Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

15 October 2020

FRANCISCO T. DUQUE III, MD, MSc
Secretary
Department of Health

Dear **Secretary Duque:**

This pertains to the request of the Department of Health - National Immunization Program to reassess the cost-effectiveness of **10- and 13- valent Pneumococcal Conjugate Vaccines (PCV)** for use in infants under one (1) year of age**.** Relative thereto, the Health Technology Assessment Council (HTAC) respectfully resubmits its **final recommendation** as contained in the herewith attached **revised** Evidence Summary. Please note that the revision is aimed at correcting typographical errors in the first version of the document which will not, in any way, change the findings of the reassessment and the HTAC recommendation submitted to your office last 24 July 2020.

The said corrections are detailed in "Annex A," for your reference.

For your information and guidance. Thank you very much.

Respectfully yours,

For the Health Technology Assessment Council

Marita V. T-Reyes

MARITA V. TOLENTINO-REYES, MD
Chair
Health Technology Assessment Council

Recommending approval of the HTAC recommendation

MARIA ROSARIO SINGH- VERGEIRE, MD, MPH CESO IV
OIC- Undersecretary of Health
Health Regulation Team

Approval of the HTAC recommendation:

FRANCISCO T. DUQUE III, MD, MSc
Secretary

CC: Undersecretary Myrna C. Cabotaje, MD, MPH, CESO III

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ANNEX A

Details of the corrections made on the Evidence Summary

Section 2: Background, page 3: Rephrasing from "This informed the decision of the DOH to adopt PCV13 in the NIP." To "This was the basis for the decision of the DOH to adopt PCV13 in the NIP."

Version 1	Version 2
The issue of whether to use PCV10 or PCV13 into the country's National Immunization Program (NIP) has been a long-standing question. The last economic assessment of PCVs conducted in 2014 by Haasis et al. showed better value for money for PCV13 with single-dose vial (SDV) preparations of the vaccines using the lowest prevailing prices globally.[3,4] This informed the decision of the DOH to adopt PCV13 in the *NIP*.	The issue of whether to use PCV10 or PCV13 into the country's National Immunization Program (NIP) has been a long-standing question. The last economic assessment of PCVs conducted in 2014 by Haasis et al. showed better value for money for PCV13 with single-dose vial (SDV) preparations of the vaccines using the lowest prevailing prices globally.[3,4] This was the basis for the decision of the DOH to adopt PCV13 in the *NIP*.

Section 4: Efficacy and effectiveness, page 7: Wrong input of the number of studies in IPD reduction of serotype 6A and 19A.

Version 1

Table 2. *Summary of identified literature evaluating PCV 10 and PCV 13 efficacy and effectiveness*

Outcomes	Vaccine serotype-specific effects			
	10-shared serotypes	Serotype 6A	Serotype 19A	Serotype 3
Reduction of IPD incidence	**Significant reduction:** PCV10 vs PCV 7/ no vaccination (RCT n=1, OS=5) PCV13 vs PCV 7 or no vaccination (OS=5)	**Significant reduction:** PCV10 vs No vaccine/PCV 7 (OS= 2) PCV13 vs PCV7 (OS= 1) **No effect:** PCV10 vs No vaccine (OS= 2) PCV13 vs PCV7 (OS= 1)	**Significant reduction:** PCV10 vs No vaccine (OS = 1) PCV13 vs PCV7 (OS= 1) **Significant increase:** PCV10 vs No vaccine/PCV 7 (OS= 2) **No effect:** PCV10 vs No vaccine (OS= 1) PCV13 vs PCV7 (OS= 1)	**Significant increase:** PCV10 vs No vaccine (OS= 1) **No effect:** PCV10 vs No vaccine/PCV 7(OS= 2) PCV13 vs PCV7 (OS= 2)

Version 2

Table 2. *Summary of identified literature evaluating PCV 10 and PCV 13 efficacy and effectiveness*

Outcomes	Vaccine serotype-specific effects			
	10-shared serotypes	Serotype 6A	Serotype 19A	Serotype 3
Reduction of IPD incidence	**Significant reduction:** PCV10 vs PCV 7/ no vaccination (RCT n=1, OS=5) PCV13 vs PCV 7 or no vaccination (OS=5)	**Significant reduction:** PCV10 vs No vaccine/PCV 7 (OS= 2) PCV13 vs PCV7 (OS= 1) **No effect:** PCV10 vs No vaccine (OS= 2) PCV13 vs PCV7 (OS= 2)	**Significant reduction:** PCV10 vs No vaccine (OS = 1) PCV13 vs PCV7 (OS= 2) **Significant increase:** PCV10 vs No vaccine/PCV 7 (OS= 2) **No effect:** PCV10 vs No vaccine (OS= 1) PCV13 vs PCV7 (OS= 1)	**Significant increase:** PCV10 vs No vaccine (OS= 1) **No effect:** PCV10 vs No vaccine/PCV 7(OS= 2) PCV13 vs PCV7 (OS= 2)

Section 4: Efficacy and effectiveness, page 8: Wrong breakdown of studies was reported. The breakdown of studies reported in the first version was supposed to be for IPD and not NP carriage.

Version 1

Lowering of pneumococcal NP carriage	**Significant reduction:** PCV 10 vs hepatitis vaccine (RCT = 1) PCV 13 vs no vaccine (OS=1) **No effect:** PCV13 and PCV 10 vs PCV 7 (OS= 2, RCT = 1)	**Significant reduction:** PCV10 vs No vaccine/PCV 7 (OS = 2) PCV13 vs PCV7 (OS= 1) **No effect:** PCV10 vs No vaccine (OS= 2) PCV13 vs PCV7 (OS= 1)	**Significant reduction:** PCV10 vs No vaccine (OS= 1) PCV13 vs PCV7 (OS= 1) **Significant increase:** PCV10 vs No vaccine/PCV 7 (OS= 2) PCV13 vs PCV7 (OS= 1)	**Significant increase:** PCV10 vs No vaccine (OS = 1) **No effect:** PCV10 vs No vaccine/PCV 7 (OS= 2) PCV13 vs PCV7 (OS= 2)

Version 2

Lowering of pneumococcal NP carriage	**Significant reduction:** PCV 10 vs hepatitis vaccine (RCT = 1) PCV 13 vs no vaccine (OS=1) **No effect:** PCV13 and PCV 10 vs PCV 7 (OS= 2, RCT = 1)	**Significant reduction:** PCV13 vs PCV7 (RCT= 1) **No effect:** PCV10 vs Hepatitis vaccine (RCT 1)	**Significant reduction:** PCV13 vs PCV7 (RCT= 1) **No effect:** PCV10 vs Hepatitis vaccine (RCT= 1)	**No effect:** PCV13 vs PCV7 (RCT= 1)

Section 5: Cost effectiveness, page 12:

1. Accidental typing of "without" instead of "with" for SDV 90% coverage.
2. Accidental typing of "5470" instead of the correct incremental cost which is "470" only.

Version 1

Table 3. *Incremental cost effectiveness ratio for: (a) PCV 10 versus no vaccination, (b) PCV 13 versus no vaccination (c) PCV 10 versus PCV 13*

PCV10 versus no vaccination			PCV13 versus no vaccination			PCV10 vs PCV13		
Inc. cost	Inc. QALYs	ICER	Inc. cost	Inc. QALYs	ICER	Inc. cost	Inc. QALYs	ICER
Multi-dose vials, 50% coverage, without herd effects (base case)								
126	0.0358	2,947	350	0.0504	6,932	-223	-0.0075	29, 605
Multi-dose vials, 90% coverage, with herd effects								
-1,816	0.0754	-24,080	-2,037	0.0885	-23,006	221	-0.0131	-16,837
Single-dose vials, 50% coverage, without herd effects								
996	0.0441	22,606	966	0.0517	18,667	29.74	-0.0077	-3,860
Single-dose vials, 90% coverage, without herd effects								
-948	0.0767	-12,369	-1,418	0.0898	-15,794	5470	-0.0131	-35,797

Note: QALY-quality-adjusted life-years, PCV-pneumococcal conjugate vaccine

Version 2

Table 3. *Incremental cost effectiveness ratio for: (a) PCV 10 versus no vaccination, (b) PCV 13 versus no vaccination (c) PCV 10 versus PCV 13*

PCV10 versus no vaccination			PCV13 versus no vaccination			PCV10 vs PCV13		
Inc. cost	Inc. QALYs	ICER	Inc. cost	Inc. QALYs	ICER	Inc. cost	Inc. QALYs	ICER
Multi-dose vials, 50% coverage, without herd effects (base case)								
126	0.0358	2,947	350	0.0504	6,932	-223	-0.0075	29, 605
Multi-dose vials, 90% coverage, with herd effects								
-1,816	0.0754	-24,080	-2,037	0.0885	-23,006	221	-0.0131	-16,837
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996	0.0441	22,606	966	0.0517	18,667	29.74	-0.0077	-3,860
Single-dose vials, 90% coverage, with herd effects								
-948	0.0767	-12,369	-1,418	0.0898	-15,794	470	-0.0131	-35,797

Note: QALY-quality-adjusted life-years, PCV-pneumococcal conjugate vaccine

Reassessment of 10- versus 13-valent Pneumococcal Conjugate Vaccines (PCV) in the Philippines

Evidence Summary

Publication Date	02 October 2020
Summary Length	25 pages
Prepared by	Health Technology Assessment Council Health Technology Assessment Unit, Health Regulation Team, Department of Health (Philippines)
Contact details	hta.philippines@gmail.com | 8-875-7734 loc. 260 or 2

Section 1.

