WHO Technical Expert Consultation Report on Optimization of PCV Impact: Review of Evidence and Programmatic Considerations to Inform Policy

Department of Immunizations, Vaccines, and Biologics

WHO HQ Salle C**,** June 12-13, 2017

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Executive Summary

A Technical Expert Consultation on optimizing pneumococcal conjugate vaccine (PCV) impact was held at World Health Organization (WHO) Headquarters June 12-13, 2017. Since licensure and prequalification in 2000, PCVs have been introduced in 141 countries and 190,000 pneumococcal deaths have been averted from 2000 to 2015. WHO recommends that the two prequalified PCV products, 10-valent (PCV10) and 13-valent (PCV13), should be administered either in a three primary doses (3p+0) or two primary doses with a booster (2p+1) schedule. Catch up vaccination is recommended as a mechanism to accelerate herd protection.

An increasing amount of evidence has accumulated since the last PCV position paper update in 2012, including from low and middle-income countries. The meeting served to review new evidence that could inform the Strategic Advisory Group of Experts Working Group for PCVs (SAGE PCV WG) of possible differences in impact and effectiveness by product and schedule for both routine infant immunization and catch-up immunization. Throughout the meeting, participants identified critical data gaps and developed a prioritized list of future PCV research directions.

Both primary evidence and modeled data were reviewed in the consultation to formulate overarching conclusions, identify data gaps, and prioritize future research questions. The meeting discussed evidence presented from PCV Review of Impact Evidence (PRIME)—an extensive systematic review of PCV impact data which was created in part to serve as an evidence base for SAGE PCV WG. The empiric evidence reviewed on immunogenicity, nasopharyngeal carriage, pneumonia, invasive pneumococcal disease, and mortality is discussed in a separate report available on the WHO SAGE website. The systematic review found a lack of available evidence to conclude a strong preference for either PCV product or schedule due to both

confounding factors across different environments and a distinct lack of head to head studies which directly compared products and/or schedules.

The participants reviewed data and discussed the programmatic implications related to a 3p+0 or 2p+1 schedule or shifting from a 3p+0 to a 2p+1 schedule. The evidence for the added value of introducing catch-up campaigns, including the age groups to be targeted, based on mathematical models, was also discussed. To fully capture the global impact of PCVs, comprehensive modeling work for both schedules and product choices in the future will require empiric evidence from a wider range of geographic regions.

Representatives from high, middle and low-income countries highlighted the drivers of decision making regarding choice of PCV product, dosing schedule, and the use of a catch-up campaign through presentations and a panel discussion. While each country shared unique experiences, common themes that influenced decisions across all settings included the importance of cost-effectiveness, the availability of local impact data, vaccine supply, and cold chain storage capacity.

The conference culminated with individual participants identifying the three highest priority research questions needed to make or affirm policy recommendations. The majority of participants recommended research topics that centered on product choice and schedule. Additionally, the participants consistently cited serotype replacement and serotype distribution as an emerging concern and pressing research gap. The presented evidence and prioritized research recommendations were taken into consideration at the PCV SAGE WG meeting, which occurred directly after the consultation.

I. Introduction

A technical expert consultation on the optimization of pneumococcal conjugate vaccine (PCV) impact was convened on June 12th and 13th 2017 at the World Health Organization headquarters in Geneva, Switzerland. The objectives of the meeting were to review available evidence regarding PCV impact in routine use settings, provide inputs to inform the subsequent deliberations of the Strategic Advisory Group of Experts Working Group (SAGE WG) for PCV, and to identify and prioritize policy relevant data gaps.

The PRIME systematic review reported evidence of PCV impact by product and dosing schedule. Emerging modelled and primary data from research institutions were also presented. In addition, key programmatic considerations related to each of the PCV products and schedules were highlighted. Country policy makers also discussed the evidence that may be required by national governments to sustain the use of PCVs in their national immunization programs. The consultation culminated in an interactive session that synthesized the evidence presented and prioritized the remaining gaps in policy-relevant evidence to optimize the global impact of PCVs.

II. Current PCV Recommendations & Considerations for Policy[1]

The current PCV recommendations from the 2012 WHO position paper, were summarized, focusing on three specific issues, namely: (1) choice of schedule; (2) choice of product; and (3) catch up vaccination at the time of introduction

The existing recommendations propose a schedule consisting of three primary doses (3p+0) or, as an alternative, two primary doses plus a booster (2p+1) for either PCV product. It is recommended that the country-level choice of product should be based on locally relevant factors such as serotype distribution, vaccine supply, cost effectiveness, and cold chain volume. Given the lack of evidence on the interchangeability between PCV10 and PCV13, WHO recommends completing a dosing schedule with the same PCV product, whenever possible. The position paper encouraged the use of catch-up vaccination as a mechanism to accelerate herd protection through the provision of two catch-up doses at an interval of at least two months to unvaccinated children 12-24 months of age and high-risk children aged 2-5 years.

