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

HTA Report

Prepared by:

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1. EXECUTIVE SUMMARY

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. Currently, PCV13 is implemented 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.

RESEARCH QUESTION 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?*

METHODOLOGY A rapid review of the clinical efficacy of PCV10 and PCV13 was conducted. A systematic search was done in MEDLINE, PubMed CENTRAL, and PROSPERO last March 18, 2020. Systematic reviews that reported vaccine type or serotype-specific effects of PCV10 and/or PCV13 on clinical outcomes such as IPD, all-cause pneumonia, and AOM were identified. Moreover, studies that evaluated the efficacy of the vaccines on surrogate outcomes such as immunogenicity and nasopharyngeal (NP) carriage were also included as they are considered valid surrogate outcomes for assessing the effects of pneumococcal conjugate vaccines.[1] In this rapid review, randomized controlled trials (RCT), cohort, and case-control studies identified in the systematic reviews were extracted and assessed against a set of inclusion and exclusion criteria. Studies submitted by stakeholders were also considered in the review. Finally, the risk of bias assessment was carried out in all included studies.

KEY FINDINGS From the 14 systematic reviews detected and studies submitted by stakeholders, 19 RCTs, 14 cohort studies, and 3 case-control studies were included in the review. Of which, only studies on AOM were subjected to meta-analyses. For IPD and all-cause pneumonia, the studies were not pooled since most were time-series population studies that are inherently heterogeneous in design. As such, only descriptive analyses were conducted. Results of studies which reported surrogate outcomes such as immunogenicity and nasopharyngeal carriage were also reported qualitatively with no pooling of results as they are also deemed important considerations in the clinical evaluation of PCV vaccines. The efficacy of existing PCV vaccines on clinical and surrogate outcomes was also examined, specifically for the three additional serotypes found in PCV13 namely, serotypes 6A, 19A, and 3. The summary of findings for specific outcomes is detailed below:

Vaccine effects on ten shared serotypes

Pomat et al. and Temple et al. assessed the comparative effects of PCV10 and PCV13 on immunogenicity.[2, 3] However, there were no head-to-head trials directly comparing their effects on primary clinical outcomes.

The overall evidence showed that both PCV10 and PCV13 are effective in reducing the incidence of IPD, pneumonia, acute otitis media and nasopharyngeal carriage when compared with PCV7, other vaccines or 'no vaccination'. However, there is insufficient evidence to show a statistically significant difference between PCV10 and PCV13 in preventing IPD, pneumonia and AOM. Findings for specific outcomes are detailed below:

IPD: Palmu et al. reported that PCV10 reduced vaccine-type IPD by up to 92% compared to hepatitis B vaccine.[4] Based on ten observational studies identified, both PCV10 and PCV13 may induce a significant reduction in IPD when compared with PCV7 or 'no vaccination' [Relative risk/Rate ratio (RR): (PCV10 vs no vaccination): Domingues et al.: 83.8% (95% CI 65.9%, 92.3%); Brandileone et al. 0.14 (95% CI 0.10,0.20); Rinta-Kokko et al. 0.27 (95% CI: 0.19, 0.39); Jokinen et al.: 0.21 (95% CI 0.15, 0.28)); (PCV10 vs PCV7): Naucler et al.: 0.76 (95% CI 0.67, 0.86)); (PCV13 vs no vaccination): Jayasinghe et al.: 0.53 (95% CI 0.50, 0.57)); (PCV13 vs PCV7): Jayasinghe et al.: 0.58 (95% CI 0.54, 0.62); Moore et al.: 86% (95% CI 75.5%, 92.3%); Naucler et al.: 0.79 (95% CI 0.70, 0.89); Picazo et al.: 0.11 (95% CI 0.06, 0.21); Varon et al.: 0.70 (95% CI 0.70, 0.89); Waight et al.: 0.68 (95% CI 0.64, 0.72))].[5, 6, 7, 8, 9, 10, 11, 12, 13, 14]

All-cause pneumonia: Kilpi et al. compared PCV10 with hepatitis B vaccines and Becker-Dreps et al. compared PCV13 with 'no vaccination' for this outcome. Both studies which evaluated PCV10 and PCV13 found that either vaccines can significantly reduce pneumonia cases by as much as 30% [RR: PCV10 vs hepatitis B vaccine: Kilpi et al: hospital diagnosed pneumonia: 0.68 (95% CI 0.48, 0.97); hospital treated primary pneumonia: 0.69 (95% CI 0.52, 0.91); radiologically confirmed pneumonia: 0.68 (95% CI 0.47, 0.89)]; [RR: PCV13 vs no vaccination: Becker-Dreps et al.: in children < 12 months: 0.67 (95% CI 0.59, 0.75); 12-23 months: 0.74 (95% CI 0.67, 0.81); 24-59 months: 0.73 (95% CI 0.66, 0.81); 5-14 years old: 0.81 (95% CI 0.72, 0.90)].[15, 16] No studies were identified directly comparing the effect PCV10 and PCV13 in reducing pneumonia incidence.

Acute otitis media: Relative risks ratios reported in two RCTs, Saez Llorenz et al., and Vesikari et al. were pooled using the fixed-effects model.[17, 18] When compared with 'no vaccination', pooled results showed that PCV10 decreased the incidence of clinically diagnosed acute otitis media (C-AOM) by as much as 10% [RR: 0.90 (95% CI: 0.83, 0.98)]. Kawai et al., and Pichichero et al., evaluated the effect of PCV13 which showed that it significantly reduced the incidence of C-AOM when compared with 'no vaccination' [RR Kawai et al.: <2 years old: 0.49 (95% CI 0.41, 0.58); 2-4 years old: 0.63 (95% CI 0.52, 0.77)] but not when compared with PCV7 [RR: Pichichero et al.: 0.75 (95% CI 0.58, 1.04)].[19, 20]

Nasopharyngeal carriage: Based on studies by Saez Llorenz et al. and Heinsbroek et al., PCV13 and PCV10 were shown to decrease *S. pneumoniae* carriage compared with 'no vaccination' or hepatitis B vaccine [RR: (PCV10 vs hepatitis B vaccine: Saez Llorenz et al.: 0.74 (95% CI 0.58, 0.96)); (PCV13 vs 'no vaccination': Heinsbroek et al.: (0.67, (95% CI 0.48, 0.93))].[17, 21] However, PCV13 and PCV10 were not shown to have added benefit in lowering *S. pneumoniae* carriage compared with PCV7, based on the cohort studies by Kaur et al. and Bosch et al. as well as in an RCT by Dagan et el. [RR: (PCV10 vs PCV7: Bosch et al.: at 11 months: 1.12 (95% CI 0.97, 1.28); at 2 years old: 1.46 (95% CI 1.26, 1.68)); Kaur et al.: 1.03 (95% CI 0.92, 1.14)); (PCV13 vs PCV7: Dagan et al.: 1.00 (95% CI 0.96, 1.04))]. [22, 23]

Vaccine effects on serotypes 6A, 19A and 3

Serotype-specific studies showed that both PCV10 and PCV13 can induce an immune response against serotypes 6A and 19A, with PCV13 having an advantage in inducing a significantly greater immune response based on RCTs by Pomat et al. and Temple et al.[2,3] Studies reporting effects on IPD reduction also show that both vaccines may reduce IPD incidence due to serotypes 6A and 19A. Both vaccines did not demonstrate IPD incidence reduction due to pneumococcal serotype 3, while only PCV13 was shown to induce an immune response against the said serotype.

Studies also showed that PCV13 reduced nasopharyngeal carriage due to serotypes 6A and 19A but not serotype 3. Meanwhile, PCV10 was not shown to reduce nasopharyngeal carriage due to serotypes 6A and 19A. No studies were found which evaluated the effect of PCV10 on nasopharyngeal carriage caused by serotype 3.

IPD: In serotype-specific studies, it was observed that PCV10 and PCV13 reduced the incidence of IPD due to serotypes 6A and 19A, but this was not observed for serotype 3.

IPD due to serotype 6A: Brandileone et al. and Jokinen et al. reported that PCV10 did not significantly reduce IPD caused by serotype 6A when compared with 'no vaccination' [RR: Brandileone et al.: 0.42 (95% CI 0.15, 1.14); Jokinen et al.: 0.00 (95% CI 0.00, 1.92)] .[7, 10] In contrast, Rinta-Koko et al. and Naucler et al. showed that PCV10 reduced the incidence of IPD caused by serotype 6A compared with 'no vaccination' or PCV7 respectively [RR: (PCV10 vs no vaccination: Rinta-Kokko et al: 95% (75%, 100%)); (PCV10 vs PCV7: Naucler et al.: 0.15 (95% CI 0.08, 0.30))].[8, 9] Two studies, Picazo et al. and Varon et al., which compared PCV13 to PCV7, did not report significant reduction while a cohort study by Naucler et al. showed that PCV13 significantly reduced IPD incidence of serotype 6A compared with PCV7 [RR: Picazo et al: 0.36 (95% CI 0.02, 6.74); Varon et al.: 0.60 (95% CI 0.22, 1.57); Naucler et al.: 0.19 (95% CI 0.08, 0.48))].[12,13, 9]

IPD due to serotype 19A: A cohort study by Jokinen et al. showed that PCV10 can significantly reduce the incidence of serotype 19A IPD compared with 'no vaccination' [RR: 0.38 (95% CI 0.14, 0.87)].[10] However, a significant increase in IPD cases caused by serotype 19A was observed in cohort studies by Brandileone et al. and Naucler et al. using no vaccination and PCV7 as a comparator respectively [RR: (PCV10 vs no vaccination: Brandileone et al.: 9.49 (95% CI 6.67, 13.50)); (PCV10 vs PCV7: Naucler et al.: 7.74 (95% CI 1.83, 32.80))].[7, 9] Picazo et al. and Varon et al. showed that PCV13 caused a significant reduction in 19A IPD incidence when compared with PCV7 [RR: Picazo et al.: 0.03 (95% CI 0.00, 0.23); Varon et al.: 0.27 (95% CI 0.16, 0.44))].[13] In a cohort study by Naucler et al. on PCV13, a non-significant increase was observed compared to PCV7 [RR: 1.06 (95% CI 0.48, 2.34)].[9]

IPD due to serotype 3: Three studies were found showing inconsistent findings on the impact of PCV 10 on IPD incidence caused by serotype 3 with the study by Brandileone et al. showing a significant increase [RR PCV10 vs no vaccination: 9.51 (95% CI 5.51, 16.40)] while two other studies, Naucler et al. and Jokinen et al. showed non-significant increase [RR: (PCV10 vs PCV7: Naucler et al.: 1.41 (95% CI 0.88, 2.28)); (PCV10 vs no vaccination: Jokinen et al.: 4.20 (95% CI 0.96, 25.17))].[7, 9, 10] The overall quality of the studies, however, were judged to be poor.

In contrast, Naucler et al. and Varon et al. which evaluated the use of PCV 13 showed a non-significant increase or decrease in IPD incidence due to serotype 3 when compared with PCV 7 [RR: Naucler et al.: 1.42 (95% CI 0.91, 2.22); Varon et al.: 0.60 (95% CI 0.22, 1.58)].[9, 13] The overall quality of these studies were found poor.

Pneumonia: There were no studies that evaluated the effect of either PCV10 or PCV13 on pneumonia caused by serotype 6A, 19A, and 3.

Acute otitis media: A cohort study by Pichichero et al. showed that PCV13 significantly reduced AOM caused by serotype 19A but not by serotype 6A and 3 when compared with PCV7 [RR: serotype 19A: 0.09 (95% CI 0.02, 0.37); serotype 6A: 0.12 (95% CI 0.00, 2.23); serotype 3: 0.83 (95% CI 0.16, 4.43)].[20] There were no studies on PCV10 that were detected which evaluated effects on AOM specific to serotypes 6A, 19A, and 3.