General information of the proposed health technology (HT)

Pneumococcal conjugate vaccines commercially available in the Philippines include PCV10 (Synflorix®) and PCV13 (Prevenar 13®). These two vaccines are both available in single-dose and multi-dose (4 doses) vial preparation. Table 1 summarizes the key characteristics of PCV10 and PCV13.

Table 1. *Characteristics of pneumococcal conjugate vaccines available in the Philippines*

Generic Name	Pneumococcal Conjugate Vaccine (PCV)	
Product Name	PCV10 (Synflorix®)[1]	PCV13 (Prevenar 13®)[2]
Philippine Food and Drug Administration (FDA)-approved Indication	Prevention of IPD, pneumonia, and AOM in the contained serotypes and cross-reactive response in serotype 19A for children 6 weeks to 5 years old	Prevention of IPD, pneumonia, and AOM in the contained serotypes for individuals 6 weeks of age and above
Proposed Indication/s	Prevention of IPD, pneumonia, and AOM in the contained serotypes and cross-reactive response in serotype 19A for infants less than 1-year-old	Prevention of IPD, pneumonia, and AOM in the contained serotypes for infants less than 1-year-old
Dosage Formulation/Strength	One dose (0.5 mL) contains 1 microgram of polysaccharide for serotypes 1, 5, 6B, 7F, 9V, 14, and 23F, and 3 micrograms for serotypes 4, 18C and 19F	One dose (0.5 mL) contains 2.2 mcg of Pneumococcal polysaccharide serotype 1, 3, 4, 5, 6A,7F, (9V, 14, 18C, 19A, 19F, 23F; and 4.4 mcg of serotype 6B
Route of Administration	Intramuscular	Intramuscular
Dosage Regimen	Infants from 6 weeks to 6 months of age: 3 primary doses with an interval of at least 1 month between doses	Infant vaccination consists of 3 doses of 0.5 mL each, at approximately 2-month intervals,

[1] Synflorix UK Product Specification
[2] Prevenar 13 US FDA Package Insert

Dosage Regimen	and a booster dose at least 6 months after the last primary dose; 2 primary doses given 2 months apart and a booster dose at least 6 months after the last primary dose. Preterm infants born after at least 27 weeks of gestational age: 3 primary doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses with a booster dose at least 6 months after the last primary dose	followed by a fourth dose of 0.5 mL at 12-15 months of age. The customary age for the first dose is 2 months of age, but it can be given as young as 6 weeks of age. The recommended dosing interval is 4-8 weeks. The fourth (booster) dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.
Therapeutic Class	Immunological agent	Immunological agent
Anatomical Therapeutic Chemical (ATC) classification	J07AL52	J07AL02
Pharmacological action	Immune stimulant	Immune stimulant

Section 2.

Background

Pneumococcal Conjugate Vaccines (PCV) are indicated for the prevention of infections caused by *S. pneumoniae*. These infections may either be invasive pneumococcal diseases (IPD) or non-invasive pneumococcal diseases.

The issue of whether to use PCV10 or PCV13 into the country's National Immunization Program (NIP) has been a long-standing question. The last economic assessment of PCVs conducted in 2014 by Haasis et al. showed better value for money for PCV13 with single-dose vial (SDV) preparations of the vaccines using the lowest prevailing prices globally.[3,4] This was the basis for the decision of the DOH to adopt PCV13 in the *NIP*.

Currently, PCV13 in SDV preparation is used by DOH in national immunization campaigns in selected regions of the country. In light of the plan to expand to universal vaccination coverage, the presence of new studies on the clinical efficacy and effectiveness of PCV10 and PCV13 , and new price quotations due to the availability of multi-dose vial (MDV) preparation for both products – which may be more cost-efficient – a health technology reassessment of PCV10 and PCV13 in the country was conducted.

2.1. Research Questions

The following research questions were answered in this assessment:

2.1.1. What is the efficacy and effectiveness of PCV10 and PCV13 in reducing the incidence of invasive pneumococcal disease (IPD), clinical pneumonia, acute otitis media (AOM), inducing an immune response, and lowering pneumococcal nasopharyngeal (NP) carriage in children under 5 years old?

2.1.2. Does PCV represent good value for money in the Philippines for preventing mortality and morbidity due to IPD, clinical pneumonia, and AOM for infants?

2.1.3. What is the budget implication of using either PCV10 or PCV13 on the Expanded Program on Immunization (EPI) and the Philippine Health Insurance Corporation (PhilHealth) benefits programs?

2.1.4. What are the ethical, legal, social, and health system implications of immunizing infants with either PCV10 or PCV13 to prevent mortality and morbidity due to IPD, clinical pneumonia, and AOM?

Section 3.

Responsiveness to disease magnitude and severity of disease

Streptococcus pneumoniae is a major cause of potentially disabling and fatal infections such as sepsis, pneumonia, meningitis, and acute otitis media. Globally, pneumococcal diseases, on account of these infections, lead to half a million deaths among children under five years of age with most deaths happening in low-and-middle-income countries (LMICs), particularly belonging to Asia and Africa. Moreover, pneumonia is the single largest cause of death in children worldwide claiming about 800,000 lives of children under 5 years old every year.[5]

In the Philippines, all-cause pneumonia was identified as the fourth leading cause of death among Filipinos in 2017 accounting for approximately 57,000 deaths across all age groups. Pneumonia also remains to be the leading cause of death among Filipino children less than 5 years old.[6] A study on invasive pneumococcal infections conducted in 2013 estimated that IPD has a mortality rate of 25-34 deaths per 100,000 or claiming around 3,300 lives of children under 5 years old annually.[7]

Local serotype prevalence data on cases of IPD is important in determining the relevance of the serotypes contained in the PCVs. A possible source of such information is the report of the Research Institute for Tropical Medicine (RITM) (*Figure 1*) on isolates of *Streptococcus pneumoniae* from blood and cerebrospinal fluid collected by RITM's network of laboratories 2012-2019 for the age group of less than 5 years old. The isolates were collected in connection with the Antimicrobial Resistance Surveillance Program (ARSP) which is designed to detect trends in antimicrobial resistance patterns of sentinel pathogens. Unfortunately, because of the small number of isolates reported owing to the passive nature of the surveillance, the variability in specimen collection, processing, and reporting that depended on laboratory capability and practices of laboratory staff and practitioners, the serotype percentages as reported may not reflect the true prevalence of individual serotypes causing IPD.

When serotype prevalence values between 2012-2014 and 2015-2019 were plotted to demonstrate a possible change in the pattern since it was in 2015 that PCV13 was included in the National Immunization Program for children below 5 years old, no change in pattern can be observed.

Nonetheless, the Health Technology Assessment Council (HTAC) recognized that the surveillance data from RITM is the only source of evidence on the prevalence of pneumococcal serotypes in the country. Data from 2015-2019 showed that the ten common serotypes found in both PCV10 and PCV13 and serotype 19A accounted for approximately 48% of IPD isolates while the additional two serotypes to which PCV13 is indicated (i.e. 3 and 6A) covered 7% of the local serotypes. Meanwhile, non-vaccine serotypes comprised 45% of all serotypes found in the RITM serotype surveillance.