Since the publication of the 2012 position paper, more data exist from a wider range of epidemiological settings with PCV10 and PCV13 administered in both the 3p+0 and 2p+1 schedule. Data on mortality, morbidity, and nasopharyngeal carriage may enable more informed recommendations on the optimal use of PCV. A recent large-scale outbreak of pneumococcal meningitis in a PCV-using country[2], primarily affecting adolescents and adults, has raised questions about the optimal schedules to promote longer term protection and/or enhance the indirect effects of vaccination.

In addition, there are a number of programmatic issues that need to be considered when updating policy recommendations:

1. Some countries find it difficult to accommodate additional parenteral vaccines into existing schedules because of concerns about multiple injections at the same visit, leading to increased interest in adopting schedules with vaccine doses in the second year of life and scale-up of vaccine delivery programs for that age group.
2. The proportion of total vaccine expenditures spent on PCV in countries (median of 37% of overall national vaccine costs)[3] is a financial challenge, especially for middle-income countries who do not benefit from Gavi support. Many of these countries also have low child mortality, and thus have difficulties justifying the introduction of the vaccine in their national programs on the basis of mortality impact alone.
3. Many countries will be transitioning out of Gavi support over the next 3-5 years and there are concerns about these countries sustaining PCV in their national program, necessitating a robust case be made to national policy-makers.

III. Overview of Current Status of PCV Use Globally

Updated estimates of deaths and cases due to pneumococcus and Hib have been developed, have been endorsed by the WHO Immunization and Vaccines Implementation Research Advisory Committee (IVIR-AC), and are under country consultation[4]. Dr. Kate O'Brien discussed current pneumococcal disease burden and the evolving global use of PCV. Among HIV-negative children, a total of 294,000 (192,000 – 366,000) deaths are estimated to have occurred in 2015, a decrease from approximately 600,000 deaths in 2000. From 2000 to 2015 it was estimated that approximately 190,000 pneumococcal deaths have been averted as a result of PCV use[4,5] . Many GAVI-eligible countries carry the highest pneumococcal disease burden, and most have been able to introduce PCV. However, introduction efforts and coverage levels must accelerate to achieve the Sustainable Development Goal (SDG) target of reducing under-five child mortality rates to at least 25 per 1000 live births[6].

Despite this progress, pneumonia remains a major contributor to child mortality, causing approximately 16% of deaths in low and middle-income countries and around 5% of deaths in high income countries[7]. Of the 10 countries with the highest numbers of pneumococcal deaths, 7 have recently introduced PCV, indicating opportunities for future significant declines in pneumococcal mortality in the upcoming years. In addition to countries with high burden of disease, future PCV work should consider focusing on large countries with moderate mortality rates and small countries with high mortality rates.

PCV product and schedule use appear to vary by geographic region. As of September 2017, 101 countries had adopted the use of PCV13 while 33 countries were using PCV10, and 8 used both[8]. While the majority of non-GAVI countries are following a 2p+1 schedule, most GAVI eligible countries have implemented a 3p+0 schedule

because this aligns with the other primary immunization schedule and is expected to facilitate higher vaccination coverage in countries with weaker health systems. Almost all Gavi-eligible countries in Africa are using a 3p+0 schedule, while currently two countries in the South-East Asia region are using a 2p+1 schedule[8].

IV. Broader Economic Impact of PCV

Dr. David Bloom presented a keynote address on the potential broader social and economic value of PCV immunization and discussed how the improved health resulting from vaccination can lead to economic growth. There is an increasing need to change the paradigm from looking solely at the effect of income on health to also looking at the effect of health on income. While economists and policy makers in the past have undervalued the economic benefits of vaccinations, data were presented that indicate a 2% improvement in health can be associated with a ten-year gain in life expectancy, which in turn can be associated with a 0.5-1 percentage point of annual per capita income growth.

A challenging research priority will be to ascertain and quantify the broader full benefits of vaccinations—such as productivity gains, decreases in antimicrobial resistance, increases in social equity, and reduction in comorbidities. Due to both the direct and indirect benefits, the economic loss resulting from neglecting to invest in vaccines are substantially higher than the costs of immunization, making it an attractive investment. Dr. Bloom argued that economists should shift away from simple assessments of cost-effectiveness and move towards benefit-cost analyses because the latter can quantify both health and non-health outcomes into more easily understood monetary value.

V. Key drivers of mathematical models & implications for interpreting empiric data

Much of the observed impact of PCVs has been due to indirect effects in unvaccinated segments of the population, particularly when assessing impact in high income countries. The extent of indirect effects from PCVs relies primarily on two opposing forces: the protection of unvaccinated individuals through reduced transmission of vaccine targeted serotypes (herd protection), and increases in the incidence of pneumococcal disease attributable to non-vaccine serotypes (serotype replacement). Mathematical models for pneumococcal transmission have performed reasonably well in predicting herd protection overall; however, a limited understanding of the key drivers of serotype specific replacement has hindered more precise prediction of the role of individual serotypes after PCV implementation.

Serotype replacement and herd protection are key to the evaluation of product and schedule choice. Critical evidence gaps that limit our understanding of those forces and hence limit the predictive capacity of models include a better understanding of serotype specific replacement in dependence of PCV formulation, the difference in time-profile of waning vaccine protection against pneumococcal carriage after 2p+1 and

3p+0 schedules, and the sources of transmission of vaccine serotype pneumococci to infants.

