Review of Changes in Incidence of Serotype-specific Pneumococcal Disease Following Routine Pneumococcal Conjugate Vaccine Introduction

Background. The pneumococcal conjugate vaccine (PCV) has been shown to reduce child morbidity and mortality. Invasive pneumococcal disease (IPD) surveillance after introduction of PCV in developed countries has consistently demonstrated a large reduction in the rate of IPD among children in age groups targeted for PCV. In many places where PCV has been introduced, IPD caused by pneumococci of serotypes included in PCV (vaccine serotypes or VT) has virtually disappeared. In contrast, many sites have seen an increase in the incidence of invasive disease caused by nonvaccine-serotypes (NVT) among the age group targeted for vaccination as well as older persons.

These increases in NVT pneumococcal disease have been interpreted as representing “serotype replacement” (i.e., a causal relationship between the rise in non-vaccine type disease and PCV use.) Attention to serotype replacement is increasing, leading some stakeholders and policy makers to question the long-term utility of PCV introduction. When interpreting observations of increased NVT IPD rates one must consider the larger context of overall IPD rates, variability of observations in pneumococcal epidemiology across sites and over time, differences in surveillance methods and in environmental factors, and all possible explanations for increases in NVT pneumococcal disease, including but not limited to PCV use.

As a large number of developing countries prepare to introduce PCV over the next few years, the World Health Organization (WHO) sees an essential need for consensus on the interpretation of surveillance data to determine the occurrence and magnitude of “serotype replacement”. WHO believes it is critical to develop a set of criteria to determine to what extent observed NVT IPD rate changes following PCV introduction represent ”serotype replacement” (i.e. implying PCV causality), and to distinguish this from post-PCV pneumococcal serotype rate changes driven by non-vaccine factors, such as surveillance methods, the environment (e.g. antibiotic use), natural variation (due at least in part to population immunity induced by circulating pneumococcal strains), and/or host factors. Without this effort to fully understand the drivers of NVT IPD disease rates, there is a risk of interpreting all changes in NVT pneumococcal disease rates as causally related to PCV, likely an incorrect inference, which could lead to inappropriate policy decisions and unnecessarily threaten vaccine programs. Therefore, WHO views this information as crucial for monitoring and setting expectations for PCV impact, for future research, for interpreting and defining surveillance data, for making regulatory decisions, and for policy development on PCV schedules.1

Objectives.

Primary objective. To provide an evidence-based evaluation of 7-valent PCV effects on serotype specific pneumococcal disease (especially NVT disease) and to provide guidance to WHO on factors influencing observed changes in serotype-specific pneumococcal disease after PCV introduction.

Secondary objectives.

1. To formulate a set of criteria for “best-practice” pneumococcal disease surveillance in countries that have introduced or are planning to introduce PCV so that new data on pneumococcal vaccine impact are collected and reported in ways that make them useful for understanding PCV effects

2. To provide an analytic framework for countries to evaluate their own data and make decisions related to their PCV immunization program

Methods.

Literature Review. This project will leverage the comprehensive literature review done as part of the PCV dosing landscape analysis being undertaken by the GAVI Accelerated Vaccine Introduction-Technical Advisory Consortium (AVI-TAC). The landscape analysis has performed a systematic literature review on the immunogenicity, effect on NP colonization and effect (direct and indirect) on disease of various PCV vaccination schedules for healthy children as well as high-risk children with underlying medical conditions (i.e. sickle cell disease and HIV). Data was obtained through a review of published reports of randomized control trials, other clinical studies (e.g. observational studies) and surveillance database analyses performed in the setting of different PCV regimens.

Only studies published in the English language were considered for review because of the low likelihood that such studies have been published in non-English journals. The literature review was done from 1994-September 2010. The search strategy was developed with the assistance of a professional librarian at Johns Hopkins Bloomberg School of Public Health (Appendix 1). The search included databases that capture published articles, as well as titles and abstracts from conferences. In addition, a manual search of abstract titles from the bi-annual pneumococcal diseases meeting, the International Symposium of Pneumococci and Pneumococcal Diseases, was performed.