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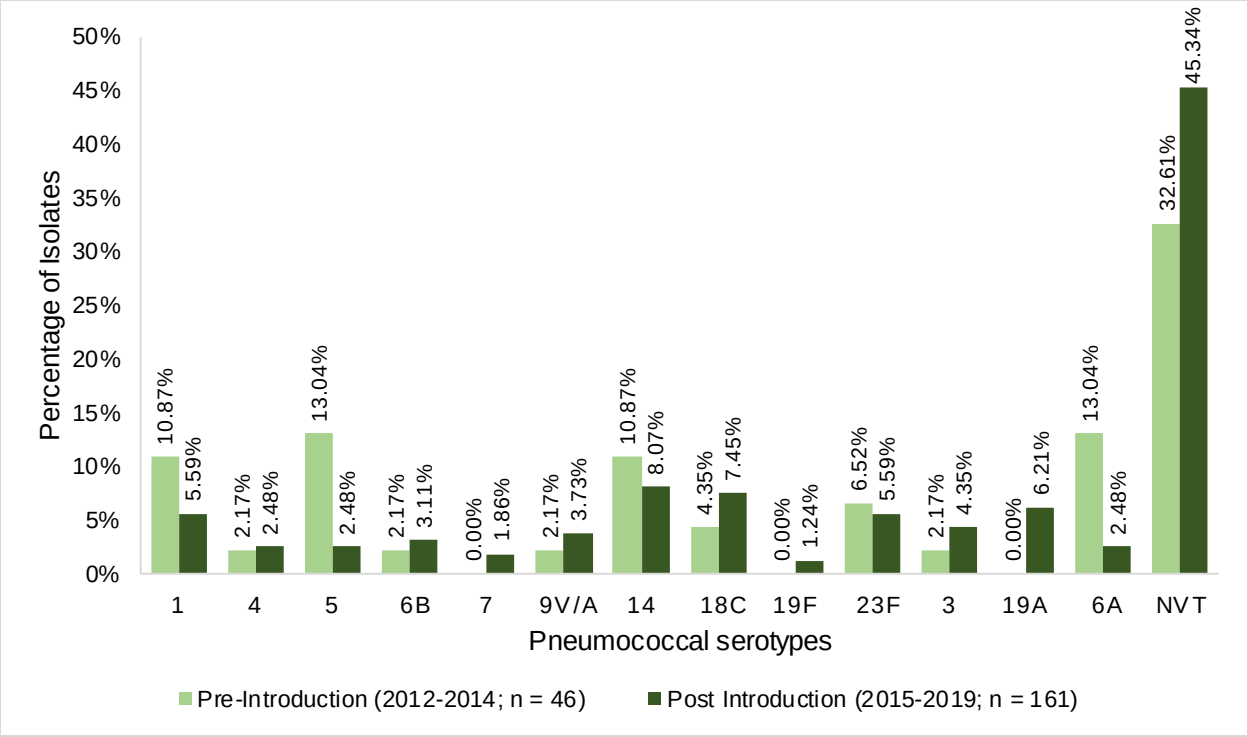

Figure 1. *Percentage of cases caused by vaccine type IPDs in children less than 5 years old, 2012-2019 (Source: RITM, 2020)*

The *Severe Acute Respiratory Infection (SARI)* surveillance data from the DOH *Epidemiology Bureau* (*Figure 2*), showed that there was a decrease in the number of reported SARI cases from 2018 to 2019. However, the data was not specific to pneumococcal respiratory infection as it also included viral infections such as influenza, severe acute respiratory syndrome (SARS), and Middle East Respiratory Syndrome (MERS). Trends can also be better appreciated with multi-year data which were not available at the time of assessment.

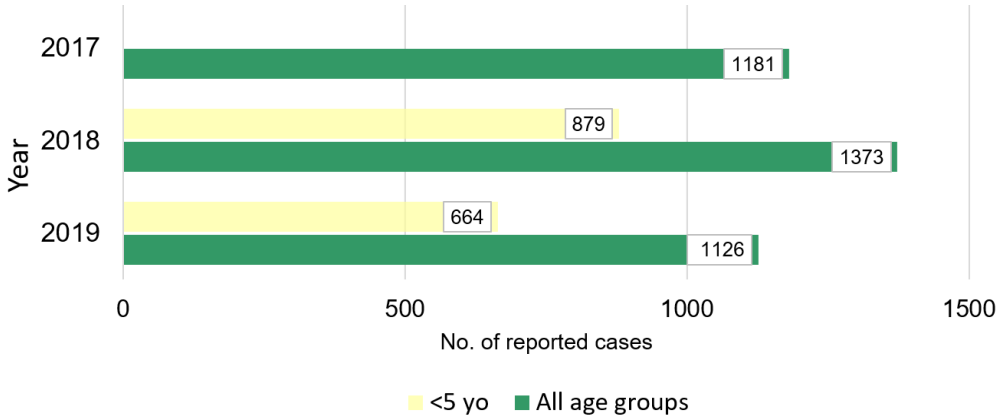

Figure 2. *Reported cases of Severe Acute Respiratory Infection for 2018-2019 (DOH- Epidemiology Bureau)*

While existing national surveillance systems may give indirect evidence that PCV13 may better address the burden of pneumococcal diseases compared with PCV10 because of increased serotype coverage, the Council also recognizes the current limitations of local data in terms of the lack of representativeness and the passive nature of surveillance. Hence, no conclusive evidence as to the overall picture of local serotype distribution nor the impact of the introduction of PCV13 in the National Immunization Program can be deduced at this time.

Section 4.

Efficacy and effectiveness

4.1 Summary of key findings of the rapid review

A systematic search using *Medline, Cochrane Central Register of Controlled Trials (CENTRAL),* and *Prospero* were undertaken in March 2020 to identify relevant studies on the topic based on the inclusion and exclusion criteria to generate current evidence on the efficacy and effectiveness of PCV10 and PCV13 in preventing invasive pneumococcal disease (IPD), clinical pneumonia, acute otitis media (AOM), inducing an immune response and lowering pneumococcal nasopharyngeal (NP) carriage in children under 5 years old.

From the list of systematic reviews included, we extracted individual studies and checked duplications to avoid overlap of evidence. The Council also reviewed the additional evidence submitted by vaccine manufacturers, as well as the evidence considered by the *Philippine Food and Drug Administration* in updating approved indications of PCV10 which included cross-reactivity for serotype 19A.

The following were the main reasons for exclusion of submitted studies from product manufacturers: (1) did not match the required PICO and study design framework, (2) insufficient follow-up period, (3) lacked ascertainment of the vaccination status of subjects, (4) did not establish vaccination coverage of at least 50% of the population studied, (5) overlapped with other studies already included in the review (e.g. *systematic reviews containing same individual studies or updated studies*), (6) cannot delineate the effects between intervention and control in observational studies; (7) evaluated vaccine effects of less than three doses. Details on the reasons for the exclusion of studies were specified in Appendix A.

4.1.1 Clinical efficacy

Randomized controlled trials (RCTs) which evaluated the effect of PCV10 on IPD, pneumonia, and AOM suggested that PCV10 is efficacious in reducing the incidence of these pneumococcal infections compared to control.

Since PCV13 deduced clinical effects from PCV7 studies, we did not identify RCTs which evaluated the effect of PCV13 on the clinical outcomes of interest. The RCTs on PCV13 were immunogenicity studies which are acceptable methods to evaluate efficacy and determine the immunological markers as substitute endpoints for clinical protection.[8] Moreover, the regulatory approval for PCV13 was based on correlation studies on serologic response among children compared with PCV7.[9]

There are two main measures for immunogenicity studies: (1) mean geometric IgG concentration and proportion of infants who achieved the ≥ 0.35 µg/mL IgG concentration which is a population-derived threshold set by WHO; (2) mean geometric opsonizing antibody (OPA) titer and proportion of infants who achieved ≥ 1:8 OPA titer which is also correlated to the WHO threshold. Based on the set thresholds, both PCV10 and PCV13 can induce an immune response against serotypes 6A and 19A, although PCV13 use resulted in a greater immune response. On the other hand, only PCV13 showed an immunogenic response for serotype 3. Although immunogenicity is accepted as a substitute endpoint for clinical protection, it is important to note that the achievement of the population-derived threshold should not be interpreted as a predictor of protection against pneumococcal infection in an individual. According to Dagan et al. the probability of acquiring nasopharyngeal carriage in children who achieved concentrations of ≥0.35 µg/mL was still high at approximately 65% to 100%.[10] This clearly demonstrates that the ≥0.35-µg/mL threshold cannot necessarily predict protection against carriage, even more so against pneumococcal infections.

4.1.2 Clinical effectiveness

From the observational and time-series studies included in the review, overall evidence suggested that both PCV10 and PCV13 were effective in reducing the incidence of IPD and clinical pneumonia caused by their ten shared serotypes when compared to PCV7, other vaccines or no vaccination. In terms of acute otitis media and nasopharyngeal carriage, both PCV10 and PCV13 were effective compared to no vaccination or to control. However, the body of evidence was inconsistent in illustrating that the additional three serotypes of PCV13 have changed vaccine impact on overall IPD disease burden.

