CALL FOR STAKEHOLDER COMMENTS ON THE PRELIMINARY RECOMMENDATION OF THE HEALTH TECHNOLOGY ASSESSMENT (HTA) COUNCIL ON PNEUMOCOCCAL CONJUGATE VACCINES FOR PEDIATRIC USE

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As of 20 September 2024, the Health Technology Assessment Council (HTA Council) has completed the evidence appraisal on the assessment of *Pneumococcal Conjugate Vaccines (PCV) for Infants less than 1 year old and children aged 13 to 23 months for catch-up immunization.* The HTA Council assessed the following PCV products for this reassessment:

- Pneumococcal Polysaccharide And Non-Typeable *Haemophilus Influenzae* (Nthi) Protein D Conjugate Vaccine, Adsorbed [PCV10-GSK]
- Pneumococcal Polysaccharide Conjugate Vaccine. (Adsorbed) (10-valent) [PCV10-SII]
- Pneumococcal Conjugate Vaccine, 13-Valent [PCV13]
- Pneumococcal Polysaccharide Conjugate Vaccine, 15 Valent (Adsorbed) [PCV15]

As such, the HTA Council hereby makes public the following preliminary recommendations, for stakeholder comments:

The HTA Council **recommends the inclusion in the Philippine National Formulary (PNF) and government financing of PCV with the same minimum *S. pneumoniae* serotypes as those recommended by the HTA Council in 2020: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F**. Maintaining the same minimum serotypes will allow the National Immunization Program (NIP) with more options which will:

- **enable more flexibility in the selection of PCVs that can address changes in the prevalent serotypes in the country through time, and meet programmatic considerations and,**
- **allow further competition to drive down the cost of PCVs.**

Further, the HTA Council recommends for the Department of Health to:

- strengthen the surveillance of *S. pneumoniae* serotypes in the country to guide the program in the yearly procurement of PCV products; and,
- consider program requirements and preferences to optimize its implementation (e.g., inclusion of vaccine vial monitors and availability in multi-dose preparation).

The HTA Council recommendation was based on the currently available evidence with respect to the following evaluation criteria provided for by the Universal Health Care Act:

(a) **Responsiveness to Magnitude and Severity**

Pneumococcal diseases, caused by *S. pneumoniae*, is one of the leading causes of morbidity and mortality globally, particularly in children <5 y/o. In 2015, there was an

estimated 3.7 million cases of severe pneumococcal disease in this age group, a significant portion occurred in developing countries in Africa and Asia.

In the Philippines, pneumonia is included in the top 10 leading causes of morbidity and mortality across all age groups. A longitudinal modeling study by Wahl, et al, 2018 estimated pneumococcal pneumonia and meningitis mortality in 2015 at 3,182 and 357, respectively, in Filipino children below 5 years old. Data from the 2015 FHSIS report showed 253,588 children <5 years old had hospitalized all-cause pneumonia and acute lower respiratory tract infection (ALRTI). This is far more than the projected value for the same period. Meanwhile, data from the DOH-Epidemiology Bureau (DOH-EB) consistently reported around 2,000 cases of acute meningitis syndrome (AMES) from bacterial cause, from 2017 to 2019 (2,101 in 2017; 2,308 in 2018; 2,001 in 2019) before it declined in 2020 (n=1,327). However, AMES cases started to escalate in the year 2021 (n=1,460) and peaked in 2023 with 3,130 cases.

DOH-FHSIS data from 2010 to 2023 including the years of PCV vaccination, generally showed a decreasing trend in hospitalized acute lower respiratory tract infection (ALRTI) and outpatient pneumonia in children under 5 years old. However, this is difficult to attribute solely to PCV vaccination because there is a decrease in incidence regardless of PCV coverage. A spike in hospitalized acute lower respiratory tract infections was observed in 2022, which may have been due to the loosening of COVID-19 restrictions. Similar trends were also observed in Regions 4B and 5 (low PCV coverage), 10 and 12 (high PCV coverage), and CARAGA. There is a perceived discordance between the PCV coverage and the decreasing trend of acute LRTI and pneumonia cases.

