

Executive Summary

SAGE October 2017, Pneumococcal Conjugate Vaccine Session

1.0 Introduction

Currently, WHO has recommended the use of either a 10-valent or 13-valent pneumococcal conjugate vaccine (PCV10 and PCV13, respectively), for all infants worldwide. For routine immunization, WHO has recommended that PCV can be administered using either a 2p+1 or 3p+0 schedule, though 3p+1 schedules are also used in some countries[1]. A total of 141 countries have introduced PCV into their national immunization program, and 7 out of the 10 countries with the highest pneumococcal disease burden have recently introduced the vaccine[2].

Since the introduction of the first PCV (PCV7) in 2000, global reductions in pneumococcal disease burden in children under 5 years of age have been observed. The number of deaths attributable to pneumococcal disease has been halved since 2000 among HIV negative children under 5, from approximately 600,000 to 294,000 deaths in 2015. It is estimated that nearly 200,000 deaths have been averted since 2000 specifically because of PCV use[3].

Despite these demonstrated reductions, pneumococcal disease burden remains high, particularly in lower income regions. Pneumonia, from all causes, accounts for approximately 16% of childhood deaths in low and middle income countries (LMICs), compared to 5% in high income countries; pneumococcus is a leading cause of these pneumonia deaths[4]. Furthermore, the substantial costs of PCV (particularly for middle or lower middle income countries not supported by Gavi) have led to gaps in the introduction and coverage of the vaccines due to concerns about the sustainability of PCV immunization programs.

As the availability of PCV impact data by schedule and product continues to accrue, the review of such evidence is necessary to facilitate countries in making decisions on which product and schedule to use, as well as whether to conduct catch up immunization programs. The Strategic Advisory Group of Experts (SAGE) on Immunizations PCV Working Group (WG) assessed results from the Pneumococcal Conjugate Vaccine Review of Impact Evidence (PRIME) Systematic Review, modelled evidence on the impact of catch up immunization, and additional ad hoc data to update existing recommendations on

three key PCV issues: **dosing schedule, product choice, and catch up immunization**. The discussions held by the WG were framed around the following three questions:

- **Question 1: Dosing Schedule**

How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?

- **Question 2: Product Choice**

Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?

Question 3: Catch Up Vaccination

What additional value does catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve healthy children offer as compared with vaccination of only age eligible children (as per the vaccination schedule in the country) in relation to the overall impact on pneumococcal disease?

The following sections of this document will provide an overview of available evidence reviewed by the WG, as well as proposed PCV policy recommendations and suggested research priorities.

2.0 Available Evidence Reviewed by the PCV SAGE WG

Section 2.0 briefly summarizes the key sources of primary and secondary data that served as the evidence base for the WG to revise recommendations.

2.1 The PRIME Systematic Review: Objectives, Approach, and General Conclusions

PRIME was a systematic review assessing primary evidence from literature assessing impact and effectiveness of each PCV dosing schedule and product. Primary evidence of catch up immunization impact was limited but assessed where available. A full report of the results from this extensive review can be found on the WHO SAGE website.

2.1.1 Context and Purpose of PRIME

A 2010 systematic review, referred to as the PCV Dosing Landscape Study, informed the scientific community and SAGE on PCV schedule(s) with a focus on the differences in immunogenicity and colonization/disease impact between 3- and 4-dose schedules using the 7-valent PCV (PCV7) product[5]. The available data were predominantly from high-income countries. The PCV Dosing Landscape Study contributed to the SAGE review to recommend the use of either a series of 3 primary doses without a booster or 2 primary doses with a booster given at 9 months of age or later.

A substantial number of immunogenicity and post-introduction disease and colonization impact assessments have become available since 2010, particularly from low-and-middle-income countries (LMICs) which are known to have pneumococcal epidemiologic characteristics that differ from those in higher income settings. Since 2010 two expanded serotype products, PCV10 and PCV13, have both been available, and PCV7 was removed from immunization programs in that year. The majority of the recent PCV impact data are from the use of these two WHO prequalified products, and these data have yet to be summarized for decision-making on the optimal use of PCV globally. Both the currently licensed PCV10 and PCV13 products contain antigens from serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. PCV13 also contains antigens from serotypes 3, 6A and 19A.

This update to the previous review provides further evidence to the scientific community and policy makers regarding which PCV schedule(s) and product(s) are optimal, considering both the direct and indirect effects of the vaccines.

2.1.2 PRIME Methods and Data Analysis:

A systematic literature review of 14 databases was conducted to include relevant data published in English from January 1, 2010-December 31, 2016, with ad-hoc additions through June 2017. All relevant citations (evaluating PCV10 and/or PCV13) included in the PCV Dosing Landscape Study

systematic review (1994-2010) were also brought into this analysis and summary document [1]. In addition, relevant unpublished data were considered.

