BACKGROUND NOTE
PCV - SEROTYPE REPLACEMENT ISSUE

Prepared by Claire Broome, Chair of the Advance Market Commitment Independent Assessment Committee (IAC), Approved by the IAC, September 2010

In April and August 2010, the Independent Assessment Committee (IAC) for the AMC reviewed two applications for AMC eligibility from WHO pre-qualified pneumococcal conjugate vaccines (PCV) respectively including 10 and 13 serotypes. In both cases, the committee concluded that the candidate products met the Target Product Profile (TPP), a set of technical criteria established by WHO. GAVI is now working with GAVI-eligible countries to introduce the pneumococcal conjugate vaccine. Based on experience in other settings where pneumococcal conjugates have been routinely used, GAVI-eligible countries introducing pneumococcal conjugate vaccine should experience a dramatic decline in vaccine type disease, and overall a substantial decline of invasive pneumococcal disease and severe pneumonia; they may also see impact on pneumococcal disease occurring outside of vaccine target ages (indirect effects). The original randomized controlled trial of a 9 serotype vaccine in the Gambia also resulted in a 16% decrease in child mortality. Although this effect of pneumococcal conjugate vaccine on child mortality may occur in GAVI-eligible countries, it will be difficult to measure by observational studies because the outcome is not specific. The AMC program will make available to GAVI-eligible countries sufficient quantities of a pneumococcal conjugate vaccine designed to prevent approximately 80% of severe pediatric disease at a fraction of the price of the vaccine in Europe and the US.

However, there are over 90 serotypes of the pneumococcus; extensive use of pneumococcal conjugate vaccine is also expected to result in some increase of disease occurrence due to serotypes not in the vaccine (referred to as “serotype replacement”). This raises the question of whether the increases could reach a point where the benefit from the vaccine is lost, or whether the increases will be small relative to the decline in vaccine type disease?

The expectation of continued benefit from pneumococcal conjugate vaccine is based on several lines of evidence. The most common pediatric serotypes producing invasive pneumococcal disease now are the same as those identified 25 years ago; furthermore, these core types causing invasive pneumococcal disease are the most frequent serotypes in all regions, suggesting that these types are the most capable of causing invasive disease, and not all serotypes may have the same invasive capacity. There is, however, variability over time in the frequency of disease caused by the less common types, including occasional outbreaks.

The experience in the US, UK, Canada, and Australia demonstrates a consistent decrease in the overall risk of invasive pneumococcal disease in the age group targeted for vaccination, reflecting a large decline in disease caused by vaccine serotypes and a relatively small or no increase in disease due to serotypes not in the vaccine. All these

studies look at experience following introduction of the 7 serotype vaccine. A substantial portion of this possible "replacement disease" is due to serotypes that we expect will be prevented by the 10 and 13 serotype products.

The epidemiology in GAVI-eligible countries may not be fully predicted by the experience in more industrialized countries. Studies attempting to monitor for serotype replacement have shown differing results in sub-populations at high risk for pneumococcal disease, with substantial increases in non-vaccine type disease among some Alaska Native populations, while the pattern seen among Navajo in the US, and Australian aborigines is similar to that seen in other US and Australian populations. Individuals with increased susceptibility to invasive pneumococcal disease such as those infected with HIV may be more susceptible to invasive pneumococcal disease from the less common serotypes, although overall the vaccine has resulted in a decrease in pneumococcal disease incidence in HIV infected adults in the United States.

