype-specific trends in IPD. Those recommendations, which apply to individual surveillance systems, are:

1. Intensity of surveillance: Active or passive surveillance is acceptable, but should be consistent over time, and assessed regularly for sensitivity of case ascertainment.
2. Type of surveillance: Population denominators are essential for calculating rates of disease and for interpreting changes in serotype-specific IPD over time.
3. Duration of surveillance: At least 2 years of surveillance before PCV introduction are needed to establish a baseline rate of IPD and at least 3 years of surveillance after PCV introduction are need to reliably detect potential serotype replacement.
4. Size of surveillance system: Datasets in which a small change in the number of isolates in any given year will substantially alter rates of IPD should not be used in an attempt to identify serotype replacement.
5. Serotyping: If it is not possible to serotype all isolates, then a representative sample should undergo serotyping so that findings can be generalized to all cases. If the percentage of isolates that are serotyped changes over-time, adjustments should be made to apply the serotype distribution of isolates with known serotypes to that of isolates with unknown serotype. Serotypes 6A and 6C should be distinguished when possible due to differences in their post-vaccine epidemiology.
6. Case definition: Surveillance should focus on hospitalized cases of IPD, where pneumococcus is identified from a normally sterile site.
7. Clinical and other variables: Key variables should be captured from surveillance systems measuring IPD, including age of cases, clinical syndrome, hospitalization status, significant
comorbidities (particularly HIV), changes in the surveillance system (e.g. case reporting, blood culturing practices).

8. Vaccine coverage: Since serotype replacement requires substantial coverage among the target population, increases in non-PCV serotypes in the setting of low PCV coverage should be interpreted with caution.

9. Supporting evidence: Other studies, such as nasopharyngeal colonization studies, observational (e.g., case-control) studies of vaccine effectiveness, and evaluation of trends in pneumonia hospitalizations can also shed light on the relationship between PCV introduction and the overall benefits of the vaccination program.

10. Collaboration: Given the complexities surrounding the evaluation of serotype replacement, investigators who plan to evaluate the early effects of PCV introduction are strongly encouraged to collaborate with other investigators with experience in the development of surveillance systems and analysis of post-PCV introduction surveillance data. Investigators are also encouraged to share their findings with collaborators and other stakeholders at an early stage; such discussions can lead to alternative and potentially important modifications to the analysis or interpretation of such data.

In settings where these recommendations cannot be implemented, introduction of PCV should still occur as quickly as possible and surveillance for IPD can still be undertaken. However, attempts to identify and characterize serotype replacement using surveillance systems that do not meet these criteria could lead to erroneous conclusions that may eventually prove to be unfounded.
References


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Tables and figures. In order of appearance

Figure 1. Summary of literature review and data collection process for datasets included in the analysis

Data not received in time, n=1
No denominator data, n=1

Data analyzed in Phase I
Presented at Expert meeting,

Refused/Ineligible, n=24
No response to emails, n=9

Data received
N=31

Contact lost/no date submitted ,
n=7

Investigators/Sites Contacted
n=71

Agree to Participate
n=38

Data analyzed in Phase II,
Presented to SAGE Nov 2011
Table 1. Surveillance system characteristics for 17 sites included in the analysis

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<td>1</td>
</tr>
<tr>
<td>0 to &lt; 18 years</td>
<td>3</td>
</tr>
<tr>
<td>0 to ≥65y</td>
<td>13</td>
</tr>
<tr>
<td><strong>Completeness of reporting verification</strong></td>
<td></td>
</tr>
<tr>
<td>Audits</td>
<td>9</td>
</tr>
<tr>
<td>Capture- Recapture</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Not done</td>
<td>3</td>
</tr>
</tbody>
</table>
Figure 2. Summary of the number of years of surveillance pre- and post-PCV7 introduction among 17 sites. Pre-PCV7 years in white, year of introduction (Year 0) in grey, and post-PCV7 years in black.
Figure 3. Average annual number of IPD cases before PCV7 introduction by site, children <5 years old (A) and persons ≥ 5 years old (B)
Figure 4. Annual average rate of hospitalized IPD in years before PCV7 introduction by site for children < 5 years old (A) and persons ≥ 5 years old (B)
Figure 5. Percentage of overall IPD due to PCV7 serotypes by site before PCV7 introduction for children < 5 years old (A) and persons ≥ 5 years old (B)
Figure 6. Box and whiskers plot on log scale of rate ratios (RR) of PCV7-serotype IPD among hospitalized children < 5 years old comparing baseline rates to those 1-2 years, 3-4 years and 5+ years after PCV7 introduction.