A set of core exclusion criteria were established for all outcomes in order to ensure that effectiveness and impact estimates were comparable across studies and technically relevant to address the proposed research questions on optimal use of PCV globally. A total of 207 studies were analyzed for the final report.

Types of Studies:

- Included: Randomized control trials (RCTs), non-randomized trials, and observational studies reporting pre (baseline) and post vaccine introduction incidence rates for disease outcomes or prevalence for carriage
- Excluded: Incidence data from only the PCV post-introduction era, and case-series data for disease outcomes (pre-post or post- only)

Outcomes:

- Direct and indirect impact on invasive pneumococcal disease (IPD), pneumonia syndrome, pneumococcal nasopharyngeal (NP) carriage, as well as pneumococcal serotype specific immunogenicity measured by antibody concentrations (IgG).
- Outcomes reporting serotype specific data (IPD, immunogenicity, and NP carriage) were prioritized for review from the WG.

Products:

- PCV13 & PCV10

Schedules:

- 3+0 and 2+1 dosing schedules (2+0 and 3+1 schedule studies were included where technically relevant)

Descriptive analyses reveal the amount and variability of the data by product, schedule and outcome evaluated. Meta-analyses were done only where appropriate (immunogenicity and NP carriage), and not for all outcomes of interests. A narrative synthesis is based on the information summarized in tables with the characteristics and findings of the included studies: country, year of publication, number of participants, age range, name of vaccine, immunization schedule, comparator, study design, outcomes, magnitude of effect, and confidence interval. Additional details regarding PRIME methodology can be found on the WHO SAGE website, in the full PRIME report of results.

2.1.3 PRIME Findings

A more detailed summary of PRIME results can be found in subsequent sections of this Executive Summary as well as in the full PRIME report available on the WHO SAGE website. In short, findings show that both products and both 3-dose schedules are immunogenic and highly effective against disease by vaccine-serotypes as a group, in the respective vaccines.

2.2 Modelled Data Assessing Catch Up Vaccination Impact

Empiric evidence reporting the impact of catch up PCV vaccination at the time of introduction among children above the birth cohort is limited. To further inform the WG of how to further optimize and update the current WHO recommendations on catch up immunization for PCV, modelled evidence on the impact of catch up immunization in Kilifi, Kenya[6] and Viet Nam (Flasche, personal communication) were reviewed.

2.2.1 About the Model

The model assessed data only from children under 5 years of age, and only from the two settings noted above (Kenya and Viet Nam). It was assumed that catch-up given as 3 doses if started in infancy and 1 dose if started at 12m or older would confer similar protection against carriage and disease as routine use in an EPI schedule. In part, this was suggested by fitting to available data from Kilifi. Additional details about modelling data can also be found in the *WHO Technical Expert Consultation Report on Optimization of PCV Impact: Review of Evidence and Programmatic Considerations to Inform Policy*, which is a meeting report found in the SAGE October 2017 Yellow Book.

2.2.2 Summary of Modelled Results

Catch-up campaigns at PCV introduction accelerate direct and indirect protection against pneumococcal disease. The model predicts that in the Kilifi, Kenya setting, PCV doses given as part of a catch-up for either children aged <1 year (3 dose), <2 years (3 dose in <1y and 1 dose after) or <5 years (3 dose in <1y and 1 dose after) prevent more IPD cases per PCV dose if compared to routine PCV use. Therefore, catch-up campaigns were highly efficient uses of PCV. Furthermore, catch up immunization accelerated the rate of PCV impact by up to 3 years. Although these data assessed impact only among children under five years old, it is possible that settings of high disease burden or carriage in older children should have larger targeted age ranges. These results were robust to a range of alternative assumptions on vaccine efficacy (VE) of the routine use, VE of the catch-up doses, and the duration of protection. Additional data using a different but similar modelling approach found similar conclusions when assessing impact in Nha Trang, Viet Nam.

If the planning of a catch-up campaign introduces substantial delays in vaccine implementation, the campaign will become less efficient overall. The efficiency of PCV use for catch-up campaigns also hinges on:

A) The disease burden in the targeted age group (additional benefit through direct protection) and;

B) The contribution of these older age groups to pneumococcal transmission to others in the community, including younger children (additional benefit through indirect protection).

Catch-up campaigns may be most efficient in low income settings where a substantial disease burden and high carriage rates extend to older children.

3.0 SAGE PCV WG Considerations and Proposed Recommendations

Section 3.0 summarizes overall considerations and conclusions the WG derived from the available evidence described in Section 2.0, and states the proposed recommendations.