Table 2. *Summary of identified literature evaluating PCV 10 and PCV 13 efficacy and effectiveness*

Outcomes	Vaccine serotype-specific effects			
	10-shared serotypes	Serotype 6A	Serotype 19A	Serotype 3
Reduction of IPD incidence	**Significant reduction:** PCV10 vs PCV 7/ no vaccination (RCT n=1, OS=5) PCV13 vs PCV 7 or no vaccination (OS=5)	**Significant reduction:** PCV10 vs No vaccine/PCV 7 (OS= 2) PCV13 vs PCV7 (OS= 1) **No effect:** PCV10 vs No vaccine (OS= 2) PCV13 vs PCV7 (OS= 2)	**Significant reduction:** PCV10 vs No vaccine (OS = 1) PCV13 vs PCV7 (OS= 2) **Significant increase:** PCV10 vs No vaccine/PCV 7 (OS= 2) **No effect:** PCV10 vs No vaccine (OS= 1) PCV13 vs PCV7 (OS= 1)	**Significant increase:** PCV10 vs No vaccine (OS= 1) **No effect:** PCV10 vs No vaccine/PCV 7(OS= 2) PCV13 vs PCV7 (OS= 2)

Outcomes	Vaccine serotype-specific effects			
	10-shared serotypes	Serotype 6A	Serotype 19A	Serotype 3
Reduction of clinical pneumonia incidence	**Significant reduction:** PCV10 vs hepatitis vaccine (RCT=1) PCV13 vs no vaccination (OS=1)	No studies found	No studies found	No studies found
Reduction of AOM	**Significant reduction:** PCV10 vs Hepatitis vaccine (RCT = 1) PCV13 vs no vaccine (OS=1) **No effect:** PCV10 vs Hepatitis vaccine (RCT = 1) PCV13 vs PCV7 (OS=1)	**No effect:** PCV13 vs PCV7 (OS=1) No study on PCV10	**Significant reduction:** PCV13 vs PCV7 (OS=1) No study on PCV10	**No effect:** PCV13 vs PCV7 (OS=1) No study on PCV10
Induction of immune response (RCT=16)	Both PCV10 and PCV13 induce a significant immune response.	Both PCV10 and PCV13 induce a significant immune response. PCV13 > PCV10	Both PCV10 and PCV13 induce a significant immune response. PCV13 > PCV10	Only PCV13 induced a significant immune response
Lowering of pneumococcal NP carriage	**Significant reduction:** PCV 10 vs hepatitis vaccine (RCT = 1) PCV 13 vs no vaccine (OS=1) **No effect:** PCV13 and PCV 10 vs PCV 7 (OS= 2, RCT = 1)	**Significant reduction:** PCV13 vs PCV7 (RCT= 1) **No effect:** PCV10 vs Hepatitis vaccine (RCT 1)	**Significant reduction:** PCV13 vs PCV7 (RCT= 1) **No effect:** PCV10 vs Hepatitis vaccine (RCT= 1)	**No effect:** PCV13 vs PCV7 (RCT= 1)

Note: IPD - invasive pneumococcal disease; AOM - acute otitis media; NP - nasopharyngeal; RCT- randomized control trial; OS - Observational studies

4.2 Philippine FDA basis for the approval of serotype 19A indication of Synflorix

According to the Philippine FDA, the inclusion of cross-reactivity against serotype 19A in the approved indication of Synflorix® in 2016 was based on the results of a series of studies which included two independent post-marketing surveillance studies (i.e. vaccine effectiveness study in Brazil and vaccine impact study in Finland) and eight company-sponsored clinical studies.

The cross-reactive response for 6A and 19A was first realized as a result of the post-licensure surveillance study done on Prevenar® in the US which showed a decrease in IPD caused by pneumococcal serotypes 6A and 19A, and an increase in the immune response of these serotypes, thus triggering for a protocol amendment in June 2006 moving the cross-reactive pneumococcal serotypes 6A and 19A from exploratory to secondary endpoints.

The Philippine FDA referred to the following studies for cross-reactivity claims of PCV10 for serotype 19A: Jokinen, 2015; Domingues, 2014; Omeñaca, 2011; Silfverdal, 2011; Vesikari, 2011; Silfverdal, 2009; and Vesikari, 2009. Note that Omeñaca, 2011, Silfverdal, 2011, Vesikari, 2011 and Silfverdal 2009 were excluded from the rapid review as they did not meet the a priori inclusion and exclusion criteria.

Based on the official response from FDA, "*the results of the effectiveness study in Brazil and the vaccine impact study in Finland, as well as the immunogenicity data on vaccine-related serotype 19A from eight trials performed in the pediatric population, validated the hypothesis that Synflorix® elicits antibody protection for serotype 19A.*"

The immunogenicity data against serotype 19A were generated from studies which implemented Synflorix® as primary, booster, catch-up, and additional dose including preterm population. The immunogenic response for serotype 19A was generally lower than those of the vaccine serotypes present in Synflorix®. However it can be boosted, and induction of immune memory was seen in the vaccinated infant.

Catch-up vaccination with Synflorix® induced antibodies and functional immune responses against serotype 19A higher than or comparable to those observed one month after a 3-dose primary vaccination. However in the same studies, evidence showed that Synflorix® had a substantially lower immune response against serotype 6A compared to Prevenar®, thus the decision not to include its cross-reactive efficacy for serotype 6A.

In summary, the Council acknowledged the inconsistency of clinical evidence in reducing IPD, pneumonia, and AOM concerning the additional three serotypes contained in PCV 13 owing to the heterogeneity of studies (e.g. study designs, small sample size, various follow-up period) as well as the probable differences in baseline risk which may be attributed to varying patterns of serotype distribution across countries which may also be different in the Philippines. Although both PCV10 and PCV13 have approved indication for serotype 19A by the Philippine FDA, uncertainty surrounding cross-protection of PCV10 for serotype 19A was noted such as the case of increased incidence of IPD due to serotype 19A in Brazil after the introduction of PCV10. The Council also noted inconsistency in evidence for clinical protection from pneumococcal infection caused by serotype 19A in PCV13 because of the inherent weakness of study designs. The Council, therefore, highlights the need for a stronger surveillance system which includes serotype

distribution to enable the monitoring of the vaccine impact on the overall disease burden specific to the Philippines.

Section 5.

Cost-effectiveness

Given the difference in the contained serotypes in existing PCV vaccines in the Philippines, the Council deemed it prudent to analyze the potential benefits of the additional serotypes through a cost-utility analysis. A cost-minimization analysis was not performed as the Council recognizes that there may be potential additional benefits to the local context of increased serotype coverage.

Apart from directly comparing the potential costs and benefits of PCV10 and PCV13, the Council also found it appropriate to compare the two vaccines to a 'no vaccination' scenario. In low middle-income countries (LMICs) like the Philippines, resource limitation and budget constraints may affect prioritization and budget allocation across different health programs each year. Disinvestments in health technologies could be made by policymakers, especially in a scenario of limited budget amid constantly emerging new health priorities such as the current COVID-19 pandemic and the necessity therefore to look for cost-efficiency. A policy option of 'no vaccination' was done to present a realistic scenario of potential health foregone should the decision-maker opt for disinvestment. Coverage scenarios such as the status quo of 50% coverage and universal coverage were also explored to illustrate to policymakers the additional costs and potential benefits in implementing the PCV program to achieve better health outcomes.

A Markov model adapted from Kulpeng et al. (2013) was used to calculate and compare the costs and health outcomes of: (a) PCV13 versus no vaccination, (b) PCV10 versus no vaccination; (c) PCV 10 versus PCV13.[11] The population of interest was 90% of the birth cohort of 2020 who would receive three doses of either PCV vaccine in the same year. A lifetime horizon with a discounting rate of 7% per annum was employed.

A base case scenario of 50% coverage without herd effects was used in the analysis as this best reflects the current low vaccination coverage which ranges from 30-60% across regions in the country. Literature suggests that herd effects could be achieved if at least 80% of the target population is vaccinated.[12] With this, an additional scenario incorporating herd effects was also evaluated given that the ideal target vaccination coverage is 90% of the birth cohort. In the model, vaccine effectiveness (VE) was estimated using RCTs of PCV10 compared with placebo, whereas the incremental effect of PCV13 was assumed from the additional serotype coverage for serotypes 3 and 6A. Computations for VE are found in Appendix B. Sensitivity analysis was also done assuming that the cross-reactivity of PCV10 for serotype 19A may not lead to the desired clinical protection.