Immunogenicity: Sixteen RCTs were identified which evaluated serotype-specific immunogenicity, where the immune responses were measured through IgG concentration and opsonophagocytic antibody (OPA) titer (Pomat et al., Temple et al. Bermal et al. (Philippines), Bermal et al. (Poland), Wysocki et al., Vesikari et al., Dagan et al., Payton et al., Amdekar et al., Huang et al., Wechx et al., Kieninger et al., Snape et al., Yeh et al., Esposito et al., Bryant et al.). [2, 3, 24,24, 23, 25-35] Achievement of IgG and OPA thresholds (i.e., IgG concentration $\geq$ 0.35 µg/mL; OPA Titer $\geq$1:8) against serotypes 6A, 19A and 3 were observed after administering three doses of PCV13. It can be observed from the studies that the proportion of infants that achieved the IgG and OPA thresholds against serotypes 6A and 19A were significantly higher in PCV13 than PCV10.[2, 3] Although a higher immunogenic response was observed with PCV13 compared with PCV10, a protective effect of PCV10 against 6A and 19A cannot be dismissed since PCV10 could also reach the IgG and OPA thresholds. For serotype 3, PCV13 showed a significant immunogenic response, which was not measured in studies of PCV10. However, caution is warranted in interpreting the results of studies on immunogenic responses induced by PCV vaccines on these specific serotypes as they may not necessarily translate to final clinical outcomes. Long term clinical impact of PCV vaccines at a population level may be better assessed using cohort studies measuring changes in the incidence of pneumonia, AOM, and IPD.

Nasopharyngeal carriage: A RCT by Saez Llorenz et al. showed that PCV10 was not associated with lower NP carriage for serotypes 6A and 19A compared with hepatitis B vaccine [RR: serotype 6A: 1.05 (95% CI 0.68, 1.60); serotype 19A: 1.88 (95% CI 0.84, 4.19)].[17]Another RCT by Dagan et al. showed that PCV13 significantly reduced carriage of serotypes 6A and 19A but not on serotype 3 when compared with PCV7 [RR: serotype 6A: 0.58 (95% CI 0.43, 0.78); serotype 19A: 0.55 (95% CI 0.44, 0.68); serotype 3: 0.99 (95% CI 0.48, 2.06)].[23]

Risk of bias assessment

Out of the 19 RCTs included, seven were of high quality, nine were of intermediate quality, and three were of low-quality. Only four out of 14 cohort studies included were of high-quality. The remaining 10 cohort studies were of poor quality. All case-control studies (n= 3) were of poor quality. Observational studies were generally judged to have low quality as these were retrospective in nature and were of insufficient comparability to cohorts.

CONCLUSION Based on the observational studies included in the review, the overall evidence showed that both PCV10 and PCV13 were effective in reducing the incidence of IPD and clinical pneumonia due to the ten shared serotypes when compared with PCV7, other vaccines, or 'no vaccination'. In terms of reducing the burden of AOM and NP carriage, both PCV10 and PCV13 were effective compared with 'no vaccination' or hepatitis B vaccine.

RCTs that evaluated the effect of PCV10 on IPD, pneumonia, and AOM show that PCV10 is efficacious in reducing the incidence of these pneumococcal infections compared with hepatitis B vaccine.

The body of evidence considered in this review did not demonstrate a clear significant difference in the vaccine impact on the overall IPD burden between PCV10 and PCV13 due to the three additional three serotypes 3, 6A, and 19A. There was also inconsistency in findings across studies regarding the impact on pneumonia and AOM incidence caused by the three additional serotypes of PCV13. This may be attributed to inherent limitations and weaknesses found in the studies such as the heterogeneity (e.g., varying study designs, small sample sizes, different follow-up periods), as well as the probable differences in baseline risks across different settings and populations. It should also be noted that there may be varying patterns of serotype distribution across countries, which may also be different in the Philippines.

RECOMMENDATION Future reassessment of clinical efficacy or effectiveness of PCV may be improved by conducting a full systematic review instead of a rapid review. The use of the more appropriate risk of bias assessment tools for time-series studies is also recommended.

RESEARCH QUESTION 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?

METHODOLOGY 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'; and (c) PCV10 versus PCV13.[11] A lifetime horizon using a discounting rate of 7% per annum was used. Results were presented as incremental cost-effectiveness ratios (ICER) and were compared against an implicit cost-effectiveness threshold. Further, changes in ICER values of the two vaccines were assessed for both multi-dose vial (MDV) and single-dose vial (SDV) preparations. The difference in coverage rates was also evaluated: low coverage as base case scenario (50% coverage; no herd protection) and high coverage (90% coverage; with herd protection).

KEY FINDINGS Significantly lower ICER values were computed for MDV preparations compared with SDV for both PCV10 and PCV13 compared with 'no vaccination', despite the higher wastage with MDV use. This shows that shifting from SDV to MDV preparations of either vaccine is the most cost-effective option in the Philippines. In the four scenarios explored in this study, the resulting ICERs of both vaccines had close values. Such as the case for base case scenario of low coverage with MDV use – ICER PCV10 vs 'no vaccination': 2,947 PHP/QALY gained; PCV13 vs 'no vaccination': 6,932 PHP/QALY gained – and all the other scenarios explored. For the high coverage scenario, PCV13 was slightly dominant over PCV10 using either SDV or MDV preparations of the vaccine, observing a higher QALY gained in PCV13 when compared with PCV10. In the cost-effectiveness acceptability curve, both PCV10 and PCV13 reflected high probabilities of cost-effectiveness using either MDV or SDV preparations, even at a lower willingness-to-pay threshold when compared with 'no vaccination'. In the sensitivity analyses, results from the base case scenario showed that the ICER was considerably sensitive to the following parameters: (1) price of the vaccine, (2) vaccine efficacy on AOM and pneumonia, (3) discounting rate, and (4) transition probability of mild AOM progressing to hearing loss. Interestingly, excluding cross-reactivity of PCV10 for serotype 19A or inclusion of serotype 6A from the base case did not significantly alter the ICER values. Despite the sensitivity of the model to the stated parameters, only the increase in vaccine price would render the model not cost-effective for both vaccines.

CONCLUSION Using an implicit cost-effectiveness threshold, PCV10 and PCV13 were both found to be cost-effective using multi-dose vials. PCV13 was associated with higher costs but also greater benefits (i.e., QALYs and LYs) when compared with 'no vaccination' and PCV10, in all the scenarios explored.

RECOMMENDATION The close ICER values computed for PCV10 and PCV13 when compared with 'no vaccination' suggest that the use of other criteria may have to be considered besides cost-effectiveness in choosing what vaccine to use. To facilitate future cost-utility analysis of PCV, further research is recommended to improve the quality of the model input parameters. This may include the conduct of active surveillance to monitor changes in serotype distribution, determination of the overall incidence of IPD, pneumonia, and AOM. Likewise, the development of a costing database and local utility values will be helpful for future assessments.

RESEARCH QUESTION 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?***

METHODOLOGY The budget impact analysis was based on the Markov model used in the cost-utility analysis.[36] The estimated budget needed to purchase PCV10 or PCV13 compared with 'no vaccination' for the target 90% of the birth cohort who would receive three doses of either vaccine for five fiscal years (2020-2024) was computed. Vaccination implementation costs that would be incurred by the National Immunization Program and treatment cost shouldered by PhilHealth were separately computed to derive the estimated total program cost. Possible herd effects were also considered in averted treatment costs.

KEY FINDINGS For both PCV10 and PCV13, the budget required for MDV was significantly lower than that of SDV. Focusing on MDV use for vaccination cost, the purchase of PCV13 was PHP 5 billion higher than that of PCV10 in over five years. On averted treatment costs, PCV10 and PCV13 use were associated with lower treatment costs by PHP 12.15 billion and PHP 14.72 billion, respectively, compared with a 'no vaccination' scenario. The estimated total program costs incurred by the government for PCV10 and PCV13 were at PHP 233.92 billion and PHP 237.96 billion for five years, respectively. Overall, additional program costs of PHP 7.21 billion for PCV10 and PHP 11.25 billion for PCV13 were projected compared with 'no vaccination'.

CONCLUSION Comparing the vaccination and treatment costs associated with PCV10 and PCV13 compared with 'no vaccination', an additional program costs of PHP 7.21 billion for PCV10 and PHP 11.25 billion for PCV13 were projected for the program cost. Given the five-year program cost of PCV10 and PCV13 which considers the new price quotation from the manufacturing companies, PCV10 use was more affordable than PCV13.

RECOMMENDATION To facilitate future budget impact analysis on PCV, cost-of-illness studies, and a standard costing database would be essential to improve the quality of input parameters.

Research Question 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?***

METHODOLOGY Assessment of the ethical, social, legal, and health systems impact of immunizing infants with either PCV13 or PCV10 to prevent IPD, pneumonia, and AOM was done through a review of literature, questionnaires sent to patient groups and civil societies, and interviews with leaders of marginalized communities for social and ethical implications. Consultation with DOH-Legal Service and an online survey with internal and external health systems stakeholders were done to assess legal implications and health systems impact, respectively.

KEY RESULTS Key findings on ethical, social, legal, and health systems impact on the use or non-use of either PCV10 or PCV13 are enumerated below:

Social and ethical implications

A patient group representative and leaders of marginalized communities (n=24) generally prefer PCV10 over PCV13 because of the perceived advantages to enable more equitable access to vaccines because of its lower price, thus providing better public health outcomes. Civil societies (n=3) prefer PCV13 over PCV10 due to the perceived benefit in terms of clinical outcomes due to the three additional serotypes (serotypes 6A, 19A, and 3) it contains.

Legal implications

Both the DOH-Legal Service and COBAC agreed that the determination of the goods and services to be 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, which shall consider the HTAC recommendation as mandated in the Universal Health Care Act. A specific inclination to a certain PCV product was deemed allowable by DOH-Legal Service given that the product will provide the country's specific needs. Therefore, specifying pneumococcal serotypes in PCV prevalent in the local setting which effectively addressing the burden may be exempted from the rules of tailor-fitting set by the DOH Manual of Procedures for Procurement of Goods.[37]

Health systems impact

Single-dose vials of PCV are rated as more acceptable by health systems stakeholders compared with multi-dose vials in terms of safety. However, multi-dose vials are more economical and beneficial in terms of supply chain management.

Based on the responses to the health systems impact survey, PCV13 has an advantage over PCV10 in terms of the confidence of health workers and public perception on the quality of service from the National Immunization Program (NIP) and the National Immunization Technical Advisory Group (NITAG). PCV10 which was perceived to have "*incomplete protection*" given that PCV13 contains more serotypes. If PCV10 were implemented, it would have to be supplemented by adequate orientation of the health workers.

CONCLUSION Results of the interviews and survey on ethical and social impact assessment showed that patient group and leaders of marginalized communities generally prefer PCV10 over PCV13 due to its advantage in enabling more equitable access to vaccines by allowing more vaccines to be purchased thus enabling the achievement of greater population coverage and better public health outcomes. Civil society organizations (CSOs), however, prefer PCV13 to PCV10 due to its perceived benefit in terms of clinical outcomes.

On legal concerns, the DOH Legal Service and COBAC both articulated that the determination of the goods and services to be procured is for the end-user or implementing unit to identify. The DOH Legal Service also affirmed that specifying pneumococcal serotypes in PCV that are locally relevant to the Philippine context and burden may be exempted from the rules of tailor-fitting set by the DOH Manual of Procedures for Procurement of Goods.[37]

On health systems impact assessment, the results of the survey reflected that SDVs are rated as more acceptable than MDVs. PCV13 has an advantage in the confidence of health workers and public perception on quality of service from NIP and NITAG compared with PCV10. The perceived advantages and disadvantages of both PCV preparations and products should be carefully balanced with other decision criteria such as clinical efficacy, cost-effectiveness, budget impact, health system impact and other valid considerations in deciding what type of vaccine preparation should be procured.