3.1 Background and Context

Both PCV10 and PCV13 have been shown to be safe, effective, and to demonstrate both direct and indirect effects against pneumococcal disease, when used in a three-dose schedule, either with 3 primary doses without a booster dose (3p+0) or 2 primary doses with a booster dose (2p+1). There is

substantial evidence on the disease impact of each schedule and each product in routine use among children, including head to head studies of immunogenicity and nasopharyngeal colonization outcomes; however, there are no head-to-head comparative studies of product or schedule on disease outcomes.

In the absence of consistent evidence to support a preference for a product or schedule, the country level choice will depend on factors such as local or regional programmatic considerations, disease epidemiology, serotype prevalence, cost-effectiveness, or other issues. The measured impact from single schedule or single product studies provides evidence for product and schedule performance; however, comparisons of impact between products or schedules from these single arm studies are subject to other factors that can influence the effect magnitude. Therefore, differences in observed impact on disease outcomes across these studies should not be used alone to infer conclusions about schedule or product differences.

The following recommendations relate to three priority topics that were considered by the WG, namely: (1) dosing schedule; (2) product choice; and (3) catch up vaccination. For each topic, preceding the recommendations, the WG summarizes evidence that was considered on immunogenicity, NP colonization and disease outcome studies, including serotype-specific outcomes for each. Immunogenicity was assessed by the fraction of immunized subjects achieving serotype specific antibody concentrations above the correlate of protection and by the geometric mean concentration achieved. Data from studies of 3p+1 schedules were reviewed non-systematically for serotype-specific outcomes where there were insufficient data from studies of 2p+1 and 3p+0 schedules. Due to limitations in the data reporting PCV impact on pneumonia and mortality, the WG primarily used serotype specific IPD data to develop the proposed recommendations.

3.2 Schedule Choice

Deliberations assessing the evidence to determine if there is a differential impact by schedule were framed around the following question:

How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?

3.2.1 Schedule Choice Considerations

Immunogenicity

There were two outcomes used to assess immunogenicity: the geometric mean concentration of antibodies (GMCs), and the proportion of participants who had an antibody response above the correlate of protection (percentage of responders).

Head to head studies demonstrate that, after the primary series, a two-dose primary schedule has lower GMCs but a similar percentage of responders compared with a three-dose primary schedule for most serotypes. For ST6A and ST6B, a three-dose primary schedule had both higher GMCs and higher percentage of responders compared to a two-dose primary schedule.

When assessing immunogenicity after the third dose of each schedule (post-booster for 2p+1 and post primary for 3p+0), a 2p+1 schedule elicited higher GMCs but a similar percentage of responders compared with a 3p+0 schedule for most serotypes, including ST6A. For ST6B, both the GMCs and percent responders indicated an advantage from a 2p+1 schedule compared to a 3p+0 schedule, post third dose.

Comparison of data across studies showed that the percentage of responders was lower in African and Asian studies than in studies from other global regions for PCV13 but not for PCV10. However, differences in immunogenicity between the two vaccines and between geographic regions observed across non-head-to-head studies may be explained by confounding factors. For example, studies evaluating a 2p+1 schedule tended to be from high income countries, often using PCV13 and with concomitant use of acellular pertussis (aP) vaccine, while those evaluating a 3p+0 schedule and PCV10 were frequently conducted in lower income countries in Africa and Asia, with the concomitant use of whole cell pertussis (wP) vaccine. Hence, differences in immunogenicity between the two vaccines and between the different regions may be explained by confounding factors such as serotype specific carriage; study population disease rates; age at vaccination; interval between doses; the adjuvant effect of whole cell pertussis vaccine; maternal pneumococcal antibodies; and maternal vaccination with diphtheria or tetanus toxoid containing vaccines.

In general, antibody responses to most serotypes increase with age at first dose, producing differences in antibody concentrations and proportions above the protective efficacy threshold both at

the post-primary and at the post-dose 3 time points. It is still uncertain the degree to which observed differences in either GMC or percent responders are clinically relevant, if at all.

Clinical Burden of Disease

IPD

No head to head studies comparing the impact or effectiveness of the two schedules were available on IPD outcomes; therefore, quantitative comparisons in disease reduction across studies of different schedules should not be made. Evidence from ecological and case control studies indicates that both schedules reduce the burden of IPD caused by vaccine-serotypes as a whole in respective vaccines, both among vaccinated and unvaccinated individuals in the population.

Evidence from studies comparing different schedules across settings is confounded by many factors including use of CV7 and differences in baseline IPD incidence. Settings with outcome data on the 2p+1 schedule tend to be high income countries, using PCV13, with prior PCV7 use, and with low IPD incidence. Conversely, settings evaluating IPD impact of a 3p+0 schedule tend to be low income countries using PCV10 without prior PCV7 use, and with high IPD incidence.