Results were presented as incremental cost-effectiveness ratios (ICER) – the ratio of additional vaccination and treatment costs to additional Quality Adjusted Life Years (QALYs) – our measure of health outcomes. The Council considered the suggestion to incorporate societal costs in the calculation of the ICERs. Although this is recognized as another acceptable method in conducting economic evaluations, the Council notes that societal costs (especially those related to intangible costs brought about by pain, suffering, and loss of life) are already captured in the QALY measure. Accounting for them separately may lead to double-counting and overestimation of cost-effectiveness. Moreover, the draft HTA methodological guidelines only require relevant direct health care costs associated with the provision of healthcare from the government public payor

perspective (i.e. DOH and PhilHealth) in cost-effectiveness calculations, which also adheres to international standards of conducting economic evaluations.[13]
In this report, new price quotations submitted by vaccine manufacturers during the appeal period were considered and were incorporated in this revised analysis to determine the impact on the ICERs and the potential budget impact on the government. Resulting ICERs illustrate that when compared to 'no vaccination', both PCV10 and PCV13 were both very cost-effective even at lower ceiling ICER threshold values, in either MDV or SDV preparations (*Table 3*). Higher coverage scenarios for either of the vaccines versus 'no vaccination' were cost-saving since the clinical benefits of vaccines could be maximized through herd immunity.

Overall, the Council noted significantly lower ICER values for MDV preparations of both PCV10 and PCV13 when compared to 'no vaccination', which indicates that shifting from SDV to MDV preparations of either vaccine is the most cost-effective option in the Philippines.

Using MDV preparations of PCV vaccines, the Council also noted that PCV10 resulted in lesser costs but also poorer health outcomes compared to PCV13 in the low-coverage scenario (50%). For the high coverage scenario (90%) using either SDV and MDV, the Council noted that PCV13 was slightly dominant over PCV10 noting the higher QALY gained in PCV13 when compared to PCV10. The Council however observed that the ICERs of both vaccines were very close when compared to 'no vaccination' even after incorporation of the revised price quotes.

The Council also considered the results of the one-way sensitivity analyses which showed that the price of the vaccine is the most sensitive parameter in the model (*Figures 3&4*). Hence, conclusions on the cost-effectiveness of existing PCV vaccines will be dependent on the procurement costs of the government which could be different from the quoted prices of vaccine manufacturers. The Council also recognized other parameters that significantly affected ICER estimates of both vaccines which include vaccine efficacy on AOM and pneumonia, discounting rate, and transition probability of mild AOM proceeding to hearing loss. Moreover, it was noted in the sensitivity analysis that excluding cross-reactivity of PCV10 for serotype 19A or inclusion of serotype 6A from the base case did not significantly alter the ICER values.

The cost-effectiveness acceptability curve (CEAC) showed that both PCV10 and PCV13 when compared to no vaccination had a high probability of being cost-effective using either MDV or SDV preparations even at lower willingness-to-pay threshold (*Figure 5*). In the high coverage scenario, both PCV10 and PCV13 showed a 100% probability of being cost-effective when compared with no vaccination regardless of vial preparation at zero threshold value. MDVs of either vaccine further showed having a higher probability of being cost-effective at a much lower threshold value (*green dots*) compared with SDV preparations.

Focusing on MDVs, comparing PCV10 versus PCV13 in a low coverage scenario showed that PCV13 preparation became the best choice at threshold starting at around *PHP 35,000 per QALY gained (Figure 6)*. In a high coverage scenario, PCV13 had also a higher likelihood to be cost-effective even at very low threshold values, owing to the resulting negative ICER values.

The Council acknowledged the limitation in terms of having more reliable sources of incidence data and a lack of head-to-head studies comparing PCV 10 and PCV 13, which makes it difficult to ascertain the differences in the potential benefits between the two vaccines in the real world, especially in the Philippines. The Council highlighted the lack of reliable local serotype distribution data as a crucial element to also determine the local appropriateness of existing PCV vaccines based on the local burden of disease. Given the uncertainties in the economic model, the Council noted that choosing between PCV10 and PCV13 is difficult given that both vaccines are potentially very cost-effective using the multi-dose vials.

Table 3. *Incremental cost effectiveness ratio for: (a) PCV 10 versus no vaccination, (b) PCV 13 versus no vaccination (c) PCV 10 versus PCV 13*

PCV10 versus no vaccination			PCV13 versus no vaccination			PCV10 vs PCV13		
Inc. cost	Inc. QALYs	ICER	Inc. cost	Inc. QALYs	ICER	Inc. cost	Inc. QALYs	ICER
Multi-dose vials, 50% coverage, without herd effects (base case)								
126	0.0358	2,947	350	0.0504	6,932	-223	-0.0075	29, 605
Multi-dose vials, 90% coverage, with herd effects								
-1,816	0.0754	-24,080	-2,037	0.0885	-23,006	221	-0.0131	-16,837
Single-dose vials, 50% coverage, without herd effects								
996	0.0441	22,606	966	0.0517	18,667	29.74	-0.0077	-3,860
Single-dose vials, 90% coverage, with herd effects								
-948	0.0767	-12,369	-1,418	0.0898	-15,794	470	-0.0131	-35,797