The potential impact of pneumococcal catch-up campaigns at the time of PCV introduction is largely driven by the time that cohort introduction takes to achieve its full population impact and hence the additional preventable disease burden that a catch-up can target. These are in turn determined by the fraction of vaccine type pneumococcal disease occurring in older children and their contribution to the transmission of pneumococci as well as the vaccine efficacy of PCV if delivered through a campaign to both young and older children and the number of doses required to achieve such protection. Recent modelling indicated that by directly protecting older children and accelerating herd protection in settings with high disease and carriage rates beyond infancy, such as Kilifi, Kenya, catch-up campaigns may prevent more cases of IPD per vaccine dose administered than the routine vaccination programme and hence present a highly efficient option for PCV use[9]. In a setting with moderate carriage prevalence, like Nha Trang, Vietnam, herd-effects establish sooner after the start of routine PCV use[10]. Hence, catch-up campaigns still substantially accelerate direct and indirect effects in lower carriage settings, but may only prevent similar or fewer cases of IPD per dose than the routine vaccination programme.

VI. PCV Review of Impact Evidence (PRIME): Systematic Review

PRIME is an extensive systematic review of PCV effectiveness and impact data led by the Johns Hopkins International Vaccine Access Center, in collaboration with WHO, the Centers for Disease Control and Prevention, the Institute of Child Health, and Agence de Medecine Preventive. It serves as an evidence base for the SAGE WG to inform their recommendations. PRIME assessed evidence on potential differences in impact by PCV product and dosing schedule, the value of catch-up vaccination, and the indirect effects of vaccination through five outcomes: Immunogenicity, Nasopharyngeal Carriage (NP Carriage), Pneumonia, Invasive Pneumococcal Disease (IPD), and Mortality. The PRIME systematic review concluded that there were no definitive preferences for a particular schedule or product. Available data assessing impact of catch up immunization were very limited. The full report of PRIME results, available on the WHO SAGE website, explains findings for each outcome in detail.

Though analyses for each outcome differed and each had a unique set of analytical challenges to consider, there were two key messages in the discussions that followed each presentation:

1) The PRIME systematic review highlighted the importance of distinguishing between a lack of available evidence on product or schedule differences and having sufficient evidence indicating that there is no significant difference in impact between products or schedules.

2) For many outcomes, the lack of head to head studies served as a major data limitation that prevented investigators from drawing clear conclusions about differences in impact by schedule or product. Single arm trials and observational studies were confounded by methodologic limitations, making it difficult to draw inferences based on quantitative comparisons across studies.

		Schedule	Product	Catch up
Mortality	**Is there sufficient evidence for a conclusion?**	No	No	No
	Preference			
	Data Gaps	Head to head studies	Head to head studies	Head to head studies
IPD	**Is there sufficient evidence for a conclusion?**	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	No
	Preference	No preference	PCV13 may have advantage in settings where IPD from 19A and 6C are common; otherwise, no preference	
	Data Gaps	Head to head studies More 3p+0 evidence	Head to head studies More PCV10 evidence	Head to head studies
Pneumonia	**Is there sufficient evidence for a conclusion?**	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	Limited evidence available due to confounding from prior PCV use and lack of head to head studies	No
	Preference	No preference	No preference	
	Data Gaps	Head to head studies More 3p+0 evidence	Head to head studies More PCV10 studies	Head to head studies
Immunogenicity	**Is there sufficient evidence for a conclusion?**	Yes	Yes	No
	Preference	Immunogenicity measured post-primary series is higher in a 3p+0 schedule, but booster in 2p+1 exhibits higher immunogenicity	PCV13 elicits higher immune response (proportion of children reaching correlate of protection) for ST3, 6A, 19A. However, clinical	

		compared to post-dose 3 in 3p+0 schedule. Clinical significance of these differences in immunogenicity is uncertain	significance of these differences in immunogenicity is uncertain	
	Data Gaps	Head to head studies	Head to head studies More data on immunogenicity on PCV10 for 3, 6A, 19A	Head to head studies directly comparing immunogenicity after 1 catch up dose to immunogenicity after 2 catch up doses
NP Carriage	**Is there sufficient evidence for a conclusion?**	Limited evidence available due to confounding by baseline carriage, prior PCV7 use, and lack of sufficiently powered studies	Limited evidence available due to confounding by baseline serotype-specific carriage and a lack of sufficiently statistically powered studies	No
	Preference	No preference	No preference	
	Data Gaps	Head to head studies and studies in settings with comparable baseline carriage rates.	Head to head studies PCV10 studies with prior PCV7 use, PCV13 studies without prior PCV7 use.	Head to head studies

Figure 1. PRIME Analysis Summary Table by outcome. Green indicates enough adequate evidence available; yellow indicates limited evidence available; red indicates not enough evidence available to draw conclusion

VII. Programmatic Considerations

Current PCV coverage levels and the timeliness of achieving the coverage levels with the 3p+0 or 2p+1 schedule were discussed. Additionally, experts from a range of geographic and resource settings shared their country-level experience regarding PCV use and impact, as well as the key programmatic factors that influenced national immunization policies.