One challenge to interpreting existing surveillance data is that serotype changes are known to occur in countries for reasons unrelated to pneumococcal conjugate vaccine use, including natural variations in serotype distributions, antibiotic pressure, and changes in the methods of surveillance. It is essential therefore to be judicious and deliberate in understanding and interpreting surveillance data comparing pre- and post-PCV introduction periods and to not assume that changes in serotype distribution are necessarily causally related to the vaccine use. Monitoring serotype replacement following introduction of pneumococcal conjugate vaccine requires carefully designed studies for the following reasons:

1) Studies must look at **incidence** of disease, not just **proportion** of invasive isolates. Use of the vaccine is expected to prevent virtually all vaccine type disease, thus decreasing the proportion of invasive pneumococcal disease due to vaccine type strains and increasing the proportion due to non-vaccine types, even though overall disease incidence may have substantially dropped. Hospital case series are particularly susceptible to this bias.
2) Studies of changes in naso-pharyngeal isolates (carriage) are not adequate to determine changes in invasive pneumococcal disease because the new serotypes may be less capable of causing invasive disease than the vaccine serotypes they replaced
3) To draw reliable conclusions studies should include a substantial number of isolates over a reasonable time period (>1 year) both prior to and following vaccine introduction because of the large number of pneumococcal serotypes, and the variability of some types over time,
4) To compare results from different studies, it must be possible to adjust for the types of patients included in different studies—age, disease syndrome (bacteremia, meningitis, etc), hospitalized vs ambulatory, underlying disease (eg HIV infected)

5) Methods for surveillance must be comparable and consistent, since monitoring for serotype replacement looks for changes in incidence of invasive pneumococcal disease due to vaccine type and total invasive pneumococcal disease before and after introduction of the vaccine. Ideally, it requires an accurate baseline for some years before vaccine introduction and consistent surveillance throughout the monitoring period. For example, if diagnostic tests such as blood cultures are obtained more frequently or in different populations after vaccine is introduced, the results may be misleading. Changes in type or quality of diagnostic procedures can also introduce artifacts.

Because of this complexity, WHO has initiated a process starting in July 2010 for systematic evaluation of the available data sets to clarify what is currently known and to provide guidance going forward on appropriate methods to collect, analyze, and interpret pneumococcal disease surveillance data before and after vaccine introduction. The process will quantify the magnitude, and observed range of changes and will assess the relationship to specific populations or risk factors. The process started with an initial meeting July 7 and 8th including groups which have conducted studies of impact of pneumococcal conjugate vaccine on epidemiology of invasive pneumococcal disease, as well as members of GAVI's Accelerated Vaccine Introduction Technical Assistance Consortium (AVI-TAC). The further analyses done using agreed upon approaches will be presented to a broad range of key stakeholders for discussion including the technical, public health, regulatory and vaccine manufacturing community. The results of this process conducted under the leadership of WHO will be presented to WHO's vaccine advisory group, SAGE, to assure that there is tight coupling of the analysis and process to policy formulation. The IAC for the AMC and the GAVI secretariat will also be kept involved and informed.

It will also be important to monitor for serotype replacement in GAVI-eligible countries or countries analogous to GAVI-eligible countries as the vaccine is introduced, but only in sites where interpretable results can be obtained. Some relevant information will be obtained in the ongoing impact studies in Gambia and Kenya. Both of these sites have a long experience with pneumococcal disease surveillance, high quality laboratory capacity and strong study infrastructures. There is also an AVI-TAC supported study in South Africa where there is high quality baseline data prior to pneumococcal conjugate vaccine use, excellent laboratory capacity, and large numbers of cases of IPD. Although these represent a small number of studies, and additional studies could be valuable, it is critical that interpretable data become available, and that results from studies with inadequate study designs do not lead to misunderstanding or misrepresentation of the outcome of pneumococcal conjugate vaccine introduction.

Over the course of future years, should serotype replacement at a level which substantially reduces the overall beneficial impact of the vaccine be documented, GAVI and the IAC may need to consider whether this would necessitate a change in the TPP, based on the provision that "… scientific advances may lead to refined criteria over the

coming years. In these cases, and as indicated in the TPP, the relevant future WHO guidelines should apply." In addition, if the common protein vaccines have been documented to be efficacious, they provide another long term approach to circumvent serotype variability; this is already envisioned in the TPP document as a possible future evolution of pneumococcal vaccines.