RECOMMENDATION A more comprehensive data collection is recommended for ethical, legal, social, and health systems impact assessment. This may include a face-to-face focus group discussion and consultations with relevant experts and stakeholders. The generalizability of the conclusions can also be improved by increasing the number of respondents.

Authors' contribution

Rapid review: Conceptualization and methodology - JRB, ITC; Analysis - JRB, SMO, JACP, GDU, IT

Cost-utility and budget impact analysis: Conceptualization and methodology - JRB, JACP; Data collection - JRB, SMO, JACP; Analysis - JRB, JACP, GDU, SMO

Ethical, legal, social and health systems impact assessment: Conceptualization and methodology - SMO, GDU; Analysis - SMO, GDU, JACP, JRB

This analysis was finalized through an internal and external review process, and the findings of this study were presented to the Health Technology Assessment Council. All authors drafted and revised the report.

Declaration of conflict of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest or in financial conflict with the subject matter or materials discussed in the assessment.

2. HEALTH PROBLEM AND CLINICAL MANAGEMENT OPTIONS

Streptococcus pneumoniae is a major cause of potentially disabling and fatal infections such as sepsis, pneumonia, meningitis, and acute otitis media. Globally, pneumococcal diseases caused half a million deaths among children under five years of age with the majority of deaths occurring in low-and-middle-income countries (LMICs), particularly in Asia and Africa. Pneumonia is also the single largest cause of death in children worldwide claiming about 800,000 lives of children under 5 years old every year.[38]

In the Philippines, all-cause pneumonia was identified to be the fourth leading cause of death among Filipinos in 2017, accounting for approximately 57,000 deaths across all age groups for that year. Pneumonia remains to be the leading cause of death among Filipino children less than 5 years old.[39] A study on invasive pneumococcal infections conducted in 2013 estimated a mortality rate of IPD of 25-34 deaths per 100, 000, which is equivalent to 3,300 deaths in children under 5 years old annually.[40]

An array of antibiotics is commonly used in the Philippines to treat pneumonia in children. In the country, the drug of choice for empiric treatment of pediatric community-acquired pneumonia (pCAP) is amoxicillin for 7 days, while azithromycin is used for those with known hypersensitivity to amoxicillin. *S. pneumoniae*-confirmed meningitis in children is treated with ampicillin or cefotaxime for children less than 2 months old and ceftriaxone or chloramphenicol for children 2 months old to 5 years old.[41] Based on the clinical practice guidelines developed by the Pediatric Infectious Disease Society of the Philippines (PIDSP), *S. pneumoniae*-confirmed meningitis in children may be treated with penicillin for 10-14 days. Alternative treatment for pneumococcal meningitis includes chloramphenicol and ceftriaxone.[42]

The 2018 annual report of *the Antimicrobial Resistance Surveillance and Reference Laboratory (ARSP*) of the *Research Institute for Tropical Medicine (RITM)* showed that there is a relatively low prevalence of penicillin resistance of *S. pneumoniae*. Isolates collected from all specimens (respiratory, blood, and cerebrospinal fluids) showed a penicillin resistance rate of 16% when meningitis breakpoints were used while there was only 1% resistance to penicillin with non-meningitis breakpoints. Resistance to ceftriaxone was low at 3%.[43] Regardless of the low prevalence of resistance to antibiotics used to treat pneumococcal infections, pneumococcal vaccination is essential to prevent significant morbidity and mortality in our setting.

The issue of which Pneumococcal Conjugate Vaccine (PCV) to use by the country's *National Immunization Program (NIP)* has been a long-standing question due to limited local pneumococcal serotype incidence data. In 2014, approximately 35% of infants were vaccinated with 3 doses of PCV10 in the CARAGA Administrative Region and Bangsamoro Autonomous Region in Muslim Mindanao (BARMM). However, after the Formulary Executive Council recommended the use of PCV13 (Prevenar 13®) based on the cost-effectiveness study conducted by *Haasis et al*., the NIP has included it as part of the *Expanded Program on Immunization (EPI)* in selected regions starting in 2015 using a 3+0 dosing schedule.[44, 45] According to the 2019 Childhood Immunization Schedule developed by the *Philippine Pediatric Society (PPS)* and PIDSP, the first, second, and third dose of the PCV primary series shall be given at 6-8 weeks (2 months), 10-16 weeks (3-4 months) and 14-24 weeks (3-6 months), respectively. A booster dose can be given at 12-15 months (~1-year-old). Catch up immunizations can be given to children ages 15 months to 5 years old.

The vaccination coverage of the NIP ranged from 30% to 60% for the period 2015 to 2019 (*Figure 2.1*). For 2020, the NIP started a nationwide implementation of PCV13 vaccination and in the same year PHP 4 billion or 61% of the NIP budget was allocated for PCV alone, with the remaining 39% of the budget shared by eight other types of vaccines. The high budgetary requirement of PCV is because of the significantly higher unit cost of PCV SDV vaccines when compared with older traditional vaccines included in the NIP. There is also a floor price set by Pan American Health Organization (PAHO) for SDV at which cost other countries cannot bring the prices lower.

Recently, the manufacturers of the PCV products available locally have offered the government a multi-dose vial (MDV) preparation, which is cheaper in terms of cost per dose and has greater price flexibility compared to the single-dose vial (SDV). The MDV preparation could potentially lower the overall procurement cost for the vaccine. However, acceptability to end-users as well as the potential health system impact of either PCV vaccine should also be evaluated. PCV10 is at least 2.5 USD lower for MDV and 1 USD cheaper for SDV as compared with PCV13. However, note that these price differences are based on the quoted price provided by the PCV manufacturers to conduct the economic evaluation – actual acquisition cost may be lower during the actual purchase.

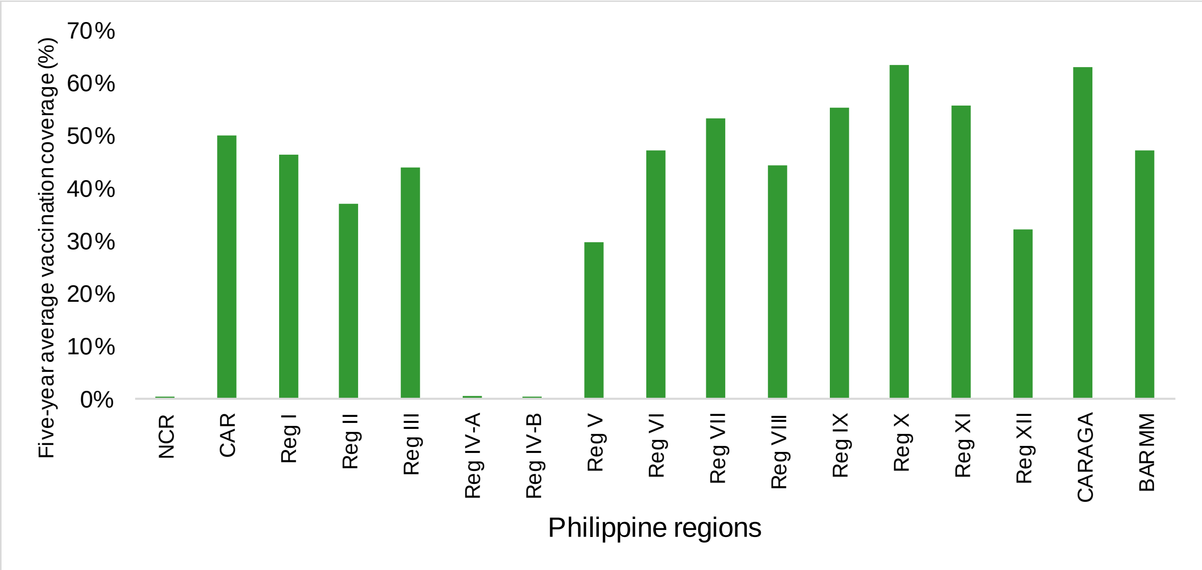

Figure 2.1. *Average regional vaccination coverage of 3rd dose of PCV13 for less than 1-year-old, 2015-2019*

Based on the recent position paper released by the *World Health Organization (WHO),* both PCV10 and PCV13 have a substantial impact against pneumonia, invasive pneumococcal diseases (IPD), and nasopharyngeal carriage. However, there is insufficient evidence to quantify the difference in their impact on major clinical outcomes. Between the two vaccines, WHO stated that PCV13 may have an advantage for settings with prevalent serotypes 19A and 6C.[46] Additional criteria were suggested in choosing a PCV product such as programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes, and antimicrobial resistance patterns. The WHO position paper also asserted that a product switch is not recommended unless there are substantial changes in epidemiologic and programmatic factors. However, if it is impossible to complete a child's vaccination series using the same type of vaccine, another PCV product can be used to complete the series.

Local serotype prevalence data on cases of IPD is important in determining the relevance of the serotypes contained in the PCVs. An important source of such information is the report of the *Research Institute for Tropical Medicine (RITM)* on isolates of *Streptococcus pneumoniae* from blood and cerebrospinal fluid collected by RITM's network of laboratories from 2012 to 2019. *Figure 2.2* shows the percentage of isolates for the age group of less than 5 years old. These 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 relatively small number of isolates reported owing to the passive nature of the surveillance, variability in specimen collection, laboratory processing, and reporting , and in case-ascertainment practices within sentinel sites, the serotype percentage as reported may not reflect the true prevalence of individual serotypes causing IPD.

When serotype prevalence values between 2012 to 2014 and 2015 to 2019 were plotted to determine changes in serotype distribution pre-and-post-PCV13 introduction, no consistent pattern can be observed. Nonetheless, surveillance data from the RITM is the only source of evidence on the prevalence of pneumococcal serotypes in the country. Data from 2015 to 2019 showed that the ten common serotypes found in both PCV10 and PCV13 and serotype 19A accounted for approximately 48% of IPD isolates. The additional two serotypes of PCV13 (i.e. 3 and 6A) comprised 7% of the IPD isolates. The non-vaccine serotypes comprised 45% of all serotypes found in the RITM serotype surveillance.