Vaccine Coverage

The relative coverage with three doses of PCV using either a 3p+0 or 2p+1 schedule were predicted, using DTP3 (as a proxy for the 3p+0 schedule) and Measles-Containing-Vaccine First-Dose, MCV1 (as a proxy for the booster dose in a 2p+1 schedule) as reference points. In countries using a 3p+0 schedule, the DTP3 and PCV3 coverage were generally comparable in a majority of countries; only 16% of the countries analyzed had a >10% coverage difference between DTP3 and PCV3, and 32%

had a >5% coverage difference. Additionally, in countries using a 2p+1 schedule, the MCV1 and PCV3 coverage levels were also similar in a majority of countries; only 32% of the countries analyzed had a >10% coverage difference between MCV1 and PCV3. Thus, in countries still to introduce PCV, the potential coverage that may be achieved could be estimated reasonably accurately using the coverage with DTP3 or MCV1, provided the third dose is provided along with these two doses, respectively. Many countries that introduced PCV in a 3p+0 schedule have low MCV2 [Measles-Containing-Vaccine Second-Dose] coverage during the second year of life, so a switch in dosing schedule from PCV 3p+0 to PCV 2p+1 where the third dose is provided in the second year of life could reduce a country's PCV3 coverage.

The timing for a child to receive the third dose of PCV using data on timing of DTP3 and MCV1 from coverage surveys was also assessed. Country programs vary extensively in their timeliness and coverage[11][12]. Therefore, the country level decision to switch from three primary doses to two doses and a booster should be based on local data and could be estimated using data from national coverage surveys.

Transmission Dynamics

The minimum population size needed to self-sustain transmission of an infectious disease without importation – the Critical Community Size (CCS) – is a critical value for understanding persistence dynamics and estimating the probability of geographically-localized fadeout or elimination of a pathogen. While the CCS has been demonstrated for pathogens inducing sterilizing immunity, immunity that results in prevention of acquisition in the future (such as measles), it is challenging to apply the same methodology to S. *pneumoniae*, due to its low case-to-colonization ratio and inconsistent surveillance across different settings. Dr. Ben Althouse presented results from a stochastic, individual-based, age-structured mathematical model of pneumococcal colonization, including biologically realistic acquisition and transmission dynamics, calibrated to settings with various forces of infection. For each setting, CCS was estimated by varying the population size probability of disease extinction with multiple stochastic realizations. Dr. Althouse found that the number of children in a given population needed for self-sustained transmission for more than 50% of all stochastic realizations is on the order of 1,000 to 10,000, with this number depending on the force of infection and acquired immunity through natural colonization. This relatively small CCS can be explained by the long duration of pneumococcal carriage in infants and toddlers, who are the transmission reservoirs. The CCS highlights the potential importance of subnational variation in PCV coverage whereby relatively small pockets of unvaccinated individuals can continue carrying and transmitting pneumococcus despite being surrounded with adequately-vaccinated populations. Assuring high and homogeneous vaccination coverage with PCV will be needed to maintain vaccine serotype pneumococcal transmission at the lowest possible levels.

Drivers of Decision-Making Regarding PCV Schedules

A panel discussion was held to get country perspectives on the rationale and factors that influenced decisions on PCV introduction, the choice of schedule and product, and evidence that may be required to sustain PCV in their national programs.

In 2010, the United Kingdom became the first country to use PCV in a 2p+1 dosing schedule, and Dr. Elizabeth Miller reflected on the factors that led to the decision to use this schedule. She indicated that a 3p+0 schedule was not considered in the UK. This was due to the fact that when 3p+0 was used with the Hib vaccine, there was an increase in incidence after a few years, which required the UK to add a booster dose. Studies did not indicate a major difference in immunogenicity between the 2p+1 and 3p+0 dosing schedules, while the 2p+1 schedule was found to be more cost-effective. PCV 13 was chosen as the product because it was licensed for use in a 2p+1 schedule and because of a concern about the prevalence of serotype 19A disease resulting from serotype replacement following PCV 7 use.