Note: QALY-quality-adjusted life-years, PCV-pneumococcal conjugate vaccine

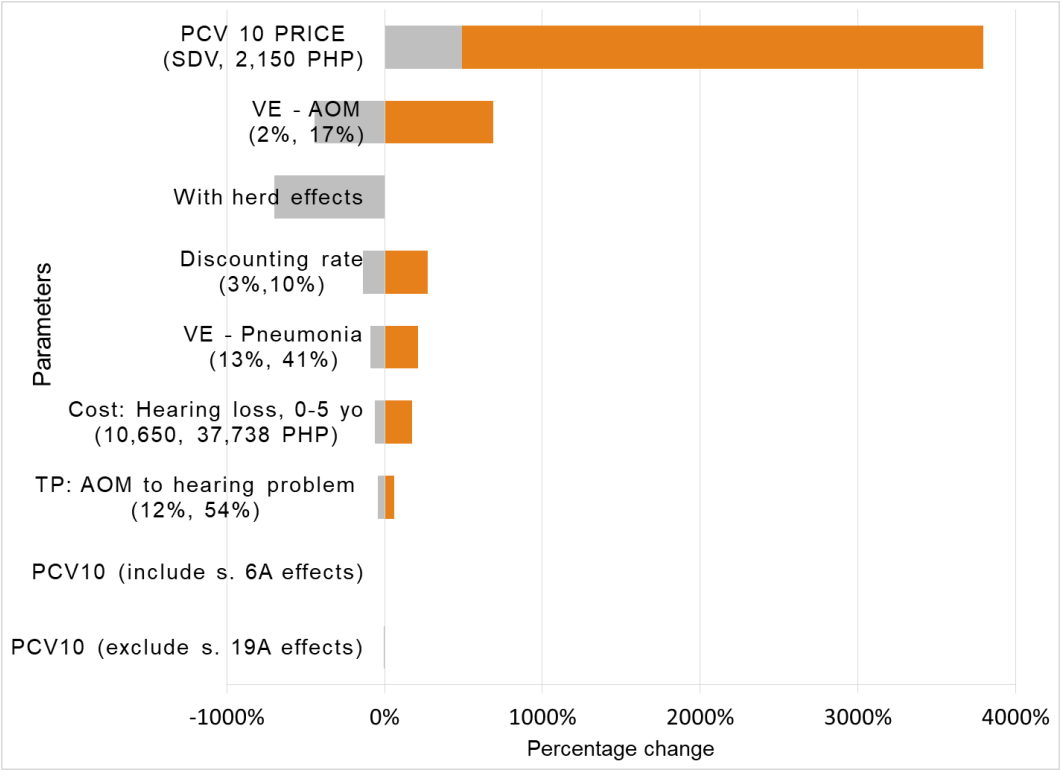

Figure 3. *One-way sensitivity analysis for parameters used in PCV10 analysis*

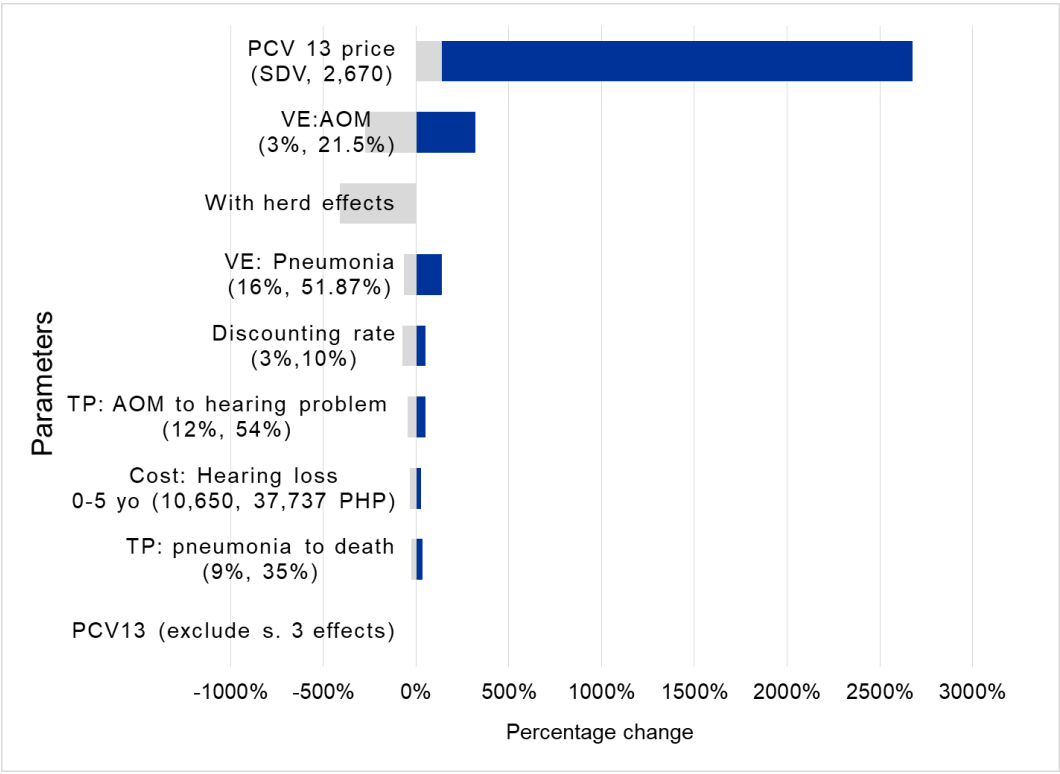

Figure 4. *One-way sensitivity analysis for parameters used in PCV13 analysis*

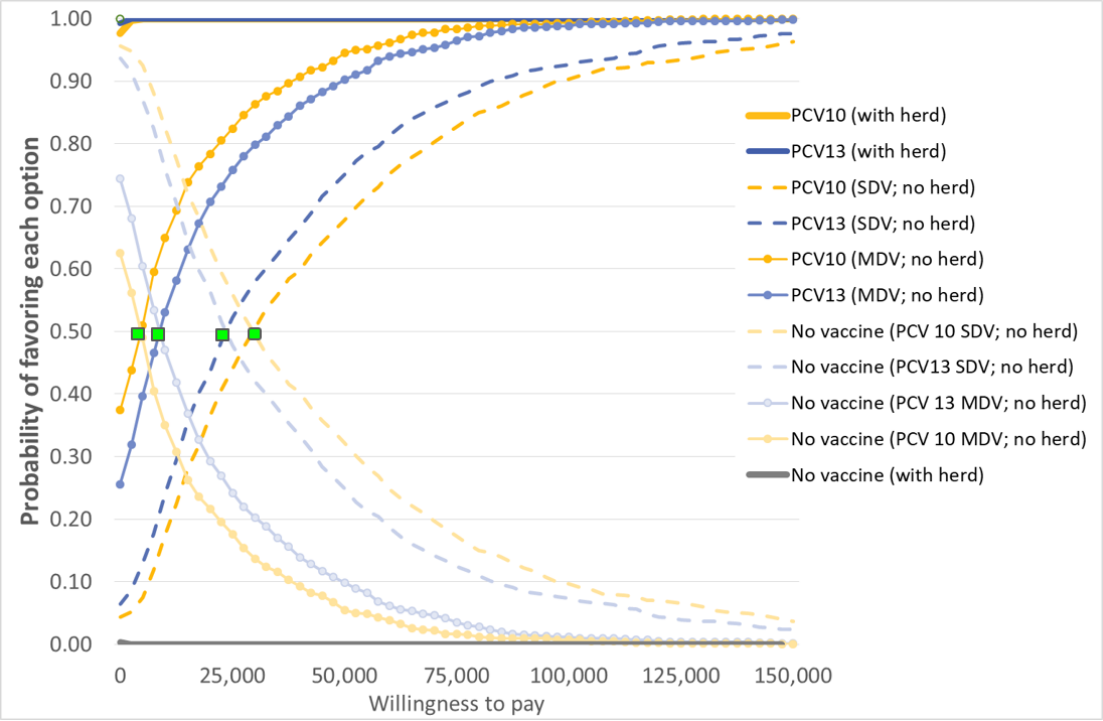

Figure 5. *Cost-effectiveness acceptability curve for PCV10 versus no vaccination, PCV13 versus no vaccination, multi-dose vials or single-dose vials, with or without herd effects*

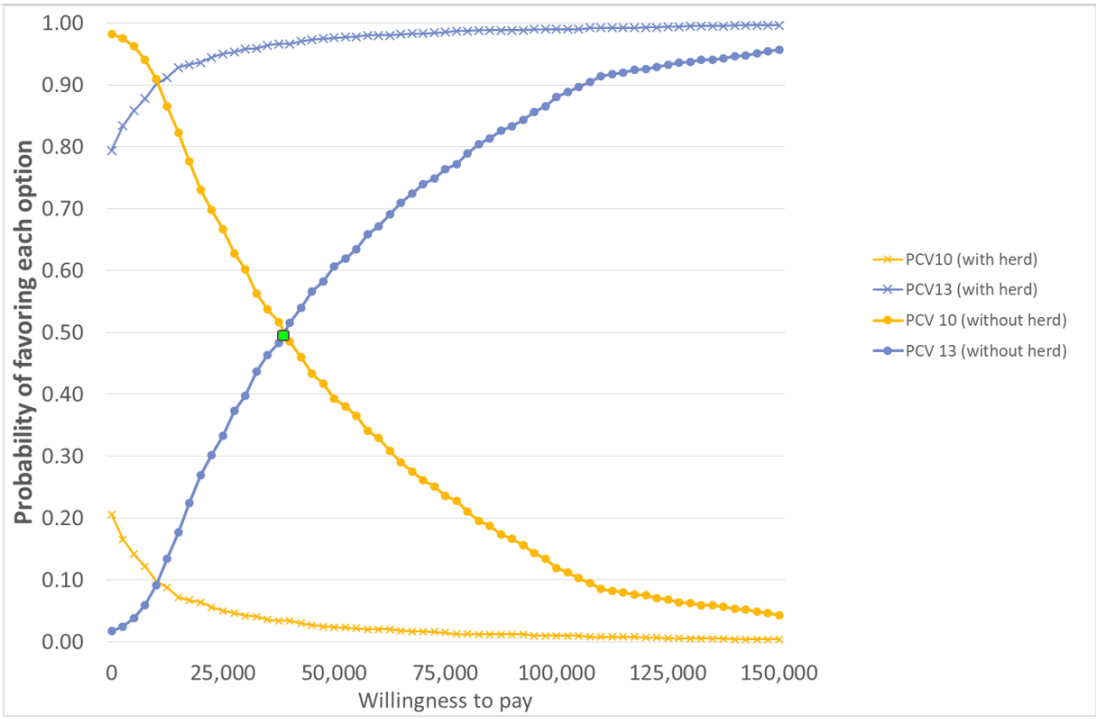

Figure 6. *Cost-effectiveness acceptability curve for PCV10 versus PCV 13 for **multidose vials**, with or without herd effects*

Section 6.

Affordability and viability

Currently, PCV is the most expensive vaccine in the NIP with the DOH spending PHP 4 billion of the total PHP 7.2 billion budget allocation of the NIP for 2020. Using the new quoted prices for both vaccines, excluding distribution cost in the analysis, and assuming that the cost of vaccines for the target 90% of the projected birth cohort would be borne by the government, the budget needed to purchase PCV10 and PCV13 compared to 'no vaccination' was determined for five fiscal years (*Table 4&5*). The budget impact analysis was based on the Markov model used in the cost utility analysis, where possible herd effects were incorporated in the averted treatment costs.

For both PCV10 and PCV13, the budget required for MDVs were significantly lower than those for SDVs. The purchase of PCV13 in MDV will require an additional PHP 5 billion compared to purchasing PCV10 in MDV for over five years (*Table 4*).