Pneumonia Syndrome

Evidence of PCV impact by schedule on syndromic pneumonia was available but was not used by the WG to develop the proposed recommendations because of confounding in the pneumonia data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review found that the amount of evidence for each schedule varied by clinical outcome (chest x-ray confirmed pneumonia, empyema, pneumococcal pneumonia), with 2p+1 impact data more available than 3p+0 data. There is no evidence available supporting an advantage of one schedule compared to the other schedule for either vaccinated and unvaccinated age groups.

Mortality

Evidence of PCV impact by schedule on mortality was available but was not used by the WG to develop the proposed recommendations because of confounding in the mortality data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review found that data assessing impact of schedule on mortality (mortality rates and case fatality rates) are limited and that comparisons of PCV schedule impact on mortality could not be made. Thus no conclusions could be drawn about differential impact by schedule.

NP Carriage

Evidence from two head to head studies assessed differential effectiveness of the two schedules. In those studies, both schedules were found to be effective in reducing overall, product specific VT NP carriage. Neither of the studies detected a significant difference in the effectiveness one schedule over another against overall VT carriage.

Evidence on differential impact of schedules on NP carriage from cross study comparisons of different schedules, conducted in various settings was inconclusive as it is confounded by many factors including use of PCV7 prior to PCV10/13 introduction, the PCV product in use, and differences in baseline carriage prevalence. As noted previously, countries evaluating 2p+1 schedules tended to be higher income, use PCV13, and have prior PCV7 use; countries using 3p+0 schedules tended to be lower income, and use PCV10 *denovo*.

3.2.2 Schedule Choice Recommendations

1. For PCV administration to infants, at least 3 doses of vaccine, administered **either** as 2 primary doses plus booster (2p+1) or 3 primary doses without a booster (3p+0), are recommended.
 - For countries that have yet to introduce PCV, decisions regarding the choice of schedule should take into consideration operational and programmatic issues, including timeliness of vaccination, the coverage expected to be achieved at the third dose, and pneumococcal disease age distribution patterns, if known. Low population vaccine coverage at visits occurring between 9-12 months of age or later may warrant the use of a 3p+0 schedule.
 - Once a program has been initiated, schedule switching is not necessary unless one or more factors that led to the original choice of schedule changes substantially.
2. A dosing interval of 8 weeks between the first two doses of a 2p+1 schedule and a dosing interval of at least 4 weeks for a 3p+0 schedule is recommended. However, the 8-week interval recommended for the 2p+1 schedules may be shortened if there is compelling reason to do so, such as timeliness in receipt of the second dose and/or higher coverage that may be achieved with the schedule. The dosing interval between primary doses within each schedule should not be shorter than 4 weeks.

3. The timing of the booster dose should be selected to maximize coverage. The selected age for administration of the booster dose in most programs is at 9, 12, 15 or 18 months, depending on operational and programmatic factors, including the timing of vaccination contacts in the national immunization schedule for other vaccines. There is insufficient evidence to inform optimal timing of the booster dose.

3.3 Product Choice

Deliberations assessing whether there was evidence indicating differential impact by PCV product were framed around the following question:

Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?

Data are summarized by serotype for product choice.

3.3.1 Product Choice Considerations

Immunogenicity

Evidence is from both single product and head-to-head studies of the two products.

VT Serotypes

Both PCV10 and PCV13 induce antibodies against the serotypes common across the two vaccines. Although there are small differences in antibody response between the two products for these serotypes, in general, PCV10 and PCV13 have comparable, albeit not identical, immunogenicity. The clinical implications, if any, of these relatively small differences in immunogenicity for the common serotypes have not been established.

Serotype 3

PCV13 induced an immune response to ST3 (documented by serotype specific IgG GMCs and the proportion of vaccine recipients with a concentration above the correlate of efficacy). PCV10 contains neither ST3 nor any cross-reactive serotypes, and therefore is not expected to induce an immune response to this serotype. Consequently, PCV10 studies, in general, do not measure immunogenicity against this serotype.

Serotype 6A

Both PCV10 and PCV13 induce an antibody response to ST6A, a serotype included in PCV13 but not in PCV10. Evidence indicates, however, that PCV13 induces higher ST6A GMCs and percentage of responders than PCV10. The clinical significance of these immunogenicity differences cannot be inferred based on the antibody levels alone.

Serotype 6C

ST6C immunogenicity data are rarely reported and thus could not be systematically assessed.

Serotype 19A

Both PCV10 and PCV13 induce an antibody response against ST19A; however, evidence indicates that PCV13 induces higher ST19A GMCs and percentage of responders than PCV10. The clinical significance of these differences in immunogenicity cannot be inferred based on the antibody levels alone.