Dr. Peter McIntyre reported on the considerations leading to Australia's decision to utilize a primary 3p+0 dosing schedule, with 3+1 for children at higher risk of IPD. In 2000, Indigenous children in northern and central Australia had the highest reported rates of IPD in the world, with high serotype diversity (serotypes in PCV7 only accounted for 35-40% of IPD) and early onset of meningitis. From 2001, conjugate pneumococcal vaccines were funded for children with medical conditions placing them at higher risk of IPD (3 +1 schedule) and for all Indigenous children (3+0 schedule), with those living in 4 jurisdictions of highest IPD incidence also recommended to receive a dose of 23 valent polysaccharide vaccine (PPV23) at 18-24 months. In 2005, PCV7 was funded universally on a 3p+0 schedule, due to primarily for cost reasons, with Indigenous and high-risk schedules continued. Impact evaluations for the PCV7 era demonstrated that the 3p+0 schedule had a similar impact to that reported by countries using 3p+1 or 2p+1 schedules. There was strong emergence of serotype 19A in non-Indigenous children, which accounted for almost 50% of IPD by 2010 when PCV13 became available. In contrast, among Indigenous children receiving PPV23, serotype 19A decreased. However, with additional serotypes in PCV13, there was deemed insufficient extra benefit to warrant continuing 23PPV; 3+0 was used generally and 3+1 for high risk children for PCV13, based on the PCV7 experience. However, 3 dose vaccine failures (primarily 19A and 3) in the second year of life with PCV13 have prompted serious consideration of moving to a 2p+1 schedule – this change is now out for public consultation (September 1 2017). Delay of the third dose to 12 months led to some concern about breakthrough meningitis between 4 and 12 months of age but the reduction in total and severe IPD (primarily pneumonia with empyema) in the second year of life and greater herd impacts was felt to justify this.

Dr. Narendra Arora reported that the Indian National Technical Advisory Group on Immunization (NTAGI) opted for the 2p+1 PCV schedule over a 3p+0 schedule due to data presented during the WHO PCV Consultation in 2016, where available data, mainly

from PCV 7, indicated that this schedule may be superior to the 3p+0 schedule. Because the country required 20 million doses for introduction, the option of multi-dose vials and the consequent lower volume of cold chain storage capacity requirements were the key factors in opting to use PCV13, available in a 4-dose presentation with preservative. However, in the longer term, given the size of the birth cohort in India and since a single manufacturer may not be able to meet the demand, the national program is open to using more than one product in the country.

Dr. Bikash Lamichhane reported on Nepal's experience with a 2p+1 PCV10 dosing schedule, with a modified schedule of 6w, 10w, and 9 months (i.e. 4 weeks, rather than 8 weeks, between the two priming doses). The country-level decision to introduce PCV in phases with a 2p+1 schedule was based on studies in Nepal that revealed that 2p+1 conferred higher antibody levels than a 3p+0 schedule following the third dose. This suggested a longer duration of protection, which was assessed as important in Nepal because IPD data indicated a predominance of disease due to serotype 1, and the age of peak incidence was above 9 months of age. Additionally, the second dose is given at 10 weeks of age rather than the usual 14 weeks of age because of concerns from health care workers about the feasibility and acceptability of delivering three parenteral vaccines in a single visit at 14 weeks of age. While the coverage with the third dose was low in the initial phases, the coverage levels are increasing and expected to be similar to MCV1.

Dr. Betuel Sigauque explained that the decision to switch from PCV10 to PCV13 in Mozambique was driven by the Ministry of Health's preference for the 13-valent formulation requested in its initial application to Gavi. While PCV10 was initially used in Mozambique, this was driven by supply constraints rather than epidemiology or cost; thus, once the supply was sufficient, the country decided to switch to PCV13. PCV13 was preferred because it was expected to cover about 85% of prevalent serotypes, whereas PCV10 was expected to cover 65%. A technical advisory group reviewed local data on colonization, IPD, and serotype prevalence and replacement, and recommended the switch in product from PCV10 to PCV13. Their decision was based primarily on local data indicating that while PCV10 had a large impact on reducing IPD and pneumonia, there was also an increase in ST19A carriage and disease which could warrant switching to a vaccine that contains that serotype.

Dr. Lucia de Oliveira, a representative from Pan American Health Organization (PAHO), clarified details surrounding major budgetary constraints that led to the discontinuation of PCV13 in Venezuela's national immunization program. While PCV13 was introduced in 2014 in Venezuela, a severe financial crisis caused the Health Ministry to discontinue PCV's inclusion in the national immunization program in an effort to sustain the less expensive vaccines in the program. This is the first case in the history of EPI in the Americas that a country has discontinued the use of a recommended vaccine.

The Ministry of Health is eager to reintroduce the lowest-cost PCV product when funds become available.

The Philippines, Bangladesh, and Tanzania have all faced similar financial challenges either because they are not eligible for Gavi support (Philippines) or are approaching GAVI-transition (Bangladesh and Tanzania). Representatives from these countries discussed their thoughts and concerns for sustaining the use of PCVs in their respective countries. Dr. John Erasmo of the Philippines said that the universal roll-out of PCV has been hindered by the high cost of the vaccine. Hence, vaccination is currently limited to those registered to be in the lowest income bracket in the country. While the country has a goal of nationwide PCV13 introduction, the desire to also introduce the dengue vaccine in some regions of the country requires careful considerations in the prioritization of the two vaccines and how to allocate limited national resources for the introduction of these vaccines. Both Dr. Samir Saha of Bangladesh and Dr. Dafrossa Lyimo of Tanzania expressed concerns on sustaining the vaccine post GAVI-graduation given the high costs involved. To sustain the use of PCVs, both emphasized the need for local data to communicate the value of PCV to those making decisions on allocation of national budgets. Dr. Saha pointed out that the decision to introduce the vaccine in Bangladesh was based on projected mortality reductions from mathematical modelling. However, for sustaining the vaccine using domestic resources, empiric data on mortality reduction may be required. In Tanzania, the decision to introduce PCV was based on high rates of pneumonia hospitalizations. Policy-makers are tracking hospitalization and outpatient visits and reduction in these parameters and resultant cost savings through prevention of disease would be important in convincing policy-makers to sustain the vaccine in the national program. She also noted that there was a strong community demand for the vaccine, which may help with sustaining the vaccine in the program.