Focusing on MDV use for vaccination costs and with the target, 90% of the projected birth cohort vaccinated per year, the total program costs (i.e. vaccination and treatment costs) that would be incurred by the government for PCV10 and PCV13 were at PHP 233.92 billion and PHP 237.96 billion respectively, for fiscal years 2020-2024 (*Table 5*). For treatment costs shouldered by PhilHealth, PCV10 and PCV13 would lower the treatment costs incurred by PHP 12.15 billion and PHP 14.72 billion respectively, when compared to a 'no vaccination' scenario.

Considering the overall comparison of the vaccination and treatment costs associated with PCV10 and PCV13 versus no vaccination, an incremental program costs of PHP 7.21 billion for PCV10 and PHP 11.26 billion for PCV13 were projected for the implementation cost. Given the five-year program cost of PCV10 and PCV13 which considers the new quoted price from the manufacturing companies, PCV10 was deemed more affordable than PCV13.

Table 4. *The projected budgetary requirement of vaccine preparations of PCV10 and PCV13, 2020-2024 (in billions PHP)*

Year	PCV10		PCV13	
	MDV	SDV	MDV	SDV
2020	3.78	5.87	4.88	6.40
2021	3.83	6.00	4.94	6.48
2022	3.87	6.02	5.01	6.56
2023	3.91	6.09	5.06	6.64
2024	3.96	6.16	5.12	6.72
TOTAL	**19.99**	**30.15**	**25.01**	**32.80**

Note: PCV-pneumococcal conjugate vaccine, MDV- multi-dose vials, SDV- single-dose vials

Table 5. *The projected program costs of PCV10 and PCV13 versus no vaccination for MDV, 2020-2024 (in billions PHP)*

Year	PCV10		PCV13		No vaccine
	Vaccination cost	Treatment cost	Vaccination cost	Treatment cost	Treatment cost
2020	3.78	18.85	4.88	18.67	20.26
2021	3.83	33.02	4.94	32.68	34.86
2022	3.87	45.42	5.01	44.89	47.81
2023	3.91	54.82	5.06	54.10	57.77
2024	3.96	62.53	5.12	61.64	66.01
TOTAL	**19.99**	214.56	**25.01**	211.99	226.71
Program cost	**233.92**		**237.96**		**226.71**

Note: PCV-pneumococcal conjugate vaccine

The Council noted the significant budgetary impact of the different preparations of both vaccines with MDV preparations resulting in potentially significant cost savings to the DOH compared to the SDV preparation. Given a fixed budget for the NIP and the significance of achieving universal PCV vaccination coverage, the Council deemed that a significantly lower-priced vaccine would be more favorable to DOH. A significantly lower vaccine price can ensure coverage of the entire birth cohort with the benefit of universal coverage compensating for the advantage of having greater serotype coverage under the current scenario where there is incomplete target population coverage because of the high price of SDV preparation of PCV13 currently implemented by NIP, hence the impossibility of having herd protection for the entire population. Having lower-priced MDV preparations for both PCV13 and PCV10 also provides an opportunity to achieve cost efficiency to the DOH, hence enabling the achievement of universal coverage.

Section 7.

Household financial impact

With the PCV implementation, households would benefit substantially as the vaccine could protect against illness across all age groups due to herd effects, especially against severe illness requiring hospitalization. Based on the 2017 case rates, the following amount is reimbursed by PhilHealth for each condition: (1) PHP 11,700- 25,700 for IPD; PHP 15,000- 32,000 for pneumonia; and (3) PHP 7,800 for severe AOM. However, PhilHealth case rates are likely to underestimate the true costs of these diseases.

Modeling suggested that PCV13 may result in larger savings with a potentially greater number of averted cases and/or deaths due to IPD, clinical pneumonia, and AOM compared to PCV10 as a result of greater serotype coverage (*Figure 7*). This is also with the assumption that the government would pay for the vaccines. With this, the Council recognizes that PCV13 use will incur lesser household financial impact as compared to PCV 10.

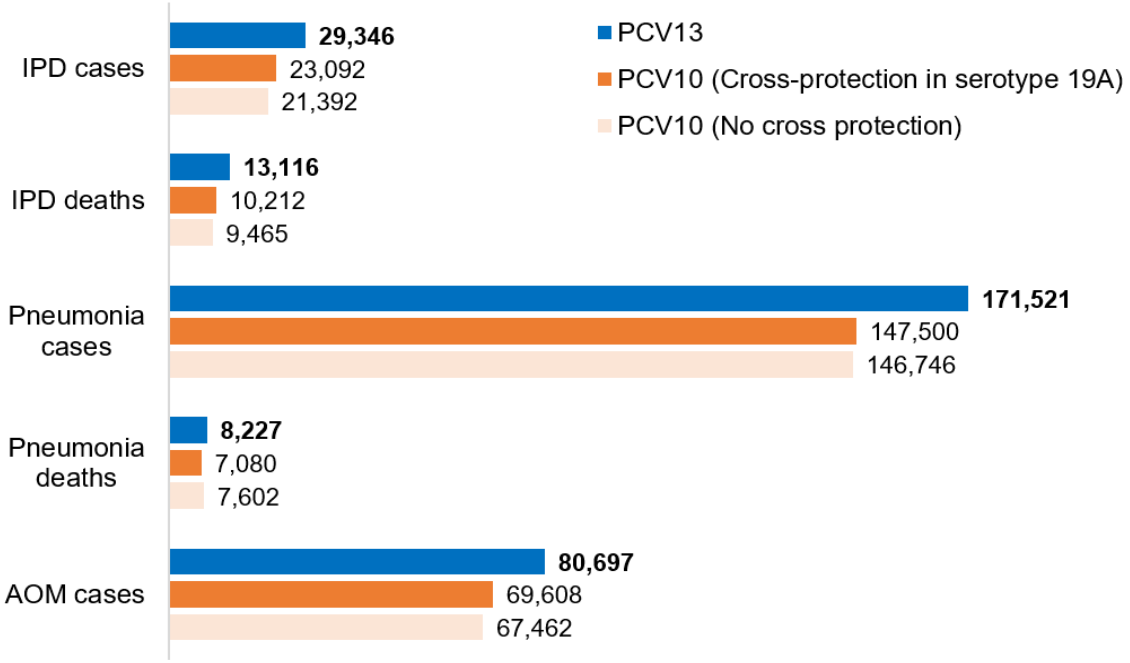

Figure 7. *Projected number of cases and deaths averted in PCV13 and PCV10 (inclusion/ exclusion of serotype 19A)*

Section 8.

Ethical, legal, social, and health systems implications

The Council noted the results of the inquiry on ethical, legal, social, and health systems implications conducted which involved 24 leaders of marginalized groups, three civil society organizations (CSO), one patient group for the social and ethical implications, DOH Legal Service, and Central Office Bids and Awards Committee (COBAC) for legal implications, and 12 internal and external stakeholders for the health systems implication. The inquiry was conducted through online communications, web-based surveys, and questionnaires.

Social and ethical implications. A representative from a patient group (n=1) and leaders of marginalized communities (n=24) generally preferred PCV10 over PCV13 given its advantage in terms of enabling more equitable access since more children will be given the vaccine. Representatives from CSOs (n=3) on the other hand, preferred PCV13 over PCV10 due to the perceived benefit in terms of health outcomes.

Legal implications. Both the DOH Legal service and COBAC advised that the determination of the goods and services procured is for the end-user or implementing unit to identify. This includes the type of PCV that will enter the bidding process, as well as the technical specifications on the bidding documents. Negotiated procurement is allowed under current procurement laws in special circumstances where there would be a sole manufacturer for the specific product to be procured, provided that sufficient evidence will be presented to show that only the said manufacturer could produce such health technology.

Given the uncertainty in the current analysis where the advantage of either PCV cannot be clearly demonstrated because of acknowledged limitations in the available epidemiologic, clinical, and economic evidence, the Legal Service deemed that it is adequate to include in procurement specifications the important pneumococcal serotypes in PCV vaccines that are locally relevant to the Philippine context to effectively address the pneumococcal disease burden in the country.

A patient group recommended a multi-year vaccine purchase to achieve economies of scale as suggested in the public consultation, but the Council deemed that this is a decision that needs to be made by the DOH as the purchaser.

Health systems impact. The SDV preparations were rated as more acceptable by health systems stakeholders (n=12; e.g. public and private practitioners, regional and national NIP staff) compared to MDVs. For the product choice, PCV13 had an advantage in terms of confidence of health workers and public perception on quality of service of the NIP and the National Immunization Technical Advisory Group (NITAG) compared to PCV10, which was perceived to have “incomplete protection”. Implementation of PCV10 would have to be supplemented with adequate orientation for the health workers and effective communication with mothers to prevent resistance from the possible product switch. Overall, the advantages and disadvantages of product preparation (SDV/MDV), and product type (PCV10/PCV13) shall be balanced with the available budget.