* Line in box is median value, bottom and top of box are 25th and 75th percentiles, respectively, whiskers represent 1.5 times the interquartile range or the maximum or minimum value if less than 1.5 times the interquartile range, and the individual markers represent individual sites. A RR of 1.0 indicates no change between pre- to post-PCV7 rates.
Figure 7. Box and whiskers plot on log scale of rate ratios (RR) of non-PCV7-serotype IPD among hospitalized children < 5 years of age comparing baseline rates to those 1-2 years, 3-4 years and 5+ years after PCV7 introduction.

* Line in box is median value, bottom and top of box are 25th and 75th percentiles, respectively, whiskers represent 1.5 times the interquartile range or the maximum or minimum value if less than 1.5 times the interquartile range, and the individual markers represent individual sites. A RR of 1.0 indicates no change between pre- to post-PCV7 rates.
Figure 8. Box and whiskers plot on log scale of rate ratios (RR) of overall IPD among hospitalized children < 5 years of age comparing baseline rates to those 1-2 years, 3-4 years and 5+ years after PCV7 introduction

* Line in box is median value, bottom and top of box are 25th and 75th percentiles, respectively, whiskers represent 1.5 times the interquartile range or the maximum or minimum value if less than 1.5 times the interquartile range, and the individual markers represent individual sites. A RR of 1.0 indicates no change between pre- to post-PCV7 rates.
Figure 9. Comparison of median rate of non-PCV7 IPD in relation to time from vaccine introduction. PCV10 (serotypes 1, 5, 7F), PCV13 (serotypes 1, 5, 7F, 3, 19A), and other non-PCV7 types not in PCV13, and rate ratios comparing baseline rates to those 5+ years after PCV7 introduction.
Figure 10. Box and whiskers plot on log scale of rate ratios (RR) of PCV7-serotype IPD among persons ≥ 5 years of age comparing baseline rates to those 1-2 years, 3-4 years and 5+ years after PCV7 introduction.

* Line in box is median value, bottom and top of box are 25th and 75th percentiles, respectively, whiskers represent 1.5 times the interquartile range or the maximum or minimum value if less than 1.5 times the interquartile range, and the individual markers represent individual sites. A RR of 1.0 indicates no change between pre- to post-PCV7 rates.
Figure 11. Box and whiskers plot on log scale of rate ratios (RR) of non-PCV7-serotype IPD among persons ≥ 5 years of age comparing baseline rates to those 1-2 years, 3-4 years and 5+ years after PCV7 introduction.

* Line in box is median value, bottom and top of box are 25th and 75th percentiles, respectively, whiskers represent 1.5 times the interquartile range or the maximum or minimum value if less than 1.5 times the interquartile range, and the individual markers represent individual sites. A RR of 1.0 indicates no change between pre- to post-PCV7 rates.
Figure 12 Box and whiskers plot on log scale of rate ratios (RR) of overall IPD among hospitalized persons ≥ 5 years of age comparing baseline rates to those 1-2 years, 3-4 years and 5+ years after PCV7 introduction.

* Line in box is median value, bottom and top of box are 25th and 75th percentiles, respectively, whiskers represent 1.5 times the interquartile range or the maximum or minimum value if less than 1.5 times the interquartile range, and the individual markers represent individual sites. A RR of 1.0 indicates no change between pre- to post-PCV7 rates.
Table 2. Summary of findings of changes in rates of IPD after PCV7 introduction using 17 datasets for children <5 years of age and persons ≥5 years of age

<table>
<thead>
<tr>
<th>Type of IPD</th>
<th>Hospitalized children &lt;5 years of age, by time post-introduction</th>
<th>People ≥ 5 years of age, by time post-introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-4 years (N=17)</td>
<td>&gt;5 years (N=9)</td>
</tr>
<tr>
<td>PCV7-serotype (Figures 6 &amp; 10)</td>
<td>Decreases in all sites; median RR* 0.087, range 0.030-0.37</td>
<td>Decreases in all sites; median RR 0.058, range 0.015-0.17</td>
</tr>
<tr>
<td>Non-PCV7-serotype (Figures 7 &amp; 11)</td>
<td>Increases in all sites; median RR 1.70, range 1.10-3.35</td>
<td>Increases in all sites; median RR 2.77, range 1.91-4.61</td>
</tr>
<tr>
<td>All serotypes (Figures 8 &amp; 12)</td>
<td>Decreases in all sites; median RR 0.50, range 0.31-0.82</td>
<td>Decreases in all sites; median RR 0.83, range 0.30-0.95</td>
</tr>
</tbody>
</table>

*RR=rate ratio, comparing rates in the time period indicated to the average pre-vaccine rate.