VII. Key Evidence Gaps & Conclusions

The final session concluded with a prioritization of key policy-relevant questions and future research directions. Participants were assigned to break out groups to discuss the following six policy-related topics:

1) Choice of Schedule
2) Choice of Product
3) Catch Up Vaccination
4) Impact of maternal immunization with tetanus-diphtheria containing vaccines
5) Impact of PCV on antimicrobial resistance
6) Prevention of and response to outbreaks

For the first three issues, the participants were asked to consider the data presented from PRIME during the consultation, identify the key evidence gaps and convert them in policy-relevant research questions. The remaining three groups were asked to identify and prioritize the policy relevant evidence gaps and research questions.

The feedback from participants corresponding to each group is briefly summarized below.

Choice of Schedule

In determining the policy recommendations on choice of schedule, the highest priority research areas identified were: (1) serotype-specific vaccine effectiveness studies, with head-to-head studies of different schedules where possible; (2) completeness and timeliness of different dosing schedules; and (3) data on the long-term impact of schedule on disease transmission and dynamics. Specifically, there was an interest in gathering studies that assessed the impact on disease in the second year of life by dosing schedule. The participants also prioritized the need for data on the duration of protection provided by different schedules on nasopharyngeal carriage and disease, particularly in low- and middle-income countries.

Choice of Product

The highest priority research gap identified for product choice was to accumulate quality, long term surveillance post introduction to better understand the correlation between antibody responses and vaccine impact, as the serotype specific correlates of protection need to still be fully established. An additional priority includes increasing the amount of studies that evaluate the effects of product interchangeability during primary immunization on immunogenicity, NP carriage, and disease. Head to head studies comparing future PCV products with existing products were also stressed. Many participants cited serotype replacement data as one of the most pressing research gaps. Assessments of the effects of dosing schedule or product interchangeability on serotype replacement should be conducted.

Catch up vaccination

The priority research gap to inform future deliberations about catch-up vaccination was to conduct cost-benefit analyses of catch-up campaigns. Most of the currently available catch-up data relies on disease transmission models, so there is a need to collect empiric data to parameterize and validate the models.

Outbreaks

The highest priority research gap identified was the need for epidemiologic data on pneumococcal disease outbreaks and of pneumococcal disease in emergency settings. It is also important to gather impact data on the strategic use of PCV in high risk settings, specifically: (1) in the meningitis belt in order to determine the optimal routine immunization schedules to reduce the risks of outbreaks and on strategies for outbreak response with vaccination; and (2) in refugee populations to determine optimal vaccination strategies in these settings.

Antimicrobial Resistance

The added economic value as a result of implementing PCV in the face of the emerging threat of antimicrobial resistance (AMR) should be studied through models. Additionally, data on the degree by which PCV use reduces the rates of antibiotic use and AMR in low- and middle-income countries should be collected.

Maternal Immunization

To understand how maternal vaccination with vaccines containing antigens that are also used as the protein carrier of PCVs alters an infant's immune response to PCV, the participants identified the importance of quantifying any blunting effect and its clinical consequences. These would be assessed through immunogenicity and clinical outcomes, especially in LMICs. Additionally, it will be important to understand decay rates for maternal antibodies and how that could affect timing of the first dose

Other outcomes

Participants described the need for future randomized implementation trials to quantify the true and wider impact of schedule, product, and catch-up choice—looking beyond the traditional immediate impact assessments on disease and estimating longer term consequences like cognitive function and increased school performance and productivity.

Overall conclusions of priority evidence gaps and research questions

The following matrix describes overall rankings of different priority research questions across all of the break-out groups. The priority 1 category reflects the research questions cited by the most participants at the meeting.

Priority	PCV evidence gaps/research questions
1	A. High quality evidence of the impact of long-term PCV use on serotype-specific disease and carriage, for both products and both schedules in various epidemiological settings with emphasis on head-to-head (H2H) studies where possible[1]
	B. Data on the long-term impacts of 2p+1 vs 3p+0 schedules on serotype-specific disease and carriage in the second year of life and beyond with emphasis on H2H studies where possible
	C. Impact of the completeness and timeliness of different dosing schedules on serotype-specific carriage/transmission and disease outcomes with emphasis on H2H studies where possible[2]

[1] Experts acknowledged that H2H studies of licensed products or different schedules that evaluate disease outcomes are highly unlikely, as are long term H2H studies with either disease or carriage outcomes. It *may* be possible to evaluate disease outcomes by comparing provinces within the same country, but this would not represent the classical H2H study. H2H studies looking at carriage outcomes are more likely/feasible.