In the Philippines, the most common pneumococcal serotypes (STs) causing invasive pneumococcal disease in the pre-PCV vaccination period (2012-2014), in order from most to least common, were 5, 14, 1, 6B and 6A and in the post-PCV vaccination period (2015-2022) were 18C and 19A. The biggest decrease in prevalence from pre- to post-PCV period was for STs 5, 6A, 1 and 14. The biggest increase in prevalence from pre- to post-PCV period were for STs 19A, 3 and 9V/A. There was also an increase in the proportion of non-vaccine serotypes (NVT) from 27% to 37% from pre-PCV to post-PCV periods. These were based on the passive surveillance from Antimicrobial Resistance Surveillance Program (ARSP) and AMES surveillance, which **may not be precisely representative of the population** as only limited isolates are serotyped from selected sentinel sites. Despite the 2020 HTAC recommendation, the prevailing poor surveillance continues to be a barrier to establishing the true burden of pneumococcal diseases in the country.

PCV10-GSK, PCV13, and PCV15 are reactive against the current top three (3) most prevalent vaccine-type serotypes in the country - 18C, 19A, and 6B. PCV10-SII does not contain ST18C, the topmost prevalent vaccine-type serotype (10%).

(b) **Clinical efficacy, effectiveness and safety**

Clinical efficacy and effectiveness

Overall, evidence on clinical effectiveness against IPD, pneumonia, AOM, and nasopharyngeal carriage are only limited to PCV10-GSK and PCV13. Majority of these are observational studies. There were no identified studies reporting clinical outcomes for PCV10-SII and PCV15 as they utilized immunogenicity studies. **Therefore, based on the current evidence, we cannot directly compare the clinical effectiveness and safety of the four vaccine brands.**

Further, there are no existing clinical studies (on clinical outcome measures) which compared the PCV vaccines to each other, except for a single study that compared PCV10 and PCV13 in terms of nasopharyngeal carriage only. Majority of the studies compared PCV10 or PCV13 with no vaccination, PCV7, or hepatitis B vaccine.

Invasive pneumococcal disease (IPD)

In terms of effectiveness against IPD, seven (7) studies (1 RCT; 2 case control; and 4 cohort studies) with very low to high certainty showed that **PCV10-GSK is more effective compared to no vaccination, hepatitis B vaccination, and PCV7**, with reported VEs ranging from 83.8% to 100%. On the other hand,, seven (7) studies (5 cohort; 2 case-control) with very low to high certainty also showed that **PCV13 is more effective than no vaccination and PCV7,** with reported VEs ranging from 84.2% to 88.7%.

In terms of effectiveness against IPD specific to Serotype (ST) 3, three (3) cohort studies with very low certainty of evidence showed **nonsignificant difference between PCV10-GSK and no vaccination;** while four (4) studies with very low to low certainty had **conflicting results on the effectiveness of PCV13 against IPD-ST3 compared to PCV7 or no vaccination**. Similarly, observational studies that evaluated effectiveness against IPD due to ST6A and ST19A with very low to moderate certainty had **conflicting results on the effectiveness of both PCV10-GSK and PCV13 against no vaccination or PCV7.**

Clinical pneumonia

Regarding all-cause pneumonia, one RCT with moderate certainty showed that **PCV10-GSK is more effective than hepatitis B vaccine** in preventing hospital-diagnosed pneumonia [RR 0.68, (0.48, 0.97)], hospital-treated pneumonia [RR 0.69 (0.52, 0.91)], and radiologically-confirmed pneumonia [RR 0.68 (0.47, 0.89)]. **PCV13 was also found to be more effective in preventing hospitalized pneumonia than no vaccination** in all age groups <5 years old [<12 months [RR: 0.67 (0.59, 0.75)]; 12-23 months [RR: 0.74 (0.67, 0.81)]; 24-59 months [RR: 0.73, (0.66, 0.81)], based on one cohort study with very low certainty. One interrupted time series study with very low certainty of evidence showed that there is a lower risk of contracting clinical and x-ray confirmed pneumonia with PCV10/PCV13 compared to PCV7.

Acute otitis media (AOM)

As to the effectiveness against AOM, the pooled analysis of 2 RCTs with moderate certainty of evidence showed that participants given **PCV10-GSK had a lower risk of AOM** compared to those given hepatitis B vaccine [RR: 0.90 (0.83 to 0.98)] while two cohort studies with very low to low certainty of evidence for **PCV13 showed inconsistent results** when compared to PCV7 or no vaccination.