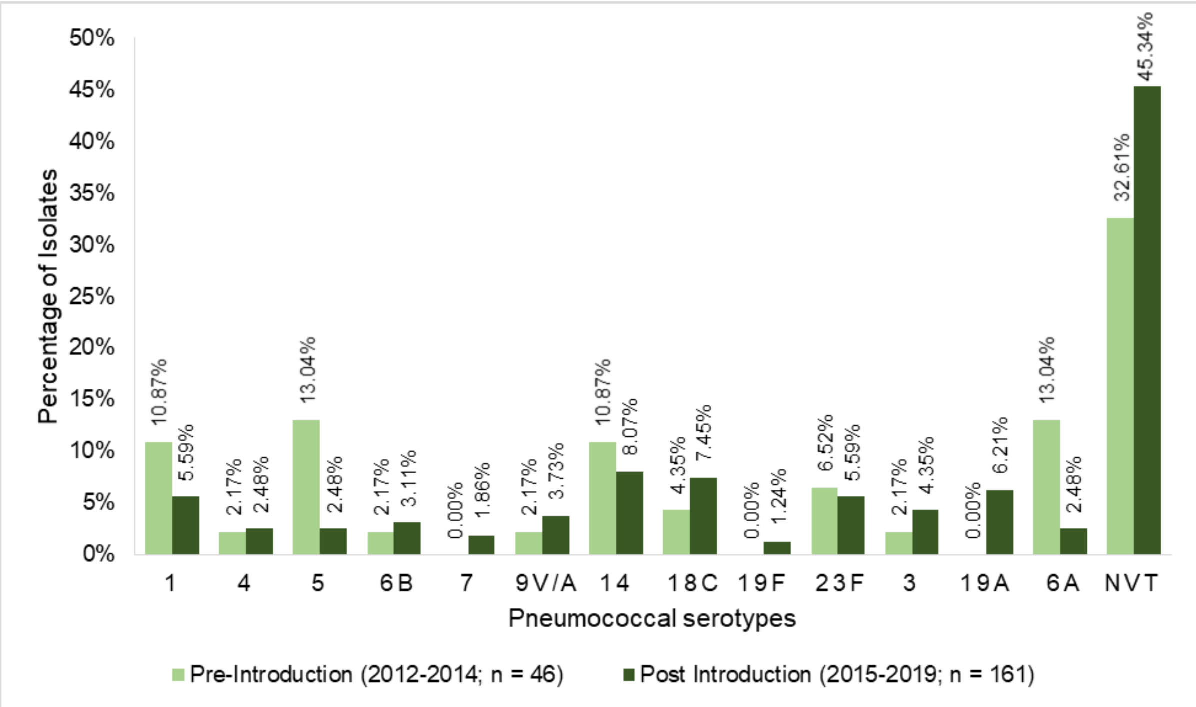

Figure 2.2. *Percentage of isolates causing vaccine type and non- vaccine type IPDs in children less than 5 years old, pre and post PCV13 introduction, 2012-2019 (Source: RITM, 2020)*

The *Severe Acute Respiratory Infection (SARI)* surveillance data from the DOH *Epidemiology Bureau* (*Figure 2.3*), showed that there was a decrease in the number of reported SARI cases from 2018 to 2019. However, this surveillance was geared toward identifying respiratory infections such as influenza, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) rather than pneumococcal infections. Trends would also have been better appreciated with multi-year data which were not available at the time of assessment.

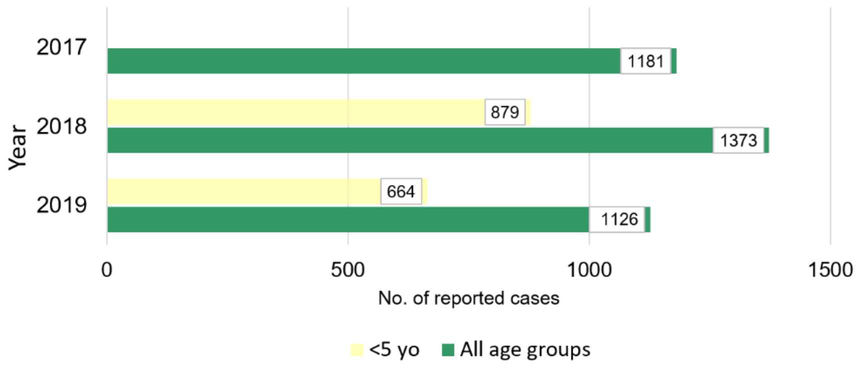

Figure 2.3 *Reported cases of Severe Acute Respiratory Infection, 2018-2019 (DOH- Epidemiology Bureau)*

The existing national surveillance systems on existing pneumococcal serotypes in the Philippines at the RITM have limitations in terms of the passive nature of data collection and the lack of representativeness due to the limited coverage of sentinel sites. The impact of implementing PCV vaccination over the past years cannot be ascertained as well because of this limitation on epidemiologic surveillance.

Currently, PCV13 in SDV preparation is used by the 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 for the 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. Two possible scenarios are foreseen as a result of the assessment, (a) the government may continue procuring and using PCV13 for its vaccination program, or (b) the government may shift in procuring and using PCV10 for its vaccination program.

3. GENERAL INFORMATION OF THE PROPOSED HEALTH TECHNOLOGY

3.1 Characteristics of PCVs

The Pneumococcal conjugate vaccines that are commercially available in the Philippines are PCV10 *(Synflorix®)* and PCV13 *(Prevenar 13®)*. These two vaccines are both available in single-dose and multi-dose (4 doses) vial preparations. *Table 3.1* summarizes the key characteristics of PCV10 and PCV13.

Table 3.1. *Characteristics of pneumococcal conjugate vaccines available in the Philippines*

Generic Name	Pneumococcal Conjugate Vaccine (PCV)	
Product Name	PCV10 (Synflorix®)	PCV13 (Prevenar 13®)
Philippine Food and Drug Administration (FDA)-approved Indication	Prevention of IPD, pneumonia, and AOM in the contained serotypes and cross-reactive response against 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 mcg of Pneumococcal 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 for serotypes 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,

	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

3.2 FDA basis for approval of serotype 19A indication of PCV10

According to the Philippine Food and Drug Administration (FDA), the inclusion of cross-reactivity against serotype 19A in the approved indication of PCV10 (Synflorix®) last 2015 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 immunogenicity clinical trials. [6, 10, 26, 47-50]

The immunogenicity data against serotype 19A were generated from studies that implemented Synflorix® as primary, booster, catch-up, and additional dose including preterm population. Serotype 19A's immunogenicity is 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 infant vaccination. In the same studies, evidence showed that Synflorix® had a substantially lower immune response against serotype 6A compared with Prevenar®, hence, the decision not to include its cross-reactive efficacy for serotype 6A. Note that these studies were also considered in the clinical assessment.

4. EFFICACY AND EFFECTIVENESS

4.1. Objective

To summarize the current evidence on the efficacy and effectiveness of PCV10 and PCV13 in children under 5 years old in terms of the following outcomes: reduction of incidence of invasive pneumococcal disease (IPD), clinical pneumonia, acute otitis media (AOM), induction of immune response, and lowering of pneumococcal nasopharyngeal (NP) carriage.

4.2. Research Question

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?

4.3. Methodology

4.3.1. Literature Search Methods

For identification of systematic reviews, MEDLINE, PubMed CENTRAL, and PROSPERO were searched last March 18, 2020, to identify relevant studies on the topic guided by the set eligibility criteria which shall be discussed in the next section. The following search terms were used: (((((PCV10) OR PCV-10) OR 10 valent pneumococcal vaccine) OR "10-valent pneumococcal conjugate vaccine" [Supplementary Concept])) OR ((((PCV13) OR PCV-13) OR 13 valent pneumococcal vaccine) OR "13-valent pneumococcal vaccine" [Supplementary Concept]). PubMed was filtered to (a) review; (b) systematic reviews; (3) meta-analysis. Meanwhile, only review articles were searched in PubMed CENTRAL. No filters were applied in PROSPERO.

Articles were screened following the PRISMA guidelines. Titles and abstracts were screened by two authors. The full text was retrieved if a decision could not be made based on the available title and abstract. Moreover, only English publications were considered. Any disagreement was resolved by consensus of two authors.

To conserve valuable resources and since updated systematic reviews (SRs) with comprehensive searches already exist, SRs were hand-searched by two authors for individual studies based on the inclusion criteria and outcomes of interest.[51,52] The full-text articles were retrieved for all identified individual studies. Any disagreement was resolved by consensus of two authors.

In addition, SRs and individual studies submitted by the vaccine manufacturers and those used by the FDA in updating the approved indications of PCV10 which included cross-reactivity for serotype 19A were considered in this review.

4.3.2. Selection Criteria and Methods

The following inclusion criteria were applied for systematic reviews:

- Participants involving healthy children (i.e. children with no pre-existing disease/infection) under five years old
- An intervention involving PCV10 or PCV13 with at least three doses, with or without co-administration of other vaccines
- Comparator could be other vaccines, PCV7, placebo, or no vaccination
- Direct effects of any of the following outcomes: IPD, clinical pneumonia, AOM, immunogenicity, NP carriage

The following inclusion criteria were applied for individual studies:

For study population:

Healthy children (i.e. children with no pre-existing disease/infection) under five years old

For intervention/control:

- An intervention involving PCV10 or PCV13 with at least three doses, with or without co-administration of other vaccines.
- Studies that measured the effect of two doses of either PCV10 or PCV13 were included in the summary of findings post hoc.
- Comparator could be other vaccines, PCV7, placebo, or no vaccination

For outcomes:

Data on the direct efficacy of PCV on each of the following outcomes (vaccine effect on ten shared serotypes, and vaccine effects on serotype 6A, 19A, and 3):

<u>Invasive pneumococcal disease (IPD)</u>–Confirmed laboratory IPD diagnosis through isolation of pneumococci from the bloodstream, cerebrospinal fluid, pleural fluids, articular fluids, and other normally sterile sites or those secondary to bloodstream spread.

<u>Clinical pneumonia</u>–Since studies evaluating pneumonia had various case definitions, the following outcomes were considered:

(a) *Consolidated pneumonia/x-ray confirmed pneumonia* - hospital-diagnosed pneumonia with pulmonary infiltrates on chest x-ray showing dense, white image, cotton wool-like appearance (alveolar infiltrate), involving one or more pulmonary segments, lobes or the whole lung, frequently presenting air bronchogram and sometimes associated with pleural effusion.

(b) *Hospital-diagnosed pneumonia/ clinical pneumonia*–includes broad pneumonia definitions based on ICD10-diagnosis code J10.0, J11.0, J12 to J18, J85.1, or J86. This could or could not result in inpatient hospitalization.[15]

(c) *Hospital-treated primary pneumonia* - hospital-diagnosed pneumonia resulting in inpatient hospitalization with pneumonia as the primary discharge diagnosis.[15]

<u>Acute otitis media (AOM)</u> - Frequency of all-cause AOM episodes with greater than one episode caused by *S. pneumoniae* serotypes. Studies including diagnosis of AOM by diagnostic code, laboratory results, or clinical definitions were considered.

<u>Immunogenicity (antibody levels):</u> could be measured by any of the following:
(a) Anti-polysaccharide IgG geometric mean antibody concentration (GMC) in micrograms per milliliter (μg/mL)
(b) Proportion of infants achieving ≥ 0.35 μg/mL serum antibody level that is considered protective against IPD by WHO[25, 55]
(c) Opsonophagocytic antibody geometric mean titers (GMTs)
(d) Proportion of infants achieving opsonophagocytic antibody titer of ≥1:8 which has been associated with protection against IPD[31]

<u>Pneumococcal nasopharyngeal (NP) carriage</u> - Data on the changes in the percentage of the study population with either vaccine type or serotype-specific pneumococcal nasopharyngeal carriage. Nasopharyngeal carriage of *S. pneumoniae* is usually determined through nasal swabs of infants. Samples are then cultured, and *S. pneumoniae* isolates are then further serotyped.

For the types of studies:

- Randomized trials (including cluster randomized trials), controlled non-randomized clinical trials
- Prospective and retrospective comparative cohort studies, and case-control or nested case-control studies
- The following additional inclusion criteria were applied:
    (a) More than 50% proportion of the population was vaccinated with PCV10 or PCV13
    (b) Interrupted time-series studies considered as cohort has at least three data points before and after the intervention.
    (c) Follow-up assessment for population[54]
        (1) At least 6 months post introduction if <1 year of age
        (2) At least 18 months post introduction if <2 years of age
        (3) At least 2 years post-introduction if <5 years of age
        (4) If the outcome is NP, at least 6 months post-introduction in children <1 year of age

<u>The following exclusion criteria were applied for individual studies:</u>

For study population:

- Studies which did not adequately report characteristics of the population evaluated to determine the approximate coverage of PCV, making it impossible to decipher if the observed effects were due to PCV or another intervention
- Studies which did not distinguish between vaccinated and unvaccinated groups

For intervention/control:

- Studies which compared different dosing schedule of the same vaccine
- Studies with more than one schedule and/or more than one product which could not be distinguished and thus effects from either schedule and/or product could not be distinguished

For outcomes:

Studies with no restrictive criteria on the definition of clinical pneumonia and IPD

For the types of studies:

Abstracts from conference proceedings or published in a language other than English.

For follow up period:

Years post-PCV introduction could not be determined – e.g. could not determine the date of surveys, introduction year of vaccine, or did not distinguish (i.e. aggregated data) between pre- and post- PCV introduction periods.