[2] Only small H2H studies comparing schedules would likely be possible, and specific transmission scales would be needed to evaluate this aspect

	D. Immunogenicity, carriage and disease data (including serotype replacement) on the interchangeability of PCV products (to inform product switching and to inform countries using more than one product)[3]
	E. A clearer understanding of the relationship between serotype-specific immune response to vaccination and disease outcomes, including serotype-specific correlates of protection
	F. Serotype distribution of residual disease and replacement data for carriage and invasive pneumococcal disease (IPD) after more than 5 years of PCV use in L/MIC[4] settings, by dosing schedule for both products, including data on the role of changes in the age distribution of disease and colonization
2	G. Head to head studies comparing future pneumococcal vaccine products to licensed PCVs with respect to immunologic and carriage outcomes
	H. Cost-benefit analysis of catch-up campaigns
	I. Epidemiology of pneumococcal disease in outbreaks and in high-risk settings such as humanitarian emergencies
	J. Estimate the economic impact of antimicrobial resistant (AMR) pneumococcal infections and the economic impact of PCV use on AMR pneumococcal disease (including indirect effects)
3	K. Impact data on the strategic use of PCV in high risk settings or outbreak situations, (which could include evaluating the value of catch-up campaigns in these settings and/or the use of adult PCV campaigns to prevent outbreaks in the meningitis belt)
	L. Impact of PCV use on rates of AMR pneumococcal infections and on rates of antibiotic usage in L/MICs
	M. Understand the clinical and biological relevance for infants of maternal vaccination with tetanus, diphtheria and pertussis vaccines, and impact on infant immune response (including blunting of the infant response as function of maternal vaccinations and decay of maternal antibodies)
	N. Empiric evidence of the impact of catch-up campaigns on carriage as a means to validate models of transmission
	O. High quality evidence of the extent of cross-serotype protection for both PCV products, post-introduction
4	P. Relative cost-benefit of different dosing schedules and products, especially for GAVI graduating countries
	Q. Economic costs of pneumococcal disease in outbreaks and in refugee/humanitarian crisis settings
	R. Define a pneumococcal outbreak and thresholds that would trigger a response of the strategic use of PCV, specifically applicable to the meningitis belt and refugee/humanitarian crisis settings
	S. Effect of concomitant vaccine administration at 9 months of age with PCV and YF, MenCV, MCV and RTS,S on immune response to antigens in all co-administered products, by PCV product (which have differing carrier proteins that may have implications for immunogenicity in the presence of other antigens)

[3] Evaluating disease outcomes in the context of the use of multiple PCV products in a single individual would be challenging. However, it may be possible to do an analysis of vaccine failures, e.g. whether a higher proportion of vaccine failures is seen in children who received more than one product during their primary vaccine series

[4] Low- and middle-income countries (L/MICs)

	T. Develop a clearer understanding around the specific circumstances in which a country should use a catch-up campaign

IX. Concluding Remarks

The WHO Technical Expert Consultation on Optimization of PCV Impact reviewed the available impact evidence with the intent of shaping SAGE recommendations to optimize future PCV use. While both products and schedules show clear overall impact against vaccine-type serotypes as a whole, differential impact between products or schedules could not ascertained due to the lack of available head to head studies, and the presence of significant confounders that complicate interpretation of comparisons. Programmatic issues and the cost of the vaccines were identified as major factors that influenced country-level decisions regarding product choice and schedule. Future research priorities were also identified and included conducting more head to head assessments of PCV impact, particularly for IPD and pneumonia outcomes, as well as further analyses of reduced dosing schedules, transmission dynamics, serotype replacement, and PCV impact on controlling outbreaks or AMR. A Strategic Advisory Group of Experts on Immunization (SAGE) Working Group on PCVs met directly after the technical consultation to discuss the evidence presented in relation to current WHO policy on PCV use and draft revisions of the recommendations. Updated recommendations based on evidence reviewed in this consultation will be presented to SAGE by the PCV Working Group, and discussed at the October 2017 SAGE meeting.

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Appendix A: PCV Technical Expert Consultation Agenda

World Health Organization

Department of Immunizations, Vaccines, and Biologicals

WHO Technical Expert Consultation on Optimization of PCV Impact: Review of Evidence and Programmatic Considerations to Inform Policy

WHO HQ Salle C, Geneva, Switzerland

12-13 June 2017

Meeting Purpose: Convene a technical review of the impact of PCV in the routine use setting, and determine the priority gaps in evidence/research questions that are key for optimizing impact of licensed PCVs.