Additionally, one study with very low certainty looked at the effectiveness of PCV13 against ST-specific AOM. PCV13 showed favorable results compared to PCV7 in preventing AOM due to ST19A but had nonsignificant results for prevention of AOM due to ST3 and ST6A prevention.

Nasopharyngeal carriage

In terms of effectiveness against nasopharyngeal (NP) carriage, three (3) studies (2 RCT and 1 cohort study) with very low to moderate certainty of evidence that looked at PCV10-GSK and five (5) studies (2 RCT & 3 cohort) on PCV13 with very low to high certainty of evidence had **conflicting evidence** on the effect of either vaccine on the reduction of NP carriage compared to hepatitis B vaccine, PCV7, or no vaccination. Additionally, 1 RCT with low certainty reported no significant difference between PCV13 and PCV10.

For ST-specific NP carriage, 1 RCT with low certainty showed that PCV10 had a **non-significant difference** on NP carriage of ST6A and ST19A vs hepatitis B vaccine while 1 RCT with high certainty of evidence showed that there is a lower risk of NP carriage of ST6A [RR: 0.58 (0.43, 0.78)] and ST19A [0.55(0.44, 0.68)] with PCV13 compared to PCV7. However, there is no significant difference between PCV13 and PCV7 in terms of effectiveness against NP carriage of ST3.

Currently, there is no available evidence that directly shows the comparative efficacy of PCV10-GSK and PCV13 in terms of primary clinical outcomes. Nevertheless, both are effective against IPD and pneumonia. As for AOM, PCV10-GSK shows clinical efficacy while PCV13 has inconsistent evidence on its effectiveness. As for NP carriage, both PCV10-GSK and PCV13 show inconsistent evidence on its effectiveness.

Immunogenicity

Overall, evidence on clinical effectiveness against IPD, pneumonia, AOM, and nasopharyngeal carriage are only limited to PCV10-GSK and PCV13. Majority of these are observational studies. There were no identified studies reporting clinical outcomes for PCV10-SII and PCV15. All supporting evidence available for PCV10-SII and PCV15 are immunogenicity studies as the requirement for licensing of novel PCVs are non-inferiority studies with a primary endpoint of immunoglobulin G antibody concentration (IgG concentration).

The PCV product assessment by the IVAC, US CDC, UCL, ADMP, and the WHO used the proportion of subjects with serotype specific IgG above 0.35 µg/mL (% responders) as a correlate of overall efficacy against pneumococcal disease due to all serotypes. This was estimated from the clinical trials of earlier PCVs (i.e., PCV7 and PCV9).

All four vaccines have available immunogenicity data; however, **there was no study which compared the immunogenicity of all 4 vaccines against the most prevalent serotypes in the Philippines.** There were 2 studies that compared the immunogenicity of PCV10-GSK and PCV13 in terms of their shared serotypes and serotypes unique to PCV13; while the remaining studies compared the novel PCV intervention to a licensed PCV at the time of publication (i.e., PCV10-GSK vs PCV7, PCV13 vs PCV7, PCV10-SII vs PCV10-GSK and PCV13, and PCV15 vs PCV13).

Based on passive surveillance data from the RITM (2023), the 10 most common *S. pneumoniae* serotypes among children <5 years old during the post-vaccination period are ST18C (10%), 19A (7%), 6B (7%), 3 (6%), 23F (6%), 14 (6%), 1 (5%), 5 (4%), 7 (4%), and 9V (4%). Further, we also looked into the immunogenicity against serotypes uniquely contained in PCV products.

Based on the currently available immunogenicity data measuring the

proportion of participants with IgG levels above 0.35 ug/mL (% responders), among the serotypes common to the four PCV products of interest in this assessment (19A, 6B, 23F, 14, 1, 5, 7F, 9V):

- Against serotypes 19A, 14, 1, 5, 7F, and 9V, **all four PCVs are not different** in inducing adequate immunogenic response.
- Against serotype 23F, **all four PCVs are generally not different** in inducing adequate immunogenic response. However, we note one study showing that **PCV10-SII did not meet the non-inferiority criterion against PCV13.**
- Against serotype 6B, **PCV10-GSK, PCV13, PCV15 are generally not different** in inducing adequate immunogenic response; however, we note one study showing that **PCV10-SII did not meet the non-inferiority criterion against PCV13 and PCV10-GSK**, and studies showing that PCV10-GSK (k=3) and PCV13 (k=2) had lower % responders than PCV7.