Clinical Burden of Disease

IPD

There were no head to head studies comparing the impact or effectiveness of the two products on IPD outcomes. Only single product studies were assessed.

VT Serotypes

Available evidence indicates both products are effective in reducing overall vaccine type IPD caused by serotypes within each vaccine as a whole among both vaccinated individuals and those who remain unvaccinated in the population. Although PCV13 contains three additional serotypes, there is currently insufficient evidence to determine whether there is any differential impact on overall IPD burden (vaccine and non-vaccine type disease combined) between the two products.

Serotype 3 IPD

As expected, PCV10 use did not result in a reduction in ST3 IPD in vaccine-eligible or non-eligible age groups, because the vaccine does not contain ST3. Evidence for direct or indirect reduction in ST3 IPD following PCV13 was inconclusive with the majority of studies showing impact on type 3 IPD in neither vaccine eligible cohorts nor in unvaccinated age groups.

Serotype 6A IPD

Data on PCV10 impact on ST6A IPD are limited but generally supportive of a direct effect. Data assessing PCV13 impact on ST6A IPD were predominantly in settings of prior PCV7 use, with very low levels of residual 6A IPD. PCV13 showed a reduction in the residual low burden of ST 6A IPD that remained after the implementation of PCV7 in both vaccine eligible and non-eligible cohorts.

Serotype 19A IPD

Case-control effectiveness studies of PCV10 against ST19A IPD indicate some protective effect in vaccine eligible age groups, but not all reached statistical significance; however, studies evaluating population-level impact were less conclusive. Among vaccine non-eligible cohorts, evidence from PCV10-using populations shows an increase or no change in ST19A IPD rates. Effectiveness and impact against ST19A IPD in vaccinated and unvaccinated cohort were both demonstrated for PCV13.

Serotype 6C IPD

There are very few data on PCV10 effects against ST6C IPD. Some studies, though not all, showed a significant impact of PCV13 on ST6C IPD.

Pneumonia Syndrome

Evidence of PCV impact by product on syndromic pneumonia was available but was not used by the WG to develop the proposed recommendations because of confounding in the pneumonia data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review of pneumonia evidence reviewed PCV impact data by product on syndromic pneumonia (including chest x-ray confirmed pneumonia, empyema, pneumococcal pneumonia). PRIME found these data were subject to confounding, however, evidence demonstrate impact from both products, both on directly vaccinated populations and unvaccinated age groups. There are currently no data supporting differential impact on overall pneumonia between the two products

Mortality

Evidence of PCV impact by product on mortality was available but was not used by the WG to develop the proposed recommendations because of confounding in the mortality data and the WG's decision to prioritize review of serotype specific data. The PRIME systematic review found that comparisons of PCV product impact on mortality could not be made, and thus no conclusions could be drawn about differential impact by product.

NP Carriage

Limited head to head evidence was available to compare differential impact or effectiveness between PCV10 and PCV13

VT Serotypes

Both products were found to be effective and have impact on carriage of serotypes included in the respective vaccines as a whole; however, quantitative comparisons across studies of individual products were difficult because of substantial confounding by schedule, local epidemiology and prior PCV7 use. PCV10 was found to decrease overall VT carriage among unimmunized populations. Data reporting on indirect effects in populations that have been using PCV13 for at least three years are limited; however, recent data from the UK indicate PCV13 also demonstrates indirect effects against overall VT carriage (Miller et al, personal communication), in line with observed herd effects in unvaccinated age groups. NP carriage with vaccine serotypes is reduced by both PCV products but non-vaccine type replacement is well described such that overall pneumococcal carriage can remain unchanged. It is currently unknown whether the net effect of VT reductions and replacement with NVTs in carriage and disease would direct choice of one product over another and further investigation is needed.

Serotype 3

No significant direct or indirect effects were found for PCV10 on ST3 carriage, as expected. No conclusive direct effect of PCV13 on ST3 NP carriage was found, as results were mixed. No data were available assessing indirect effects of PCV13 on ST3 NP carriage.

Serotype 6A

Direct effects on ST 6A carriage, for both products, were observed but there was insufficient evidence to conclude whether the magnitude of impact differed between products. Possible indirect effects against ST6A carriage have been demonstrated for PCV10 in studies where there was no prior use of PCV7. No evidence on indirect effects is available for PCV13 because carriage had already been substantially reduced due to prior PCV7 use where this was studied.

Serotype 19A

PCV10 use was associated with statistically significant increases in ST19A carriage in some studies and non-significant increases or reductions in ST19A carriage in other studies with low pre-study carriage; statistically significant reductions in 19A carriage were observed from PCV10 in settings of high baseline carriage, though non-vaccine related reduction in 19A carriage, i.e. natural temporal variation, cannot be excluded. Evidence on indirect effects of PCV10 suggests a non-significant increase in ST19A carriage in settings where the vaccine is used.