This project will only include articles identified by the dosing landscape analysis that have an IPD outcome. For inclusion in the final analysis, the established search strategy for the landscape analysis will be rerun in June 2011 to capture articles that became available after September 2010.

Besides the literature review for the dosing landscape analysis, investigators with relevant datasets that are not yet published or presented will be sought through solicitation of established surveillance networks, such as PAHO and the European Centre for Disease Control, as well as by word of mouth from experts in the pneumococcal field.
Inclusion criteria for datasets.
1. Data published or collected from 2000-present.
2. Population where at least some children < 15 years of age have received PCV. Fifteen years of age was selected to allow for inclusion of data on catch up schedules.
3. At least 25 percent PCV coverage among those recommended to receive the vaccine.
4. Randomized control trials (RCTs), non-randomized trials, or surveillance database analyses of any PCV schedule on IPD.
   a. For studies that analyze surveillance data, we will include only those with at least one year of data before introduction and at least one year of data after vaccine introduction. The first year of introduction will be the year in which the vaccine was recommended and introduced for any segment of the population.
5. Isolates from at least 50 percent of all reported IPD cases have been serotyped.
6. Measurement of direct or indirect effects of PCV. (i.e. can include data on the age group targeted for vaccination or age groups not targeted for vaccination, such as older children and adults.)
7. Products: We will focus on licensed or about-to-be licensed products (e.g. Wyeth, GSK) but will also collect data on products that are not being further pursued (e.g. Merck and Aventis products). The rationale for inclusion of data on products that are not headed to commercialization is based on the notion that some attributes of dosing and relative immunogenicity may be generalizable across PCV products.

Exclusion criteria for datasets.
1. We will exclude case-control studies, indirect cohort studies, or studies that use the screening method.

Data collection. Two types of data will be collected. First, descriptive data will be collected on the timing and schedule of PCV introduction into the country, and the characteristics of the surveillance system from which the data were collected. Some of these data will be abstracted from available articles and abstracts, while some of it will need to be requested from investigators. Secondly, we will collect incidence rates of serotype-specific IPD pre- and post-PCV introduction. To obtain these data will necessitate going back to the investigators for data as we expect little data will be available in the published literature in the structured format for this analysis. Data will be requested in a standardized and structured format from all sites to allow comparison, and possibly combined analysis. The categories of data are based on epidemiologic strata in which variable serotype-specific responses to PCV introduction might be expected. Individual serotypes will be evaluated separately based on their inclusion in PCV7, PCV10 or PCV13. This will also allow analysis using various combinations of serotypes, which might be relevant for prediction of serotype replacement in countries introducing different PCV vaccines.

The requests for data will be structured in the following categories:
1. Year – organized by years before and after PCV intro. i.e. -2, -1, 0, +1, +2 etc. (No more than 5 years pre-PCV will be requested.)
2. Serotype groupings of IPD – This includes PCV7, nonPCV7 types, and the top 20 serotypes in the pre-PCV period from each region of the world. It is expected that these are the nonPCV7 types most likely to result in replacement disease.
a. All IPD cases  
b. PCV7  
c. 6A true  
d. 6C  
e. 6A/6C undistinguished  
f. Serotypes not in PCV7  
g. 19A  
h. 7F  
i. 1  
j. 5  
k. 3  
l. 2  
m. 12F  
n. 12A  
o. 8  
p. 46  
q. 15B  
r. 45  
s. 9A  
t. Other serotypes of local importance/interest (up to two)  
u. IPD isolates that were not serotyped  