4.3.3. Data Extraction

<u>Systematic reviews:</u>

Data extraction form for systematic reviews was used to identify individual studies which were already included in the systematic reviews: (1) general information of the study (2) study characteristics (3) outcome assessed (4) type of studies (5) appraisal method (6) meta-analysis results if performed *(Appendix A, Tables 1&2)*.

<u>Individual studies:</u>

Separate data extraction form was used for individual studies identified in previous systematic reviews that met the inclusion criteria. This form is designed to retrieve information on the following domains: (1) general information of the study; (2) vaccination schedule details; and (3) outcome assessment (*Appendix A, Tables 3-16*).

One author independently extracted and summarized key domains using a standard extraction tool with one author doing quality checks. If there was uncertainty, it was solved by a discussion by the two authors.

4.3.4. Data Synthesis

Included studies were classified based on the five outcomes of interest. If data is available, studies were further sub-grouped depending on whether they measured vaccine effect on the ten shared serotypes and/or serotype-specific effects on 6A, 19A, and 3.

If permissible, the pooling of results was done using a fixed-effect model or random effects, depending on the data. From the discussion of the systematic reviews, pooling may not be feasible in other outcomes due to methodological and clinical heterogeneity of outcome measures and vaccination schedule used. Moreover, pooling was not performed for surrogate outcomes but were included in the systematic review. Hence, treatment/ vaccine effects were computed for each study as applicable:

1. The rate ratios or relative risk ratios were computed for studies that evaluated incidence data to compare the relative effect of treatment to the control arm.
2. Relative risk ratios were calculated for case-control studies and RCTs which measured the proportion of subjects achieving the specified threshold for immunogenicity.
3. Mean difference was computed for studies that reported continuous outcomes, i.e. geometric mean IgG concentration and geometric mean OPA titer.

4.3.5. Critical appraisal of included studies

Systematic review:

Included systematic reviews were assessed using AMSTAR-2. AMSTAR-2 comprises critical (7 items) and non-critical domains (9 items). One author independently assessed the quality of each study and uncertainties were solved by a discussion with another author. Confidence in the review was graded through:

- *High confidence* - Complied with all critical and non-critical domains or violated only one non-critical domain
- *Moderate* - Complied with all critical domains with more than one non-critical domain violated
- *Low* - At least one critical domain is violated, but without non-critical domain violated
- *Critically low* - If at least one critical domain and non-critical domain were violated

Individual studies:

- *For randomized control trials*, Cochrane Collaboration's risk of bias version 1 was used. Subsequently, an overall evaluation of the risk of bias for each of the included trials was performed. The risk of bias was judged based on extracted information and rated as 'high risk' or 'low risk'. If the study report did not provide sufficient details, the risk of bias was considered 'unclear'. Studies marked with 1-3, 4-5, 6-7 under low risk were considered low, intermediate, and high quality, respectively. The risk of bias assessment was done by two authors. In case of disagreement, a consensus among authors was done.
- *For case-control/ cohort studies*, the Newcastle - Ottawa quality assessment scale was used. The risk of bias assessment was done by two authors. In case of disagreement, a consensus among authors was done. A threshold for converting the Newcastle-Ottawa scale was used:
    - *Good quality*: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

- *Fair quality*: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- *Poor quality*: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

4.4 Results

4.4.1 Characteristics of included studies

Systematic review:

Thirteen systematic reviews (SRs) were identified from the search strategy (*Figure 4.1*). Besides eligible articles identified in the search strategy, the 2017 WHO systematic review on PCV was also included resulting in 14 SRs.[55] This study was not detected in the search strategy since the WHO is not included in the databases used for this rapid review. Three systematic reviews were submitted by PCV manufacturers. Of these three, two were removed after deduplication while the other one did not meet the inclusion criteria, thus it was excluded in this review.[58]

The SRs identified used PCV10 and/or PCV13 as the intervention and included RCTs, cohort studies, case-control studies, and time-series studies. The comparator was not specified in the research question mainly to allow flexibility in the inclusion criteria. Only one SR included all age groups in the review while the remaining SRs focused on pediatric populations. In the 14 SRs included, five studies performed meta-analysis (Immunogenicity n=3; IPD n=1; pneumonia n=1).

Table 4.1 *Systematic reviews on PCV with outcomes on IPD, pneumonia, acute otitis media, immunogenicity, and nasopharyngeal carriage*

Author, Year	Outcome	Total studies/ outcome	With meta? (Y/N)	Funding
WHO, 2017	IPD	31	N	WHO
	Pneumonia	37	N	
	Immunogenicity	114	Y	
	NP Carriage	22	N	
Ciapponi, 2016	Immunogenicity	4	N	PAHO
De Oleivera, 2016*	IPD	4	N	PAHO
	Meningitis	5	N	
	Pneumococcal Pneumonia	13	N	
Alicinio, 2017	Community-acquired pneumonia	12	Y	None
Duan, 2016	Immunogenicity	2	N	None
Choe, 2019	Immunogenicity	69	Y	
Berman Rosa, 2020	IPD	12	N	None
	AOM	4	N	
	NP Carriage	4	N	
Tin Tin Htar, 2019	IPD	18	N	Pfizer
	Pneumonia	5	N	
	Otitis Media	4	N	
	NP Carriage	7	N	
Sings, 2018*	IPD	6	Y	Pfizer

Author, Year	Outcome	Total studies/ outcome	With meta? (Y/N)	Funding
Fortanier, 2019	AOM	11	N	None
McGirr, 2019	IPD	11	N	GSK
Moreira, 2016	IPD	6	N	GSK
	Pneumococcal pneumonia	2	N	
Ruiz-Aragon, 2013	Immunogenicity	9	Y	None
Sucher, 2011	Immunogenicity	5	N	None

*Note: *Submitted by proponents*
For details, refer to Appendix A Tables 1 and 2.

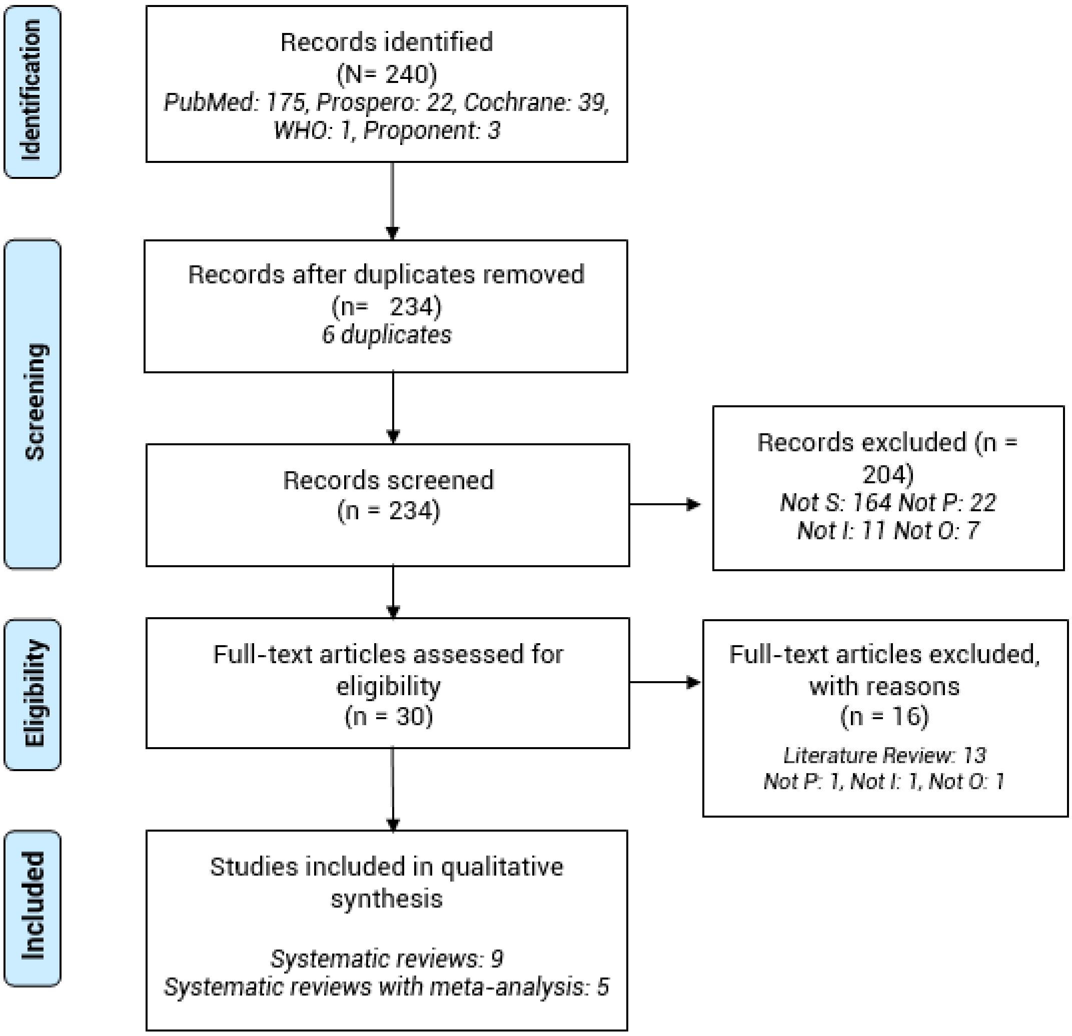

***Figure 4.1.** PRISMA flowchart detailing identification and selection for the inclusion of systematic reviews*

Individual studies:

We hand-searched individual studies from the 14 identified SRs as reference for the efficacy of the relevant outcomes. From the 14 SRs, 28 primary studies were included, comprising 17 RCTs, nine cohort studies, and three case-control studies. Out of the 69 individual studies forwarded by proponents or PCV manufacturers, only four cohort studies met the inclusion criteria and were included in the review. Seven studies that were used by the Philippine FDA in their approval of PCV10 indication for serotype 19A were also identified, of which, one RCT was included. Additionally, members of the HTA Council and HTA unit also provided six additional studies which were screened resulting in the addition of one RCT and one cohort study. Finally, 19 RCTs, 14 cohort studies, and three case-control studies were included in the review (*Figure 4.2).*

The following were the main reasons for excluding some of the 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 the same individual studies or updated studies), (6) could not delineate the effects between intervention and control in observational studies; and (7) evaluated vaccine effects of less than three doses. Details on the reasons for the exclusion of studies from proponents are specified in Appendix C.

Individual studies were summarized based on the five outcomes of interest. The context of PCV10 and PCV13 introduction differ in each country, limiting the ability to make quantitative comparisons across studies. For example, some countries have established PCV7 vaccination before introducing either PCV10 or PCV13, while others did not have prior pneumococcal vaccination. Baseline prevalence and baseline risk also differ per setting.[55] The summary of the included articles is found in Appendix A *Tables 3-16*, arranged per outcome of interest.