PCV13 studies demonstrated more consistent reductions in ST19A carriage in children age-eligible for vaccination in routine use settings. Analyses of PCV13 indirect effects are not available.

Serotype 6C

No clear conclusion can be drawn as availability of results for impact of vaccination on ST6C colonization were limited for both products and generally underpowered. Only one PCV13 study had sufficient power and it showed substantial reduction.

3.3.2 Product Choice Recommendations

1. Both vaccines have impact against overall vaccine-type disease and carriage. PCV13 may have additional benefit in settings where disease attributable to ST19A or ST6C constitutes a significant public health problem; however, there is at present no supportive evidence of different net impact on overall disease burden between the two products.
2. The country-level product choice should consider programmatic characteristics, vaccine supply, vaccine price, local/regional vaccine serotype prevalence, antimicrobial resistance patterns among vaccine serotypes.
3. Given the relative comparability of existing PCV products and programmatic challenges that may be associated with product switching, once a program has been initiated product switching is

not recommended unless one or more factors that led to the original choice of product changes substantially (see Recommendations 1 and 2).

4. Interchangeability between PCV10 and PCV13 has not been studied in the 2 or 3-dose *primary* series; however, limited evidence suggests that products confer comparable immunogenicity for the *booster* dose regardless of which product was used in the primary series. Therefore, when a 2- or 3-dose primary immunization series is initiated with one of these vaccines, ideally the remaining doses needed to complete the primary series should be administered with the same product. If it is not possible to complete the primary series with the same product, the other vaccine should be used, rather than miss a primary or booster dose. There is no evidence to suggest that restarting the vaccination series is necessary if a product switch occurs, therefore restarting the series is not recommended even for the primary series.

3.4 Catch Up Vaccination

Deliberations assessing whether there was evidence assessing impact of catch up vaccination were framed around the following question:

What additional value does catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve healthy children offer as compared with vaccination of only age eligible children (as per the vaccination schedule in the country) in relation to the overall impact on pneumococcal disease?

3.4.1 Catch Up Considerations

Evidence regarding the impact of catch up immunization is limited across different age groups; however, the available evidence suggests PCV immunization, at the time of national introduction, for children outside the birth cohort accelerates both direct and indirect protection and thereby hastens the impact of PCV. Modeling of NP carriage and IPD in Kilifi, Kenya demonstrated that at the time of PCV introduction a catch-up campaign in those under 5 years of age can accrue a greater benefit per dose administered than would smaller campaigns in more narrow age strata, or compared with routine infant vaccination alone. Limited evidence exists on the effectiveness of PCV as a means of response to pneumococcal disease outbreaks or to supplement ineffective routine vaccination in humanitarian crises.

Based on available evidence, any catch up vaccination program confers additional direct and indirect benefits compared with routine immunization alone. If logistically feasible, catch-up campaigns

at PCV introduction can enhance the benefit per dose of the PCV program in settings with high VT carriage and disease beyond infancy. After PCV introduction vaccination, PCV catch up campaigns may also be desirable in settings with a weak routine vaccination program or when rapid disease control is sought. Example situations include settings of vaccine serotype disease outbreaks caused by VT pneumococci or humanitarian emergency settings with high risk of pneumococcal disease. Limited evidence is available to determine whether a single dose is sufficient or whether 2 doses are required for catch up vaccination beyond infancy. The benefits of a catch up campaign are lessened if the resources needed for the campaign diverts resources and negatively impacts PCV coverage in the birth cohort, if the resources for the campaign result in delayed introduction of PCV in the birth cohort, or if the epidemiologic setting is one where there is only moderate vaccine serotype carriage and disease in those in the catch up age cohort. The relative benefit of conducting a catch up campaign at the time of introduction also depends on the cost and vaccine supply.

3.4.2 Catch Up Recommendations

1. Catch-up vaccination as part of PCV introduction will accelerate both direct and indirect protection and therefore accelerate PCV impact on disease, particularly in case of high VT carriage prevalence and disease burden in children aged 1 to 5 years old.
2. Catch-up vaccination with PCV can be done with 1 dose of vaccine for those initiating vaccine at age 24 months and older. For those who are 12-23 months at the time of first vaccination some programs have used 2 PCV doses separated by at least 8 weeks, and others have used 1 dose. For those initiating vaccination at age 6 months or under, a 3 dose regimen should be offered. For infants aged 7-11 months, some programmes have used 2 doses, and others have used 3 doses. If there is limited availability or capacity for catch-up immunization, the youngest children should be prioritized to receive catch-up doses of PCV because of the higher pneumococcal disease risk.
3. Unvaccinated children up to 5 years of age who are at high risk for pneumococcal infection based on a medical condition (e.g. HIV infection, sickle cell disease) should receive at least 2 PCV doses separated by at least 8 weeks to assure immunogenicity.
4. In areas/communities where low vaccination coverage has permitted sustained vaccine serotype pneumococcal transmission (or disease), especially those with coverage below 50%, catch up campaigns (also termed periodic intensification of routine immunization) can be used to reduce the disease burden.