Against serotypes 18C and 4 which are included in all PCV products *except PCV10-SII*, **all three PCV products (i.e., PCV10-GSK, PCV13, and PCV15) are not different** in inducing immunogenic response. **There was no evidence found for PCV10-SII compared with other PCVs**. However, it is noted that serotype 4 is not in the top ten most prevalent serotypes in the country.

Against serotype 3 which is present only in PCV13 and PCV15, **PCV13 had greater % responders than PCV10-GSK**. Further, **PCV15 is non-inferior to PCV13**. There was no evidence for PCV10-SII compared against other PCVs.

Although serotypes 6A, 22F, and 33F are not included in the top 10 most common serotypes in the Philippines, the following key findings are noted as these serotypes are unique to some PCV products under consideration:

- Against serotype 6A which is present in PCV10-SII, PCV13 and PCV15 but *not in PCV10-GSK*, **PCV13 and PCV15 are not different** in inducing immunogenic response. Meanwhile, **PCV10-GSK has either lower % responders (k = 1) or is comparable (k=2) to PCV10-SII**. Lastly, the comparison of immunogenic response between **PCV10-SII and PCV13 is unclear.**
- Against serotypes 22F and 33F, which are the additional serotypes in PCV15, **PCV15 is superior to PCV13**.

Safety

For PCV10-GSK, Silfverdal (2017) showed that the most reported solicited local AEs was redness at the injection site after the primary vaccination, while the frequently reported systemic AE was irritability. In terms of unsolicited AEs, nasopharyngitis was the most reported outcome while pyrexia was the most reported vaccine-related AE. The certainty of evidence across all outcomes for PCV10-GSK was very low.

PCV10-SII and PCV10-GSK are comparable in terms of the incidence of local [(RR: 0.941 95%CI (0.766, 1.156)] and systemic [RR: 0.969 (0.777, 1.210)] AEs while the results were **inconclusive for serious AEs** based on two pooled RCTs (Clarke 2021 and Adigweme 2023) with low certainty of evidence. A comparison between **PCV10-SII and PCV13 showed inconclusive results** for local, systemic, and serious AEs.

For PCV13, the systematic review of Thompson (2013) showed that the local AEs, specifically redness and tenderness, were more common in PCV13 than PCV7 during the 2nd dose but treatment arms had similar rates after the 3rd dose. For systemic AEs, rates of fever were similar between PCV13 and PCV7. There were only a few serious vaccine-related AEs (0.13% for PCV13; 0.18% for PCV7) and deaths (0.063% for PCV13; 0.036% for PCV7) reported for both arms. The certainty of evidence across all outcomes for PCV13 was moderate.

For PCV15, pooled data from 5 RCTs (Lupinacci, 2023; Martinon-Torres, 2023; Benfield, 2023; Suzuki, 2023; and Banniettis, 2023) showed that PCV15 had comparable rates of serious AE [RR 1.03 (0.88, 1.19)] versus PCV13 based on moderate quality of evidence, while PCV15 and PCV13 had equivalent rates of ≥1 AE [RR: 1.00 (0.99, 1.01)] and vaccine-related AE [RR: 1.01 (0.99, 1.02] based on high certainty of evidence. Meanwhile, the same 5 RCTs showed inconclusive results in terms of death [RR: 0.97 (0.16, 5.81)] based on moderate certainty of evidence. All 5 deaths that occurred in the trials were due to non-vaccine related reasons.

