The impact of pCVs on preventing nasopharyngeal colonization. 

As of December 2012, 87 countries had introduced pCV into their routine immunization schedule (including a ceremonial launch in 1 country), of which 24 were GAVI-eligible countries. An additional 27 GAVI-eligible countries are approved for introduction of pCV in 2013 and beyond. PCVs are being implemented globally, including the poorest countries of the world, at a pace exceeding that of other previously developed vaccines. These vaccines were designed to prevent pneumococcal disease in infants and toddlers, age groups for which previous pneumococcal vaccines were insufficiently protective. The introduction of PCV has been associated with a dramatic decline in pneumococcal disease caused by serotypes included in the vaccine (ie, vaccine-type disease), in children targeted for vaccination and older persons not intended for vaccination (the indirect effect of vaccination). The indirect effect on disease results from the impact of PCVs on preventing nasopharyngeal colonization.

Effective vaccines to prevent pneumococcal disease in children exist; access to these life-saving pneumococcal conjugate vaccines (pCV) has become possible in many developing countries through the focused, coordinated efforts of the GAVI Alliance, including all of the key Alliance partners. The World Health Organization, the technical partner that provides global vaccine policy recommendations, advises that pCV be a part of the routine infant vaccine schedule for all countries, but particularly those with highest infant mortality rates and death counts. As of December 2012, 87 countries had introduced pCV into their routine immunization schedule (including a ceremonial launch in 1 country), of which 24 were GAVI-eligible countries. An additional 27 GAVI-eligible countries are approved for introduction of pCV in 2013 and beyond. PCVs are being implemented globally, including the poorest countries of the world, at a pace exceeding that of other previously developed vaccines. These vaccines were designed to prevent pneumococcal disease in infants and toddlers, age groups for which previous pneumococcal vaccines were insufficiently protective. The introduction of PCV has been associated with a dramatic decline in pneumococcal disease caused by serotypes included in the vaccine (ie, vaccine-type disease), in children targeted for vaccination and older persons not intended for vaccination (the indirect effect of vaccination).

The indirect effect on disease results from the impact of PCVs on preventing nasopharyngeal colonization.

Reduced colonization leads to reduced spread of the pneumococcus and thus less disease in the unimmunized. To assure that the enormous investments being made in PCV achieve the greatest disease impact, we must move beyond gross metrics of counting the number of countries introducing the vaccines. The focus should now be on achieving optimal vaccine implementation, including but not limited to optimizing vaccine coverage, in all countries. As important as targets are for achieving timely and thorough vaccine coverage, this is an intermediate goal and not the end goal, which is disease prevention and mortality reduction. Toward that goal, we must understand the relationships between dosing schedules, measuring and understanding the magnitude of change in disease, colonization and pathogen characteristics with the intention and focus on achieving the greatest disease impact of the vaccine programs.

Vaccine delivery policy decision makers in countries, regions and globally must be able to include in their assessments evidence for how to administer these products to achieve maximal and optimal impact of the doses being administered and resources expended. This evidence should include the disease impact on both the age groups intended for vaccination and those who are not eligible for vaccination (ie, younger or older than the immunization age group). Impact in both groups contributes to the overall effect and therefore the assessment of return on investment in the health of the population as a whole. A variety of PCV immunization schedules have been assessed in controlled trials and in observational studies for a wide range of disease and pathogen outcomes. Exactly which of these schedules are preferred over others, if there is any preference to be made, has not been not fully understood and therefore recommendations on preferred schedules cannot be made to the policy decision makers.

We therefore undertook a comprehensive, systematic assessment of the absolute and relative benefit of PCV schedules to establish if there is evidence of preferred or sub-optimal schedules and to identify where essential gaps in knowledge lie so that targeted, strategic studies can be planned to assure a decisive evidence base for dosing schedule optimization. As with any vaccine, a limited number of randomized controlled trials have been conducted and these cannot answer the diverse range of biologic questions about dosing schedules. We therefore undertook this assessment putting together all of the evidence in the literature, with controlled trials and observational studies alike, aiming to be as inclusive as possible since the largest body of evidence would reveal a consistency in lessons learned even if any given trial was not the optimal study.

There are important factors to consider when weighing the benefits of different schedules. From an epidemiologic standpoint, it is important to account for differences in organism transmission dynamics in various geographic, disease burden and community settings; concluding that an introduction and dosing schedule are optimal should consider both the direct and indirect effects of the vaccine and will be influenced by the existing transmission and carriage rates in the community. From a policy standpoint, the deciding factors for a country should also take into account programmatic considerations for integrating PCV into existing vaccine schedules and the need to maximize limited financial resources. The performance of the vaccine program to deliver high coverage at each time point in the immunization schedule will likely strongly influence
TABLE 1. Policy Directed Questions That Guided the PCV Dosing Landscape Analysis Project

| Dosing Issue | Specific Questions |
|--------------|--------------------|
| Number of doses in primary series | Is there evidence that a 3-dose primary series is superior or inferior to a 2-dose primary series? Given a 3-dose schedule, is there evidence that it should be administered on a 2+1 or on a 3+0 schedule? |
| Timing of primary series | What interval of PCV doses should be recommended? Is there evidence for guiding the optimal age for initiating PCV dosing? |
| Booster dose | Is there evidence that a schedule including a booster dose is superior to one without a booster dose? |
| Indirect effects | Do certain dosing schedules result in greater indirect impact (i.e., reduction of vaccine-type disease among unimmunized age strata)? |

decision making regarding PCV schedule choice since ultimately delivering all the doses in a schedule is likely to outweigh any relative benefit of one schedule over another.

Furthermore, as infant vaccine schedules become increasingly crowded, it is essential to integrate new products into existing schedules so that parents and caretakers will not be burdened by making additional visits; this must be weighed against the acceptability of multiple injections at a single visit and against the disease epidemiology across age strata. In many European countries, a 2+1 schedule with doses at 3, 5 and 12 months coordinates well with existing schedules whereas a 3+1 schedule at 2, 4, 6 and 12 months fits into the current US immunization schedule. Most developing countries have adopted a 3+0 schedule (6, 10 and 14 months) as measured by disease and colonization impact is the purpose of this systematic assessment. We approached the review with a series of policy questions (Table 1) serving as guiding principles behind the methods, analysis and conclusions. We aimed to have as much methodological consistency across the outcomes as possible while maintaining the most inclusive principles for any given analysis. Therefore, each outcome has been customized to the degree necessary to assure that the largest set of data is considered to inform the analysis and conclusions. These findings were reviewed at a meeting of experts held by WHO, subsequently presented to the WHO Strategic Advisory Group of Experts on Immunizations in November 2011, and are now provided here in this supplement.

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