5. Catch-up vaccination to replace missed doses among individual children should be encouraged with particular focus on children at highest risk of pneumococcal disease.
6. In humanitarian or emergency situations, age-appropriate schedules of PCV vaccination should be implemented, certainly for children under 1 year of age, and usually for children up to 5 years of age as indicated by the situation, through the use of the framework for vaccination in humanitarian emergencies. Immunization of children over age 5 may be indicated in certain situations.
7. Vaccination may be considered in response to outbreaks of confirmed VT pneumococcal disease, based on the characteristics of the outbreak, including the outbreak size, duration and age group affected.

3.5 Surveillance and Research Recommendations

Based on current evidence and remaining evidence gaps, the WG proposes several recommendations to guide future surveillance and research efforts.

3.5.1 Surveillance Recommendations

1. High quality, long-term, post-introduction, serotype-specific pneumococcal surveillance is needed in a representative number of settings.
2. **Methodology of disease surveillance:** Pneumococcal surveillance can be conducted as population-based or only in sentinel health facilities (which is not population-based). While population-based surveillance is required to document disease impact and serotype replacement, non-denominator based IPD surveillance in sentinel sites provides additional information on the distribution of serotypes in the PCV routine use era and a qualitative measure of PCV impact. Population-based surveillance may not currently be feasible in a sufficient number of representative countries and sites, so high quality sentinel site surveillance can provide useful complementary data. In addition to disease surveillance, periodic carriage surveillance could offer insight on the case-carrier ratio and ongoing circulation of vaccine serotypes. Pneumococcal surveillance does not need to be conducted in every country, but SAGE encourages countries to conduct high-quality surveillance with the ambition for surveillance and laboratory capacity to be strengthened everywhere.
3. **NP colonization surveillance:** Since pneumococcal colonization is a critical driver of population level disease and PCV impact, periodic monitoring of carriage is an important adjunct to disease surveillance. It offers a means to interpret pneumococcal disease and syndromic surveillance

findings, and provides important insights into case-carrier ratios, ongoing circulation of vaccine serotypes, and a means to monitor the PCV program implementation.

4. ***Diseases under surveillance:*** Pneumococcal surveillance can monitor not only IPD, but also other syndromes caused by pneumococcus, such as meningitis, pneumonia, and sepsis. At a minimum, we recommend that meningitis be monitored due to the severe nature of the disease, the need for identification of etiology for clinical management, and the higher yield of pathogens from cerebrospinal fluid, compared with the yield from blood cultures which are usually obtained from children with pneumonia and sepsis.
5. ***Duration of surveillance:*** Surveillance should be sustained indefinitely during the post-introduction period. The minimum duration is 5 years following PCV introduction, as evidenced by the time required for a plateau in IPD serotype replacement and PCV impact on overall IPD as concluded by a previously published global analysis. However, changes in distribution and pneumococcal disease impact are still being seen in many settings up to 17+ years following PCV introduction and use.
6. ***Location of surveillance:*** Surveillance should be conducted in a representative number of settings to monitor changes in disease following the use of different PCV products, in different dosing schedules, and in different geographic and epidemiologic settings with different pneumococcal burden and transmission.
7. WHO should periodically review global pneumococcal surveillance data to identify specific evidence gaps that need to be addressed through additional surveillance or special studies, including periodic cross-sectional studies on NP carriage prevalence.

3.5.2 Schedule Choice Research Recommendations

1. Additional data from head-to-head studies of schedules are needed to address differences in biological outcomes such as NP carriage, immunogenicity, duration of protection, and transmission dynamics, including herd immunity.
2. Coverage achieved by different PCV schedules, including the timeliness of vaccination, and the age of vaccination should be evaluated.
3. Serotype specific quantitative immune correlates of protection against invasive pneumococcal disease should be investigated from different epidemiologic settings. These can be carried out by using data from serotype specific vaccine effectiveness studies, with nested immunogenicity data.

4. Studies to evaluate the serotype specific duration of protection from different schedules are needed, especially to inform modeling efforts on schedule optimization.
5. Modeling studies should be undertaken to systematically evaluate key drivers of the relative benefits of 2p+1 vs 3p+0 schedules. Such drivers may include local epidemiology of carriage and disease, demographic structure, vaccine efficacy, timeliness and booster dose coverage. These models should further help quantifying scenarios under which one schedule can achieve a discernably higher impact than the other.