Meeting Objectives:

1. Assess the evidence from PCV Review of Impact Evidence (PRIME) to inform decisions on optimal PCV dosing schedules for each of the available products
2. Understand programmatic considerations related to each of the PCV dosing schedule options
3. Understand the evidence needs of country policy makers to sustain PCV in their national immunization programs
4. Develop a consensus and prioritization on the gaps in evidence for optimizing impact of PCVs

MEETING AGENDA

Monday, June 12, 2017

Session/Time	Opening – Importance of this Work	Chair / Presenter
08:30 (15 min)	Welcome & Introductions	Thomas Cherian
08:45 (10 min)	Opening Remarks and Review of Meeting Objectives	Andy Pollard
08:55 (5 min)	Housekeeping	Olivia Cohen
Session I	**Where we come from, where we are, & where we are going:**	**Chair: Andy Pollard**
09:00 (55 min)	1. Current PCV recommendations & considerations for policy (15 min) a. Evidence and resource needs 2. Overview of current status of PCV use globally (20 min) a. Epidemiology and burden overtime	Thomas Cherian Kate O'Brien

	b. Introduce the 'Evidence and Note Tracking Table' & final session VI 3. Clarifying Questions/Discussion (20 min)	
9:55 (30 min)	**Coffee Break**	
10:25 (50 min)	**Looking to the future: the broader economic impact of pneumococcal vaccination** 1. Presentation (30 min) 2. Clarifying Questions/Discussion (20 min)	David Bloom
11:15 (1 hr)	**Key Model Drivers & Implications for Interpreting Empiric Data:** • Presentation (30 min) • Discussion (30 min)	Stefan Flasche
12:15 (45 min)	**Lunch (sandwiches provided outside meeting room)**	
Session II.	**Presentations on PRIME systematic review of empiric data**	**Chair: Claire Broome**
13:00 (1 hr)	1. Methods of PRIME systematic review (15 min) 2. Impact on IPD (by schedule and product) (30 min) 3. Discussion and identification of key gaps (15 min)	Olivia Cohen Tamara Pilishvili
14:00 (45 min)	4. Impact on Pneumonia (by schedule and product) (30 min) 5. Discussion and identification of key gaps (15 min)	Jennifer Farrar
15:00 (30 min)	**Coffee/ Tea Break**	
15:30 (30 min)	6. Impact on mortality by measure of effect, dosing schedules (and product) (15 min) 7. Discussion and identification of key gaps (15 min)	Kate O'Brien

Session III	Programmatic considerations of dosing schedules	Chair: Narendra Arora
16:00 (1 hr 50 min)	1. Global and regional vaccination schedules (with specific focus on number of vaccines being given at 14 weeks, 9 months, and 2YL) and coverage with different vaccines at different ages, including in 2YL (15 min) 2. Modeling work on the critical community size required for coverage to be achieved in for PCV impact (20 min) • Clarifications (5 min) 3. Timeliness of vaccination in relation to coverage, focusing on immunizations in the 2nd year of life • Clarifications (5 min) 4. Alternate 2p+1 schedule lessons learned (15 min) 5. Group discussion (30 min)	Tomoka Nakamura Ben Althouse Colin Sanderson Bikash Lamichhane
18:30-21:00	**Group Cocktail Hour (WHO Café)**	

Tuesday, June 13, 2017

Session IV.	Continued presentations of PRIME systematic review	Chair: Liz Miller
9:00 (5 min)	Welcome to Day 2	Thomas Cherian
9:05 (1 hr 30 min)	1. PCV immune response by dosing schedule (and product) (30 min) 2. Impact on NP Carriage by dosing schedule (and product) (30 min) 3. Discussion and identification of key gaps (20 min)	Jennifer Moisi Maria Knoll
10:35 (30 min)	Emerging immunogenicity data on dosing and product comparisons from Nepal and Viet Nam	Andy Pollard Kim Mulholland
11:05 (30 min)	Modelling the added value of catch-up (20 min) for PCV impact Group discussion (10 min)	Stefan Flasche

11:35 (15 min)	**Coffee Break**	
Session V	**Panel Discussion: What impact evidence do country policy makers use?**	**Chair: David Golblatt**
11:50 (1 hr 10 min)	Moderated 'television panel' on country-level decision-making experience. Decisions of interest include: <u>2p+1 dosing schedules:</u> • UK • Australia • India <u>Product switch</u>: • Mozambique <u>Program Risk/Expansion:</u> • Venezuela • Philippines <u>Transition from Gavi Support</u>: • Bangladesh • Tanzania	<u>2p+1 dosing schedules:</u> Liz Miller Peter McIntyre Narendra Arora <u>Product switch</u>: Betuel Sigauque <u>Program Risk/Expansion:</u> Lucia Oliveira John Erasmo <u>Transition from Gavi Support</u>: Samir Saha Dafrossa Lyimo
13:10 (1 hr)	**Lunch**	
Session VI	**Final Session: Articulate the Key Gaps and Technical Needs**	**Chair: Kate O'Brien**
14:10 (1 hr 20 min)	• Quick introduction to activity (5 min) • Breakout session: in groups complete table on evidence to consider and remaining gaps for each central policy issue (1 hour 10 min)	<u>Group Leaders</u>: Kim Mulholland Lieke Sanders Anthony Scott Ron Dagan Fiona Russell Laura Hammitt
15:30 (30 min)	**Coffee/Tea Break**	
16:00 (45 min)	Continue Session VI… • Presentation and group discussion (45 min)	Moderated by Chair
Session VII	**Closing Remarks**	
16:45 (15 min)	• Next steps for SAGE Working Group & SAGE Policy Process • Closing remarks • (10 min)	Thomas Cherian

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