The Council recognizes the clamor of the community for higher coverage and the ability to access the health intervention to achieve equity in health, which can be better addressed by having a lower-priced vaccine. The Council also noted the potential health system implications of adopting MDVs of existing PCV and noted that this could be addressed through adequate preparation, training, and orientation of program implementers and communities with adjustments in standard operating procedures similar to other DOH programs. It is also recommended for DOH to ensure effective communication to mothers, local governments, and communities to minimize vaccine hesitancy and ensure the social acceptability of the vaccination program.

Section 9.

Recommendation

The health technology assessment attempted to determine which PCV will be of better value for money in the country. The recommendation was based on six decision criteria: (1) responsiveness to disease magnitude and severity of disease, (2) efficacy and effectiveness, (3) cost-effectiveness, (4) affordability and viability, (5) household financial impact; (6) ethical, legal and social health systems implications. Upon deliberation, the Council determined that a specific PCV product may not be able to fulfill all dimensions of the decision criteria. Supported by the legal advice of the DOH, identifying specific serotypes may be allowed in the DOH procurement rules given that sufficient evidence was included in the analysis. The HTA Council, therefore, recommends the PCV indicated for the most important pneumococcal serotypes that are relevant in the country, noting the limitations in current serotype distribution data which limit the ability to determine with absolute certainty the real local burden of disease due to different pneumococcal serotypes. Moreover, the price at which both vaccines will be offered during the actual purchase will also be crucial. The Council, therefore, deemed that a competitive tendering process to ensure affordability and better value for money will be important.

The HTA Council **recommends the multi-dose vial preparation of pneumococcal conjugate vaccines (PCV)** indicated for the following minimum serotypes: **1, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.** Both PCV10 and PCV13 which are currently authorized by the Philippine FDA on the publication date of this evidence summary represent good value for money, with the potential of reducing pneumococcal diseases in the country. To ensure equity, affordability, and universal vaccine coverage which can only be ensured by obtaining lower vaccine prices, a competitive tendering process is important.

In addition to the product specifications, the Council likewise recommends the following in terms of surveillance and research:

1. Program evaluation should be in place to measure the impact on the burden of pneumococcal disease and changes in serotype distribution with the use of PCV vaccines.
2. DOH should ensure high-quality surveillance following the WHO guidelines and this should begin within the year to enable the conduct of impact monitoring and assessment.
3. DOH should also consider periodic surveys of nasopharyngeal carriage that will characterize changes in serotype distribution.
4. Studies should be commissioned to determine the clinical and economic burden of pneumococcal diseases in the Philippines.

Section 10.

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16. *DOH Rapid Review Report on Pneumococcal Conjugate Vaccines (2020)*

APPENDIX A
REASONS FOR EXCLUSION OF SUBMITTED REFERENCES

Source of Reference	Citation	Included? (Y/N)	If excluded, state reason for exclusion
GSK	Deceuninck, 2015	N	Did not evaluate effect of 3 doses
GSK	Andrews,2014	N	Single-arm study only
GSK	Diawara, 2015	N	No vaccination status ascertainment
GSK	Andrade, 2017	N	Did not establish vaccination coverage
Pfizer	Moore, 2014	N	Overlap with Moore 2016
Pfizer	Verani, 2015	N	Overlap with Dominguez 2014
Pfizer	Harboe, Dalby, 2014	N	Did not establish vaccination coverage
Pfizer	Le Poutre, 2015^	N	Overlap with Varon 2015
Pfizer	Miller, 2011^	N	Evaluated effect of at least 1 dose only
GSK	Izurieta, 2018	N	Did not match PICO
GSK	Kandasamy, 2019	N	Insufficient follow-up period
GSK	Gisselsson-Solen, 2017	N	Cannot extract data on treatment effect
Pfizer	Ben-Shimol, 2014	N	Evaluated effect of at least 2 doses only
Pfizer	Steens, Bergsaker, 2013	N	Cannot delineate effect of PCV13 vs PCV7
Pfizer	Ben-Shimol,2014	N	Evaluated effect of at least 2 doses only
Pfizer	Danino, 2019	N	Cannot extract raw data on vaccine effect
Pfizer	Ladhani, 2018	N	Did not establish vaccination coverage
Pfizer	Lopez, Glatstein, 2018	N	Insufficient follow-up period
Pfizer	Cassiolato, 2018	N	Did not establish vaccination coverage
Pfizer	Setchanova,2018	N	Did not match PICO
Pfizer	Azzari, 2019	N	Did not match PICO
Pfizer	Lu, 2019	N	Cannot delineate effect of PCV7, PCV10, PCV13

Source of Reference	Citation	Included? (Y/N)	If excluded, state reason for exclusion
Pfizer	Prichter, 2019	N	No vaccination status ascertainment
Pfizer	Potin, 2016	N	No full text found
Pfizer	Moreno, 2020	N	Cannot delineate effect of PCV7 and PCV10
Pfizer	Van der Bergh, 2013	N	No full text found
Pfizer	Negash, 2019	N	Did not match PICO
GSK submitted to FDA	Vesikari, 2011	N	Did not match PICO
GSK submitted to FDA	Omenaca, 2011	N	Single arm study only
GSK submitted to FDA	Silfverdal, 2009	N	Did not match PICO
GSK submitted to FDA	Silfverdal, 2009	N	Did not match PICO
Pfizer	Hammitt, 2014	N	Did not establish vaccination coverage
Pfizer	Angoulvant, 2014	N	Did not match PICO
Pfizer	Lau, 2015*	N	Cannot delineate effect of PCV13 vs PCV7
GSK	World Health Organization 2017	Y	
GSK	de Oliveira, 2016	Y	
GSK	Naucler, 2017	Y	
GSK	Domingues, 2014	Y	
Pfizer	van der Westen, 2015	Y	
GSK	Jokinen, 2015	Y	
GSK	Moore, MR. 2014	Y	
GSK/FDA/Pfizer	Vesikari, 2009	Y	
GSK	Sings, 2019	Y	
Pfizer	Moore 2016	Y	
Pfizer	van der Linden, 2016	Y	
Pfizer	Sings, 2019	Y	
Pfizer	Temple, 2019	Y	
GSK	International Vaccine Access Center (IVAC), 2017 (Also, WHO, 2017)	Y	

Source of Reference	Citation	Included? (Y/N)	If excluded, state reason for exclusion
Pfizer	Waight, 2015^	Y	
Pfizer	Varon 2012,2013	Y	
GSK/ Pfizer	Rinta-Kokko, 2018	Y	
Pfizer	Kawai, 2018	Y	
Pfizer	Brandileone, 2018	Y	
Pfizer	Picazo, 2019*	Y	
Pfizer	Wouters, 2020	Y	
Pfizer	Vesikari, 2016	Y	
Pfizer	Desmet, 2018	Y	

APPENDIX B

Vaccine efficacy computations in relevant outcomes

PCV10 (1,5,6B, 7F, 9V, 14, 19F, 23F, 4, 18C)	
VE to prevent IPD caused by vaccine serotype	VE (IPD) = VE $PCV10_{(2+1)}$ x local vaccine serotype IPD coverage of PCV10 VE (IPD) = (0.92) x (0. 5047) = **46.43%**
VE to prevent pneumonia	VE (Pneumonia) = $PCV10_{(2+1)}$ VE (Pneumonia) = **28%**
VE to prevent AOM	VE (AOM) = 1- (rate ratio of PCV10 in C-AOM) = **10%**
PCV13 (PCV10 serotypes + 3, 6A, 19A)	
VE to prevent IPD caused by vaccine serotype	VE (IPD) = VE $PCV10_{(2+1)}$ x (local VE IPD coverage of PCV13) VE (IPD) = (0.92) x (0.5849) = **53.81%**
VE to prevent pneumonia	VE (Pneumonia) = $PCV10_{(2+1)}$ x (local VE IPD coverage of PCV13 / local vaccine serotype IPD coverage of PCV10) VE (Pneumonia) = (0.28) x (0.5849/0.5047) = **32.45%**
VE to prevent AOM	VE (AOM) = VE AOM of $PCV10_{(2+1)}$ x (local VE IPD coverage of PCV13 / local vaccine serotype IPD coverage of PCV10) VE (AOM) = (0.10) x (0.5849/0. 5047) = **11.59%**