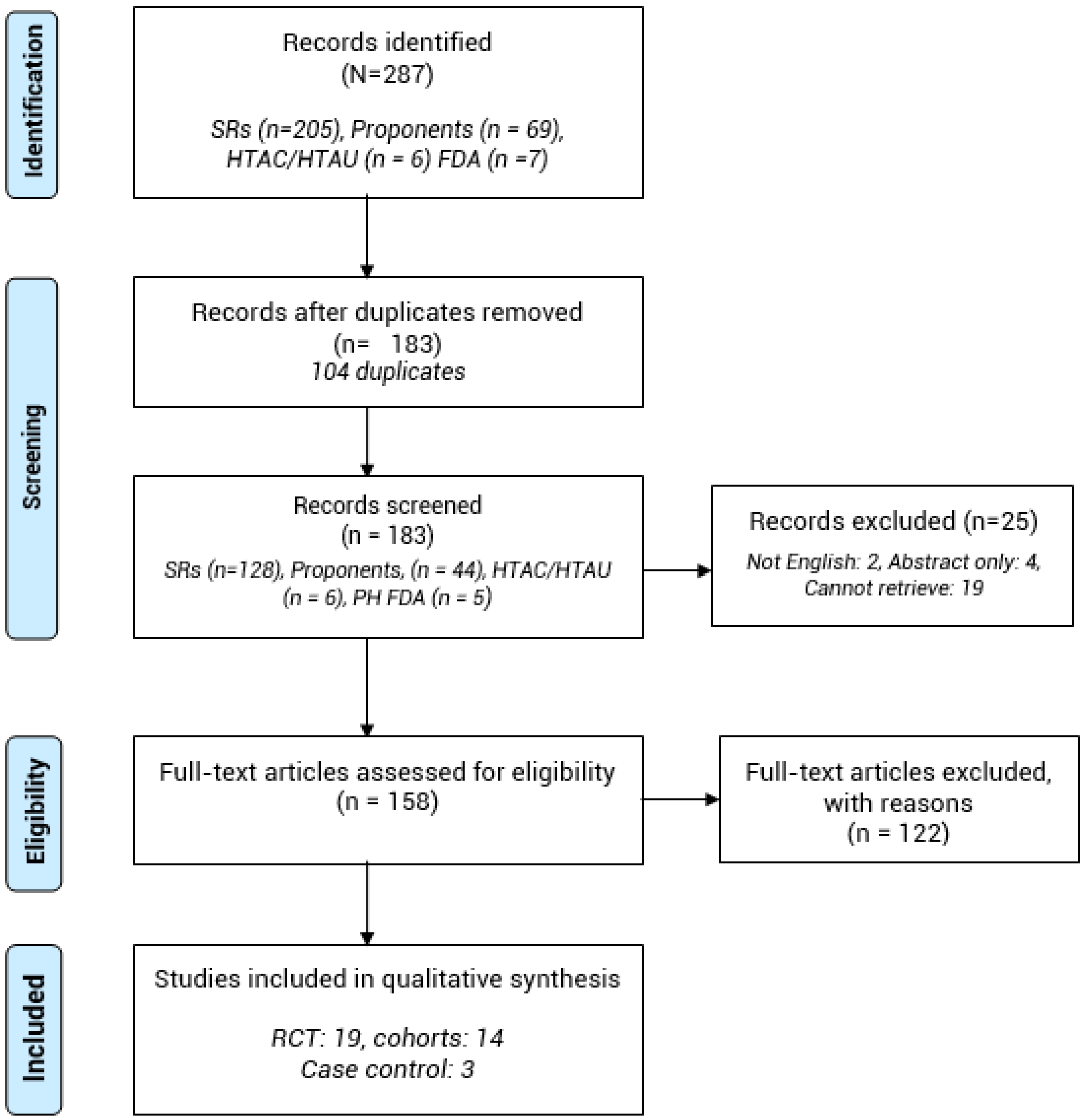

Figure 4.2 *PRISMA flowchart detailing identification and selection for the inclusion of individual studies*

4.4.2 Summary of Findings

Invasive Pneumococcal Disease (IPD) One randomized controlled clinical trial by Palmu et al. evaluated the effect of PCV10 on IPD incidence reduction.[4] Since PCV13 deduced clinical effects from PCV7 studies, we did not identify RCTs which evaluated the effect of PCV13 on IPD and other clinical outcomes of interest.[57]

All observational studies on IPD (n= 10) identified IPD cases through national surveillance and were classified as either case controls or cohorts. The incidence of IPD after PCV13 or PCV10 introduction was considered as the incidence in the intervention arm while the incidence of IPD during the years of PCV7 implementation or 'no vaccination' was considered the incidence in the control arm.

Case-control and cohort studies have demonstrated a significant reduction in overall IPD incidence cases in the latter years after the implementation of PCV10 and PCV13 when compared with PCV7, or 'no vaccination'. These studies reported a statistically significant reduction of IPD but were of low quality because of a lack of control of confounders in observational studies. 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.

Vaccine effects on IPD burden due to the ten shared serotypes

One RCT by Palmu et al. reported that the reduction in IPD caused by PCV10-serotypes was 92% (95% CI: 75, 99%) for PCV10 versus hepatitis B vaccine as control.[4]

Results from ten observational studies (*Table 4.2*) showed that the use of PCV10 or PCV13 resulted in a significant reduction of IPD incidence compared with PCV7 or 'no vaccination' (PCV13 vs no vaccination: Jayasinghe et al.; PCV 13 vs PCV 7: Moore et al., Jayasinghe et al., Picazo, et al., Naucler et al., Varon et al., Waight et al.; PCV 10 vs 'no vaccination': Domingues et al., Brandileone et al., Rinta-Kokko et al., Jokinen et al.; PCV 10 vs PCV 7: Naucler et al.).[5-14] The outcomes presented considered combined vaccine and non-vaccine serotypes (*Table 4.2*).

Table 4.2 *Identified studies evaluating vaccine effects on IPD (case-control)*

Author, Year (Quality of evidence)	Vaccine		Outcome measure	Vaccine type effectiveness
	I	C		Vaccine effectiveness = (1-OR) x 100
Moore, 2016* USA (Poor)	PCV 13	PCV 7	Vaccine Effectiveness	86% (95%CI: 75.5, 92.3%) S
Domingues, 2014*& Brazil (Poor)	PCV 10	'no vaccination'		83.8% (95%CI: 65.9, 92.3%) S

Note: ***Submitted by proponents; & Included in the FDA review; **S**-Significant results; **NS**- non-significant results*
For details, see Appendix A Table 3

Table 4.2 *Identified studies evaluating vaccine effects on IPD (cohort)*

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Relative risk/Rate ratio (95% CI)
Brandileone, 2018* Brazil (Good)	Cohort	PCV10 'no vaccination'	IPD Incidence	28/247	1041/1313	0.14 (0.10, 0.20) S
Rinta-Kokko, 2018* Finland (Good)	Cohort	PCV10 'no vaccination'	IPD incidence	23/114	391/520	0.27 (0.19,0.39) S
Naucler, 2017*	Cohort	PCV 10 PCV 7	IPD Incidence / 100,000	14.4 (13.6,15.3) (N = 1169)	17.7 (16.0,19.7) (N = 344)	0.76 (0.67,0.86) S

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Relative risk/Rate ratio (95% CI)
Sweden (Poor)						
Jokinen, 2015*[&] Finland (Good)	Cohort	PCV 10 'no vaccination'	IPD Incidence / 100,000 *(any culture confirmed IPD)*	12.9	62.9	0.21 (0.15,0.28) S
Jayasinghe, 2020 Australia (Poor)	Cohort	PCV 13 'no vaccination' / PCV 7	IPD Incidence /100, 000 - All serotypes : all ages	A: 6.0 (1336) B: 6.6 (1350)	11.3 (2156.7)	*PCV 13 vs 'no vaccination'* 0.53 (0.50,0.57) S *PCV 13 vs PCV 7* 0.58 (0.54,0.62) S
Picazo, 2019* Spain (Good)	Cohort	PCV13 PCV7	IPD Incidence Rate	2.97	27.06	0.11 (0.06, 0.21) S
Naucler, 2017* Sweden (Poor)	Cohort	PCV 13 PCV 7	IPD Incidence / 100,000	10.8 (10.3,11.5) (N = 1219)	13.2 (11.8,14.7) (N = 332)	0.79 (0.70,0.89) S
Varon, 2015 France (Poor)	Cohort	PCV 13 PCV 7	IPD Incidence	181/343 (52.8)	388/581 (66.8)	0.79 (0.70,0.89) S
Waight, 2015* UK (Poor)	Cohort	PCV 13 PCV7	IPD Incidence / 100, 000 All serotypes: all ages	6.85	10.14	0.68 (0.64,0.72) S

Note: *******Submitted by proponents;* ***&*** *Included in the FDA review;* ***S****-Significant results;* ***NS****- non-significant results*
For details, see Appendix A Table 3

Vaccine effects on IPD burden due to serotypes 6A, 19A and 3

For serotype-specific studies, it was observed that PCV10 and PCV13 significantly reduced the incidence of IPD due to serotypes 6A and 19A but not IPD incidence due to serotype 3. However, it cannot be assumed that disease reduction due to 19A and 6A is the same for both vaccines due to the difference in baseline prevalence or risk in the population of the studies.

IPD: Serotype 6A

A cohort study by Rinta-Kokko et al., which compared the effect of PCV10 with 'no vaccination' showed that PCV10 significantly reduced the incidence of IPD caused by serotype 6A.[8] Meanwhile, Brandileone et al. and Jokinen et al. showed that PCV10 did not significantly reduce

IPD caused by 6A compared with 'no vaccination'.[7, 10] When compared with PCV7, a cohort study by Naucler e al. showed that PCV10 significantly reduced the incidence of serotype 6A IPD incidence.[9]

Cohort studies by Picazo et al. and Varon et al. showed that PCV13 did not cause a significant reduction of IPD caused by serotype 6A when compared with PCV7. Meanwhile, a cohort study by Naucler et al. which compared the effect of PCV13 to PCV7 showed that PCV13 significantly reduced IPD incidence caused by serotype 6A (*Table 4.3*).[9,12, 13]

Table 4.3 *Included studies evaluating vaccine effects on IPD reduction against serotype 6A*

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Relative risk/ Rate ratio (95% CI)
Brandileone, 2018* Brazil (Good)	Cohort	PCV10 'no vaccination'	IPD incidence	4/247	51/1313	0.42 (0.15, 1.14) NS
Rinta-Kokko,2018* (Finland) (Good)	Cohort	PCV10 'no vaccination'	IPD relative incidence reduction	N/A	N/A	95% (75, 100) S
Naucler, 2017* Sweden (Poor)	Cohort	PCV 10 PCV 7	IPD Incidence/ 100,000	0.2 (0.1,0.3)	1.1 (0.7,1.7)	0.15 (0.08, 0.30) S
Jokinen, 2015*& Finland (Good)	Cohort	PCV 10 'no vaccination'	IPD Incidence/ 100,000	0	2.2	0.00 (0.00,1.92) NS
Picazo, 2019* Spain (Good)	Cohort	PCV13 PCV7	IPD Incidence Rate	0.00	0.36	0.36 (0.02, 6.74) NS
Naucler, 2017* Sweden (Poor)	Cohort	PCV 13 PCV 7	IPD Incidence/ 100,000	0.1 (0.0,0.2)	0.5 (0.3,0.9)	0.19 (0.08, 0.48) S
Van der Linden, 2016* Germany (Poor)	Case-control	PCV 13 PCV 7	A: Cases for 3 doses; B: Control for 3 doses (vaccinated: unvaccinated)	A: 0:4 B: 74:20	A: 0:4 B: 38:27	N/A
Varon, 2015 France (Poor)	Cohort	PCV 13 PCV 7	IPD Incidence	1/181	3/388	0.60 (0.22,1.57) NS

Note: ***N/A*** *- data not reported;* ****-*** *Submitted by proponents,* ***&*** *- Included in the FDA review;* ***S****-Significant results;* ***NS****- non-significant results*

For details, see Appendix A Table 4

IPD: Serotype 19A

A study by Jokinen et al. reported that PCV10 significantly reduced IPD incidence caused by serotype 19A compared with 'no vaccination', while Rinta-Kokko et al. reported a non-significant reduction.[8,10] In contrast, Brandileone et al. and Naucler et al. which compared PCV10 to 'no vaccination' and PCV7, respectively, showed that PCV10 use led to a significant increase in the incidence of IPD caused by serotype 19A.[7, 9]