3. Age groups  
a. 0-1  
b. 2-4  
c. 5-17  
d. 18-49  
e. 50-64  
f. ≥65  

4. Hospital status  
a. Inpatient only (children < 5 years only)  
b. Outpatient only (children <5 years only)  

5. Site of specimen  
a. Meningitis  
b. Non-meningitis  

Data analysis. A descriptive analysis of available data will be undertaken. First, this will include summary and presentation of the characteristics of the surveillance systems and studies included in the analysis (e.g. region, dosing schedule, active/passive, etc). Particular attention will be given to describing surveillance characteristics that might influence serotype-specific IPD, such as changes in the surveillance system or the host population surveyed over time. Second, we will summarize the pattern of pre- and post-PCV serotype specific epidemiology in each site, stratified by the categories outlined above. The incidence rates of IPD will be plotted.
for all sites with relevant data using a standardized format in which year 0 will be the year that PCV was introduced and pre-PCV years represented as -1, -2, -3, etc and post-PCV years represented as +1, +2, +3, etc. Figures will be grouped according to key categories, such as age, hospitalized vs. ambulatory, and meningitis vs. non-meningitis. The evaluation of changes in serotype-specific IPD rates will be both qualitative and quantitative. Figures will demonstrate visually changes in rates before and after PCV introduction. Several quantitative measures of serotype-specific IPD rate changes pre- and post-PCV introduction will be evaluated. These will include a) absolute change in vaccine and non-vaccine serotype rates, b) proportionate changes in vaccine and non-vaccine serotype rates, c) a ratio of changes in vaccine and non-vaccine serotype rates, and d) changes in vaccine and non-vaccine serotype rates as proportion of baseline IPD rates.

If possible, serotype-specific changes in the various datasets will be evaluated using a meta-analysis for some outcome measures. The ability to combine data from various sites into a meta-analysis will be determined by the heterogeneity of site characteristics and data available. Once the data is available, data characteristics will be evaluated according to the implicit assumptions of meta-analysis to determine the feasibility of undertaking such an analysis.

Key outputs. The analysis will have several key outputs.

- Prepare data for WHO-sponsored meeting of experts and key stakeholders, including investigators contributing data. (September 2011)
- Presentation to WHO’s Strategic Advisory Groups of Experts (SAGE) for use in an updated PCV recommendation, which can be incorporated into an updated WHO position statement on PCV (November 2011).
- Prepare report of project results for WHO and paper for publication in peer-reviewed journal on results of analysis.

Investigators and Advisory group.
WHO’s Department of Immunization, Vaccines and Biologicals (WHO/IVB) provides policy advice and technical support to WHO Member States on the use of vaccines and has successfully convened many meetings of technical experts for input and recommendation. WHO is a partner of the Accelerated Vaccine Initiative (AVI), the GAVI Alliance effort on PCV and rotavirus vaccine introduction. In 2009 AVI funded, through an proposal process, a Technical Assistance Consortium (AVI-TAC) to provide technical expertise and support on anticipated and unanticipated issues relevant to PCV and rotavirus vaccine introduction; serotype replacement following PCV is exactly the type of issue that the AVI-TAC was put in place to address. WHO is therefore leveraging its key technical partners in AVI-TAC to undertake the systematic review; the AVI-TAC pneumococcal technical partners are Johns Hopkins University Bloomberg School of Public Health’s International Vaccine Access Center (JHSPH-IVAC) and the U.S. Centers for Disease Control and Prevention (CDC), Respiratory Diseases Branch.

A Technical Advisory Group will be formed at the outset of the project. This will be a group of approximately 10 persons, representing experts in the pneumococcal field from the major WHO regions introducing PCV and a statistician. The Group will review the status of the work on a
regular basis, make recommendations for possible changes, additions, or subtractions to the process, and serve as consultants on key decision points in that analysis as they arise.

**Timeline:**
The project began in October 2010 and will continue through March 2012.

| Study Design | x | x | x |
| Literature search | x* | x* | x | x |
| Data solicitation/collection | x | x | x | x** |
| Database development | x | x |
| Data entry/cleaning | x | x |
| Data analysis | x | x | x | x |
| Rerun lit search | x |
| WHO meeting | x |
| Refine analysis | x |
| SAGE meeting | x |
| WHO position paper | x |
| Reports/publication | x |

*Identify relevant articles from dosing landscape analysis **for new datasets found in June 2011 lit search