Currently, there is no available evidence that directly compares the safety profile of the four PCV vaccines. All vaccines have documented AEs of different severities but there is no clear evidence on the disadvantages of each PCV over the other. There were no alarming safety concerns on any of the PCV. While having adverse effects following immunization (AEFI) data has improved research on tracing the causality of AEs, one limitation observed was the difficulty in directly pinpointing AEs due to PCV because of concomitant vaccinations scheduled during infancy. Another limitation seen was the short observation period in RCTs which was only until 7-14 days for vaccine-related AEs and up to six months after final dose for serious AEs, which could possibly result in underestimation of the AEs related to PCVs. Additionally, **safety data for pediatric vaccination may not be attributed to a single vaccine as several vaccines are included in the childhood immunization schedule.**

(c) **Cost-effectiveness**

All PCV vaccines compared to no vaccination, in all scenarios (base case and sensitivity analyses), show that vaccinating children <1 y.o. is cost-saving. **All the PCV products are cost-effective vs no vaccination, at varying levels of the cost-effectiveness threshold (0.3x, 0.5x, 1x GDP per capita).** When compared with each other, PCV15 ranked highest followed by PCV13, PCV10-GSK, and PCV10-SII. However, between PCV15 and PCV13, the incremental QALY was considered marginal.

Adding PCV15 to the current PCV products that meet the current PCV specifications in the PNF will result in an additional cost-effective option.

The ICER results of all vaccine brands are most sensitive to the incidences and costs of treatment for acute otitis media and pneumonia.

(d) **Affordability and Viability**

The potential 5-year budget impact of pneumococcal vaccination, including vaccination and treatment costs, ranges from Php 133.5 B to Php 141.3 B. It is projected to be lower than the potential five-year budget impact of no vaccination (Php 189.9 B), which only includes treatment costs. In terms of vaccination cost,

none of the vaccines are considered affordable (i.e. within the 2024 and 2025 PCV budget). Further, if PCV15 were to be procured, the total 2025 NIP budget will not even be enough for PCV.

The PCV budget of the NIP which is Php 1.2 B for 2024 and Php 1.3 B for 2025 are insufficient to cover 90% of the target population with 3 doses of any of the vaccine brands. The budget should increase by 1.6x to 5.1x in 2024 and 1.5x to 4.8x in 2025 in order to cover the said population.

(e) **Household Financial Impact**

There is still a wide range of out-of-pocket (OOP) costs for pneumococcal diseases despite the availability of PhilHealth case rates. Based on PhilHealth data from 2017 to March 2023, the median range of OOP costs was Php 595.00 for pneumonia moderate-risk to Php 15,262.00 for meningitis per patient. Meningitis had the highest median OOP cost at Php 15,262.00 followed by otitis media at Php 3,140.00. High-risk pneumonia had the third highest median OOP cost at Php 3,000.00, followed by newborn sepsis, sepsis, and moderate-risk pneumonia at Php 1,264.00, Php 1,033.00, and Php 595.00, respectively. While the 30% inflation adjustment of case rates (PhilHealth Circular No. 2024-0001) and the increase in the case rate for high-risk pneumonia from Php 32,000 to Php 90,000 are expected to reduce individual household OOP costs for hospitalization due to pneumococcal disease, the PCV vaccines still have the potential to reduce total OOP cost due to decreased incidence of pneumococcal diseases.

The OOP cost of antibiotics to treat non-hospitalized pneumonia in children ranges from Php 367.00 to Php 1,801.00. Total OOP cost of antibiotics ranges from Php18.94 million to Php 92.99 million utilizing the estimated number of cases of nonhospitalized pneumonia due to *S. pneumoniae*. While some of the OOP costs can be covered by the Konsulta Package of PhilHealth, **PCV vaccines still have the potential to reduce the OOP costs of households due to the reduced incidence of the disease.**

(f) **Ethical, Legal, Social and Health System Impact (ELSHI)**

Ethical and Social Implications

Based on a survey of 25 parents or caregivers of infants for immunization, respondents deemed the efficacy and effectiveness of the vaccine as the most important factor on the selection of PCV. Other determinants were safety and government approval. For the important characteristics of a PCV, respondents gave higher preference for broader serotype coverage over the cost of the vaccine and the potential population volume coverage of the vaccine. However, when asked what should be included in the NIP, the respondents had preference for vaccines with lower price, thus covering more infants.

Further, the brand, country of origin, or the pharmaceutical company is foremost in the choice of PCV as they are seen to be safer, more effective, and have better quality (14/25; 56% of respondents). Logistics (e.g. limited vaccination schedules, long queues at health centers, vaccine stockouts) and quality of service from public facilities remain to be barriers for parents in deciding for the availment of vaccines for their children.