Three cohort studies evaluated the effect of PCV13 versus PCV7. Picazo et al. and Varon et al. showed that PCV13 significantly reduced IPD incidence caused by serotype 19A, while the study by Naucler et al. showed that PCV13 caused a non-significant increase in IPD incidence caused by serotype 19A *(Table 4.4)*.[9, 12, 13]

Table 4.4 *Included studies evaluating vaccine effects on IPD reduction against serotype 19A*

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Relative risk/ Rate ratio (95% CI)
Brandileone, 2018* Brazil (Good)	Cohort	PCV10 'no vaccination'	IPD incidence	75/247	42/1313	9.49 (6.67, 13.50) S
Rinta-Kokko, 2018* Finland (Good)	Cohort	PCV10 'no vaccination'	IPD relative incidence reduction	N/A	N/A	26 (-13, 51) NS
Naucler, 2017* Sweden (Poor)	Cohort	PCV 10 PCV 7	IPD Incidence/ 100,000	1.8 (1.6,2.2)	0.2 (0.1,0.9)	7.74 (1.83,32.8) S
Jokinen, 2015*& Finland (Good)	Cohort	PCV 10 'no vaccination'	IPD Incidence/ 100,000	2.1	5.5	0.38 (0.14,0.87) S
Picazo, 2019* Spain (Good)	Cohort	PCV13 PCV7	IPD Incidence Rate	3.77	9.11	0.03 (0.00, 0.23) S
Naucler, 2017* Sweden (Poor)	Cohort	PCV 13 PCV 7	IPD relative incidence reduction	0.5 (0.4,0.7)	0.5 (0.2,1.0)	1.06 (0.48,2.34) NS
Varon, 2015 France (Poor)	Cohort	PCV 13 PCV 7	IPD Incidence	16/181 (8.8)	128/388 (33)	0.27 (0.16, 0.44) S

Note: ***N/A*** *- data not reported;* ********Submitted by proponents,* ***&****Included in the FDA review;* ***S****-Significant results;* ***NS****- non-significant results*

For details, see Appendix A table 4

IPD: Serotype 3

One good quality cohort study by Brandileone et al., which evaluated the effect of PCV10 compared with 'no vaccination' showed that PCV10 significantly increased the incidence of IPD caused by serotype 3.[7] Meanwhile, Jokinen et al. and Naucler et al. showed that PCV10 led to a non-significant increase in serotype 3 IPD incidence when compared with 'no vaccination' or PCV7 respectively.[9, 10]

On the other hand, Naucler et al. showed that PCV13 caused a non-significant increase in the incidence of IPD caused by serotype 3 when compared with PCV7.[9] Meanwhile, a cohort study by Varon et al. showed that PCV13 caused a non-significant reduction of IPD caused by serotype 3 compared to PCV7.[13] *(Table 4.5).*

Table 4.5 *Included studies evaluating vaccine effects on IPD reduction against serotype 3*

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Relative risk/ Rate ratio (95% CI)
Brandileone, 2018* Brazil (Good)	Cohort	PCV10 'no vaccination'	IPD incidence	34/247	19/1313	9.51 (5.51, 16.40) S
Naucler, 2017* Sweden (Poor)	Cohort	PCV 10 PCV 7	IPD Incidence/ 100,000	2.0 (1.7,2.4)	1.4 (0.9,2.1)	1.41 (0.88,2.28) NS
Jokinen, 2015*& Finland (Good)	Cohort	PCV 10 'no vaccination'	IPD Incidence/ 100,000	2.1	0.5	4.20 (0.96, 25.17) NS
Naucler, 2017* Sweden (Poor)	Cohort	PCV 13 PCV 7	IPD Incidence/ 100,000	1.1 (0.7,1.7)	1.6 (1.4,1.9)	1.42 (0.91,2.22) NS
Varon, 2015 France (Poor)	Cohort	PCV 13 PCV 7	IPD Incidence	5/181 (2.8)	18/388 (4.6)	0.60 (0.22, 1.58) NS

*Note: **N/A** - data not reported; *****Submitted by proponents, **&**Included in the FDA review; **S**-Significant results; **NS**- non-significant results*
For details, see Appendix A Table 4

All-cause pneumonia Results from one good quality RCT by Kilpi et al. showed that PCV10 significantly lowered the incidence of all-cause pneumonia by 13-32% when compared with hepatitis B vaccine as control.[15] A poor quality cohort study by Becker-Dreps et al. revealed that PCV13 also significantly lowered the incidence of all-cause pneumonia by 19-33% (*Table 4.6*).[16]

There were no studies which evaluated the effect of PCV10 and PCV13 specifically on serotypes 6A, 19A, and 3.

Table 4.6 *Identified studies evaluating vaccine effects on all-cause pneumonia*

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Rate Ratio (95% CI)
Kilpi, 2018 Finland (Good)	RCT	PCV 10 Hepatitis B vaccine	Incidence rate per 1000 person-years of: A: Hospital-diagnosed pneumonia B: Hospital treated primary pneumonia C: Radiologically confirmed pneumonia *First number is incidence measured before 7 months of enrollment, second is measured after 7 months	A: 9.9, 10.1 B: 4.3, 3.8 C: 4.9, 5.2	A:13.3, 15.1 B: 6.0, 4.4 C: 6.8, 9.0	A. Before 7 months of enrollment: 0.72 (0.59, 0.87) S After 7 months of enrollment: 0.68 (0.48 , 0.97) S B. before 7 months of enrollment: 0.87 (0.49-1.60) NS After 7 months of enrollment: 0.69 (0.52, 0.91) S C. Before 7 months of enrollment: 0.71 (0.51, 0.99) S After 7 months of enrollment: 0.68 (0.47 , 0.89) S

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Rate Ratio (95% CI)
Becker-Dreps, 2014 Nicaragua (Poor)	Cohort	PCV 13 'no vaccination'	Incidence rate/1000 person-years in infants aged: A: in <12 months B: in 12-23 months C: in 24-59 months D: 5-14 years	N/A	N/A	A: 0.67 (0.59, 0.75) S B: 0.74 (0.67, 0.81) S C: 0.73 (0.66, 0.81) S D: 0.81 (0.72, 0.90) S

Note: ***S****-Significant results;* ***NS****- non-significant results*
For details, see Appendix A Table 5.

Acute otitis media Two RCTs and two cohort studies were identified which evaluated the impact of PCV vaccines on AOM. Studies which evaluated PCV10 used hepatitis B vaccine as control while PCV13 was compared with either PCV7 or 'no vaccination'. Two studies evaluated the reduction of at least one episode of AOM while two studies reported results of overall AOM incidence reduction.

Vaccine effects on AOM due to the ten shared serotypes

Two RCTs, Saez Llorenz et al. and Vesikari et al. assessed the effects of PCV10 in reducing the incidence of AOM with differences in the quality of evidence.[17, 18] These studies were pooled using a fixed-effect model since heterogeneity was low (*Table 4.7*). Meta-analysis results showed that PCV10 decreased at least one case of clinically diagnosed acute otitis media (C-AOM) by as much as 10% compared with 'no vaccination' (*Figure 4.3*). PCV10 also reduced all cases of C-AOM by 7% (*Figure 4.4*).

Two cohort studies were identified which evaluated the effect of PCV13. Kawai et al. showed that PCV13 significantly reduced AOM incidence compared with 'no vaccination'.[19] In contrast, PCV13 did not significantly reduce AOM incidence when compared with PCV7 based on the results of the cohort study by Pichichero et al.[20]

Saez Llorenz et al. also evaluated the effects of PCV10 on reducing at least one case of C-AOM caused by *H. influenzae*. This study illustrated that reduction in C-AOM cases from *H. influenzae* was not significant [RR: 0.84 (95% CI: 0.44,1.58), P = 0.5526].[17] Note that this finding was noted to determine the effect of PCV10 on AOM caused *H. influenzae* since the pneumococcal serotypes contained in PCV10 are conjugated to protein D of non-typeable *H. influenzae*.

Meta-analyses using random-effects model were also done to combine the results of the two studies to show the difference in results (*Figures 4.5 and 4.6*).

__Table 4.7__ Identified studies evaluating vaccine effects on acute otitis media

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Relative risk (95% CI)
Saez Llorenz, 2017 (Low)	RCT	PCV10 Hepatitis B vaccine	≥1 AOM episode	6/3010	18/2979	0.83 (0.70, 0.98) S
Vesikari, 2016* (Good)	RCT	PCV10 Hepatitis B vaccine	≥1 AOM episode	589/942	892/1329	0.93 (0.84, 1.03) NS
Pichichero, 2018# (Poor)	Cohort	PCV13 PCV7	AOM incidence	53/223	89/284	0.75 (0.58, 1.04) NS
Kawai, 2018* (Poor)	Cohort	PCV13 'no vaccination'	AOM incidence A. <2 yo B. 2-4 yo	A.826/1000 B.153/1000	A. 596/1000 B. 265/1000	A. 0.49 (0.41, 0.58) S B. 0.63 (0.52, 0.77) S

*Note: #Submitted by HTAC subcommittee on vaccines*Submitted by proponents; **S**-Significant results; **NS**- non-significant results*

For details, see Appendix A Table 6

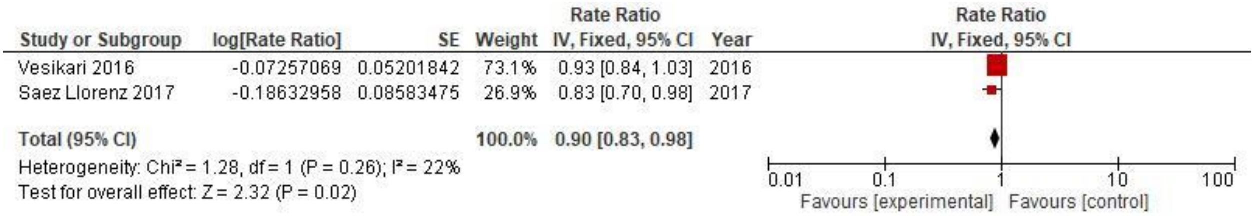

***Figure 4.3.** Reduction of at least one episode of AOM between PCV10 and hepatitis B vaccine (fixed effects model)*

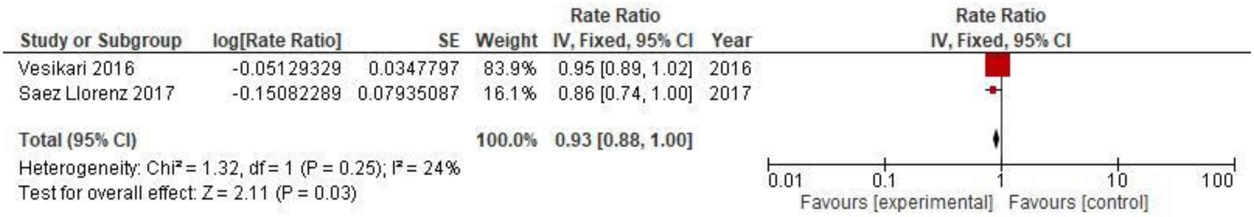

Figure 4.4. *Reduction of all-cause AOM between PCV10 and hepatitis B vaccine (fixed-effect)*

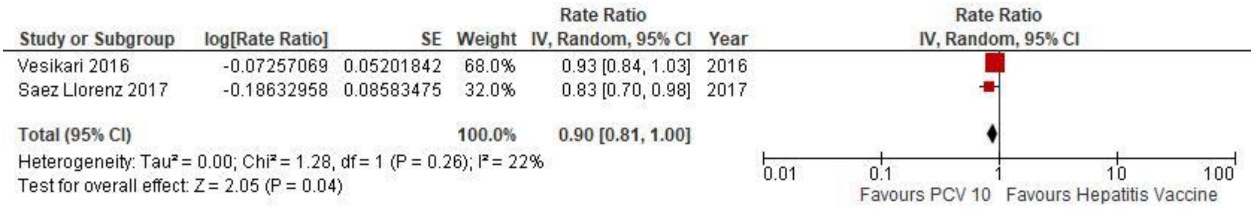

Figure 4.5 *Reduction of at least one episode of AOM between PCV10 and hepatitis B vaccine (random-effects model)*