3.5.3 Product Choice Research Recommendations

1. Field data and modeling are needed to better understand the drivers of, and predictors of pneumococcal serotype replacement in disease. Specifically, potential differences in product-specific serotype replacement need to be characterized to better understand their differential impact on pneumococcal disease.
2. Head to head studies comparing immunological and carriage impact of future and existing PCV products are needed to adequately inform product and schedule choices for maximum control of pneumococcal disease. Assessment of PCV impact on carriage has additional value in predicting herd effects of vaccination and pneumococcal circulation, whereas measuring immunogenicity is important for establishing correlates of protection against IPD and carriage.
3. Studies are needed to understand the effects of maternal antibodies and maternal immunization with vaccines containing diphtheria and/or tetanus toxoid proteins on infant vaccination with PCVs containing pneumococcal polysaccharides conjugated to CRM, diphtheria, or tetanus toxoid proteins. These assessments should also include the effect of maternal vaccination on early infant PCV and diphtheria, tetanus, and pertussis (DTP) immunization in terms of optimizing timing of the first infant dose.
4. Data are needed on PCV product interchangeability to inform the effects of product switching during the primary immunization series (i.e. when programs switch PCV products) and on the use of schedules intentionally using different products to optimize impact.

3.5.4 Catch Up Research Recommendations

1. Further assessment is needed of pneumococcal epidemiology in outbreaks, and outbreak response opportunities with PCV.
 - a. A better understanding of ST1 epidemiology is needed for directing immunization efforts to prevent or control outbreaks of this serotype. Also review of historical data on

pneumococcal outbreaks, particularly of ST 1, may be useful to define outbreak thresholds and age groups for vaccination

2. Further assessment is needed of the benefits or limitations of developing and using PCV products containing single or a limited number of outbreak-associated serotypes as a tool for controlling pneumococcal outbreaks.
3. Studies should be conducted in settings where outbreaks or humanitarian emergencies have recently occurred to evaluate risk of pneumococcal disease, including pneumonia, and assess impact of PCV use in these settings.
4. A systematic analysis of evidence comparing 1-dose versus 2-dose catch-up vaccination at the time of vaccine introduction should be conducted. Data to compare 1-dose vs 2-dose catch-up vaccination at the time of vaccine introduction should be collected for systematic analysis.
5. Additional data are needed, through modeling or impact studies, on the relative benefit and cost of catch-up vaccination at the time of PCV introduction or switch to PCVs containing different serotypes or valencies.

4.0 Concluding Remarks

The review of available PCV evidence and conclusions of the WG highlight the sufficient amount of evidence indicating that both products and schedules have overall benefit, as well as the lack of head to head evidence that would be valuable in determining whether a particular product or schedule has added benefit, particularly for disease outcomes. Furthermore, there are few empiric, primary data available to analyze the effects of catch up vaccination in children above the birth cohort.

The nuances of analyzing pneumococcal epidemiology and the presence of several key confounding factors make assessing PCV impact particularly challenging. As countries continue rapidly introducing these vaccines, and as new conjugate and non-conjugate pneumococcal vaccines continue to advance through the product development pipeline, optimizing research endeavors to better quantify the benefits, and possible limitations, of pneumococcal vaccination is vital to direct program optimization.

5.0 References

- [1] The World Health Organization. Weekly epidemiological record Relevé épidémiologique hebdomadaire: Pneumococcal Vaccines WHO Position paper 2012;87:129–44.
- [2] International Vaccine Access Center. VIEW-hub n.d. <http://view-hub.org/viz/> (accessed February

19, 2017).

- [3] Wahl B, O'Brien K, Greenbaum A, Liu L, Chu Y, Majumder A, et al. Global, regional, and national burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in children in the era of conjugate vaccines: updated estimates from 2000-2015. *Submitt Publ* 2017.
- [4] Black RE, Levin C, Walker N, Chou D, Liu L, Temmerman M. Reproductive, maternal, newborn, and child health: key messages from Disease Control Priorities 3rd Edition. *Lancet* 2016;388:2811–24. doi:10.1016/S0140-6736(16)00738-8.
- [5] Deloria Knoll M, Park DE, Johnson TS, Chandir S, Nonyane BAS, Conklin L, et al. Systematic Review of the Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Immunogenicity. *Pediatr Infect Dis J* 2014;33:S119–29. doi:10.1097/INF.0000000000000079.
- [6] Flasche S, Ojal J, Le Polain de Waroux O, Otiende M, O'Brien KL, Kiti M, et al. Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya. *BMC Med* 2017;15:113. doi:10.1186/s12916-017-0882-9.