Legal Implications

There are no new laws and policies relevant to the implementation of PCV products in the Philippines, since the 2020 PCV assessment.

In terms of vaccine bidding and procurement process, the DOH Legal Service and DOH Central Office Bids and Awards Committee clarified that the choice of goods and services will be specified by the end-user or identified by the implementing unit. In the case of PCV procurement, indicating pneumococcal serotypes and other technical specifications in the bidding documents are permissible and may be exempted from the rule of tailor fitting as long as the product is able to address the burden of disease in the country. Lastly, multiyear vaccine purchasing, as suggested in the public consultation in the 2020 PCV reassessment, may be considered in future purchases once there is improvement in data surveillance in the country.

The DOH Administrative Order 2019-0041 or the *"Implementing Guidelines in Assuring the Efficacy, Quality and Safety of Pharmaceutical Products in the Public Health Facilities",* imposes, if applicable, the requirement for WHO prequalification for vaccines procured for special DOH programs, including the Expanded Program on Immunization. Additionally, the WHO considers the vaccine vial monitor (VVM) as a critical characteristic that will affect acceptance for prequalification. While compliance to critical characteristics is compulsory for WHO prequalification, should there be a deviation to this, the decision on the programmatic suitability of the proposed vaccine can be subjected to further discussion upon consultation with the manufacturer, procuring agents, and technical experts. Nevertheless, the proposed vaccine for WHO prequalification will still undergo in-depth assessment of the VVM, preservative, and antigenic stability criteria. Of the four PCV products, only 3 (PCV10-GSK, PCV10-SII, and PCV13) are compliant to the requirements of the DOH NIP for WHO prequalification and have the vaccine vial monitor (VVM) which is considered critical for WHO prequalified vaccines.

Health Systems Implications

In terms of the public health sector perspective, FGD respondents deemed that sudden switch from PCV with broader to narrower serotype coverage could possibly result in higher incidence of IPD, thus requiring judicious monitoring and well-implemented surveillance system. Meanwhile, there were no parental nor caregiver refusals to the introduction of a new brand or an additional dose to complete the vaccination schedule, as long as it is government-approved and recommended. Additionally, neither adverse events related to vaccines nor challenges were encountered during the implementation of the vaccine switch from PCV13 to PCV10 in terms of supply chain management, training, handling and preparation.

In general, the public health sector considers all PCV vaccines acceptable as long as they are government-recommended based on efficacy, effectiveness and the vaccine serotype-coverage addresses those causing disease in the country. Public health sector practitioners also emphasized the importance of providing timely training and close coordination with the immunization program implementers, and proper communication with parents and caregivers.

The public health practitioners believed that vaccines from renowned pharmaceutical companies are better in terms of safety and effectiveness.They also noted that despite the ease with which PCV15 can be monitored and administered due to its single dose vial (SDV) preparation, it requires more cold chain equipment space and

does not have vaccine vial monitors (VVM), which is important in regions with hard-to-reach communities.

Meanwhile, among private practitioners, about 71% (10 out of 14 respondents) also considered brand, country of origin, and manufacturer as important factors in choosing a PCV product for inclusion in the NIP. Notably, PCV13 was the vaccine of choice (mean score = 4.7/5) among private health practitioners due its broad serotype coverage and cost compared to other PCV vaccines.

Supporting evidence and discussions that informed the recommendation of the HTA Council can be found in the presentation accessible through this link: **https://bit.ly/PCVPedsPrelimAdvisory**. **All comments, inputs, and/or appeals may be submitted until 09 October 2024 (Wednesday)** for the consideration of the HTA Council, through email at hta@dost.gov.ph.

Please use the prescribed form for appeals indicated in the HTA Philippines website [https://hta.dost.gov.ph/appeals-2/]. **Appeals not following the prescribed format, and those submitted beyond the deadline shall not be entertained.**

Should you have any questions or concerns regarding the preliminary recommendation, please do not hesitate to contact us *via email* at hta@dost.gov.ph.or *via telephone call via 8651 7800 loc 2410*.

Thank you very much and best regards.

Very truly yours,

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