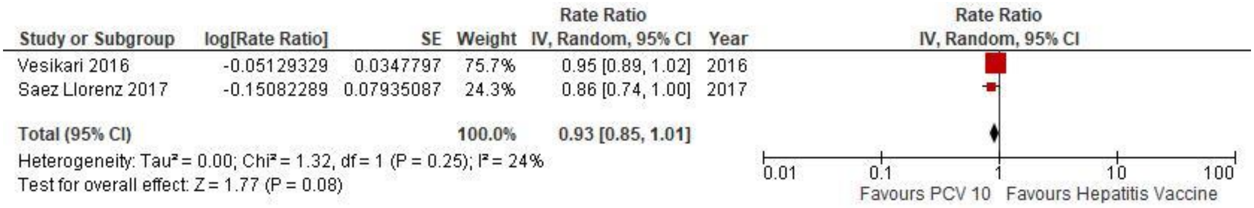

Figure 4.6 *Reduction of all-cause AOM between PCV10 and hepatitis vaccine (random-effects model)*

Vaccine effects on AOM due to serotypes 6A, 19A and 3

A cohort study by Pichichero et al. comparing PCV13 and PCV7 evaluated effects specifically for serotypes 6A, 19A, and 3. Based on the results, the use of PCV13 significantly reduced AOM caused by serotype 19A. The non-significant reduction was observed for serotypes 6A and 3.[20] No studies on PCV10 evaluated its effect on AOM caused by serotypes 6A, 19A, and 3 *(Table 4.8).*

Table 4.8 Identified studies evaluating vaccine effects on acute otitis media specific to serotype 6A, 19A and 3

Author, Year Country (Quality of evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Relative risk (95% CI)
Pichichero, 2018# (Poor)	Cohort	PCV13 PCV7	AOM incidence Serotype 6A	0/53	6/89	0.12 (0.00, 2.23) NS

			AOM incidence Serotype 19A	2/53	36/89	0.09 (0.02, 0.37) S
			AOM incidence Serotype 3	2/53	4/89	0.83 (0.16, 4.43) NS

*Note: #Submitted by HTAC subcommittee on vaccines; **S**-Significant results; **NS**- non-significant results*
For details, see Appendix A Table 7

Immunogenicity studies 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 opsonophagocytic antibody (OPA) titer and proportion of infants who achieved ≥ 1:8 OPA titer which is also correlated to the WHO threshold. Fifteen RCTs measured immunogenic response by determining the proportion of infants who achieving ≥0.35 μg/mL antibody level, and also the geometric mean of IgG concentration of the infants vaccinated as a measure of immunogenicity. Meanwhile, five RCTs measured immunogenicity using the proportion of infants achieving opsonophagocytic antibody titer of ≥1:8 and mean OPA titers. These measures are considered as acceptable methods to evaluate the efficacy and determine the immunological markers as substitute endpoints for clinical protection.[1]

In studies that evaluated IgG concentration and opsonophagocytic antibody titers, overall findings showed that: (1) with serotype 6A and 19A, the immunogenic response induced by PCV13 is significantly higher than PCV10. Although a higher immunogenic response was observed with PCV13 use compared with PCV10, the protective effect of PCV10 cannot be dismissed altogether as infants vaccinated with it also achieved the thresholds; (2) with serotype 3, PCV13 induced significant immunogenic response which is not observed with PCV10.

Immunogenicity studies are acceptable methods to evaluate the efficacy and determine the immunological markers as substitute endpoints for clinical protection. Although this is the case, it is important to note that the achievement of the population-derived threshold (0.35ug/mL IgG concentration) should not be interpreted as a predictor of protection against pneumococcal infection in an individual.

Immunogenicity: Serotype 6A

Serotype 6A: IgG concentration

Based on the study by Pomat et al. which directly compared the immunogenicity of PCV10 and PCV13, the use of PCV13 resulted in a significantly higher proportion of infants achieving the IgG concentration threshold and higher mean IgG concentration.[2]

Payton et al., Amdekar et al., Huang et al., Wechx et al., Kieninger et al., Snape et al., Yeh et al., Esposito et al., and Bryant et al. showed that three doses of PCV13 resulted in a significantly higher proportion of infants with ≥0.35 μg/mL antibody level compared with PCV7.[27-35] Payton et al., Amdekar et al., Huang et al., Wechx et al., Snape et al., Yeh et al., Esposito et al., and Bryant et al. studies also showed that PCV13 resulted in higher mean IgG concentration as compared with PCV7.[27-30, 32-35] Bermal et al. (Philippines), Bermal et al. (Poland) and Wysocki et al. showed that infants vaccinated with PCV10 also achieved the threshold but are considered non-significant when compared with PCV7 while Vesikari et al. showed that PCV10 results in lower proportion of infants achieving the set IgG concentration threshold compared with PCV7 (*Table 4.9*).[24-26] Vesikari et al. also showed that when PCV10 is compared to PCV7, the use of PCV10 resulted in significantly lower mean IgG concentration for serotype 6A (*Table 4.9*).[52]

Table 4.9. *Included studies evaluating vaccine effects on IgG concentration for serotype 6A*

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/ Mean difference (95% CI)^
Pomat, 2018 Papua New Guinea (Good)	PCV 10 PCV 13	% achieving IgG conc. ≥ 0.35 µg/mL	After 4 months: 35.8 (26.5,45.1) S After 9 months: 37.9 (28.36, 40.75) S	After 4 months: 77.5 (69.3,85.6) After 9 months: 64.3. (54.8,73.8)	After 4 months: 2.85 (1.94, 4.19) S After 9 months: 1.74 (1.28, 2.36) S
		IgG GMC	After 4 months: 0.24 (0.21 , 0.29) After 9 months: 0.26 (0.22, 0.30)	After 4 months: 0.85 (0.69,1.04) After 9 months: 0.49 (0.41, 0.60)	After 4 months: -0.61 (-0.79, -0.43) S After 9 months: -0.23 (-0.33,-0.13)S
Bermal 2009 Philippines (Good)	PCV 10 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	45.6 (39.7,51.6)	37.9 (28.1,48.4)	1.20 (0.90,1.60) NS
		IgG GMC	0.30 (0.26,0.35)	0.23 (0.18,0.30)	N/A
Bermal 2009 Poland (Good)	PCV 10 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	30.9 (25.6,36.6)	39.6 (29.7,50.1)	0.78 (0.58,1.06) NS
		IgG GMC	0.17 (0.15, 0.20)	0.26 (0.20,0.33)	N/A
Wysocki, 2009 Germany, Poland, Spain (Low)@	G1: PCV 10 +MenC-CRM G2- PCV 10 +MenC-TT G3- PCV 10 +Hib-MenC G4- PCV 7 +Hib-MenC	% achieving IgG conc. ≥ 0.35 µg/mL	(G1): 41.3 (33.8,49.2) (G2): 33.3 (26.9,35.9) (G3): 28.5 (21.9,35.9)	(G4): 43.4 (35.7,51.3)	G1:G4 0.95 (0.74, 1.22) NS G2:G4 0.76 (0.58,1.00) NS G3:G4 0.65 (0.49, 0.87) S

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/ Mean difference (95% CI)^
		IgG GMC	(G1): 0.24 (0.19,0.29) (G2): 0.18 (0.15, 0.22) (G3): 0.16 (0.13, 0.19)	(G4):.24 (0.19,0.29)	N/A
Vesikari, 2009[&] Finland (Intermediate)	PCV10 PCV7	% achieving IgG conc. ≥ 0.35 µg/mL	9.7 (6.5, 13.8)	19.4 (11.9, 28.9)	1.12 (1.06, 1.18) S
		IgG GMC	0.07 (0.06, 0.08)	19.4 (11.9, 28.9)	-19.33 (-27.83, -10.83) S
Dagan, 2013[#] (Intermediate)	PCV13 PCV7	IgG GMC	2.53	0.36	2.17
Payton, 2013 USA (Good)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	97.3	40.3	57.0 (49.2, 64.5) S
		IgG GMC	2.21	0.28	7.82 (6.75, 9.07) S
Amdekar, 2013 India (Low)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	90.0 (84.9, 93.8)	36.1 (29.3, 43.4)	53.9 (45.4, 61.7) S
		IgG GMC	1.44 (1.25, 1.66)	0.28 (0.25, 0.31)	5.19 (4.33, 6.23) S
Huang, 2012 Taiwan (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	100 (95.5, 100)	77.1 (66.6, 85.6)	0.03 (0.00, 0.44) S
		IgG GMC	4.57 (3.92, 5.34)	0.79 (0.63, 0.99)	3.78 (2.95, 4.61) S
Wechx, 2012 Brazil (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	97.4	52.6	0.05 (0.02, 0.14) S
		IgG GMC	3.52 (3.06, 4.04)	0.39 (0.32, 0.46)	3.13 (2.64, 3.62) S
Kieninger, 2010 Germany (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	91.9 (88.1, 94.8)	31.6 (26.1, 37.5)	0.12 (0.08, 0.18) S
		IgG GMC	1.33 (1.18, 1.49)	0.23 (0.20, 0.26)	1.10 (0.94, 1.26) NS
Snape, 2010 UK (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	98.0 (92.9, 99.8)	71.7 (64.4, 80.6)	0.07 (0.02, 0.29) S

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/ Mean difference (95% CI)^
		IgG GMC	6.27 (5.12, 7.69)	0.87 (0.64, 1.18)	5.40 (4.09, 6.71) S
Yeh, 2010 USA (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	96 (92.8, 98.1)	42.5 (36.2,49)	0.07 (0.04, 0.14) S
		IgG GMC	2.19 (1.93, 2.48),	0.25 (0.21, 0.29)	1.94 (1.66, 2.22) S
Esposito, 2010 Italy (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	99.6 (97.7, 100.0)	86.4 (81.5, 90.5)	13.2 (9.1, 18.1) S
		IgG GMC	6.78 (6.04, 7.61)	1.42 (1.21, 1.66)	4.77 (5.79, 13.93) S
Bryant, 2010 USA (Good)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	96.8 (90.86, 99.33)	34.0 (25.04, 43.80)	0.05 (0.02, 0.15) S
		IgG GMC	2.29 (1.86, 2.82)	0.27 (0.22, 0.33)	2.02 (1.54, 2.50) S

*Note: ^Risk ratio is computed for the proportion of infants achieving IgG threshold; Mean Difference is computed for IgG GMC (geometric mean concentration); #Submitted by HTAC subcommittee on vaccines; &Included in the FDA review; **S**-Significant results; **NS**- non-significant result. @MenC-CRM (Meningitec) or MenC-TT (NeisVac-C) or Hib-MenC-TT (Menitorix) were N. meningetidis conjugate vaccines co-administered with PCV10 in the Wysocki et al.*
For details, see Appendix A Table 8

Serotype 6A: Opsonophagocytic Antibody Titer

One good quality RCT by Temple et al. directly compared PCV10 and PCV13, where PCV13 had a significantly higher proportion of infants achieving OPA titer threshold and overall mean OPA titer.[3] In a study by Vesikari et al., PCV10 resulted in a significantly lower proportion of infants achieving the OPA titer threshold compared to PCV7. However, the same study showed that there is a non-significant difference between PCV10 and PCV7 in terms of the mean IgG concentration.[26] Three studies, Kieninger et al., Yeh et al., and Bryant et al., showed a significantly higher proportion of infants achieving OPA titer threshold and mean OPA titer with PCV13 compared to PCV7 (*Table 4.10*).[31, 33, 35]

Table 4.10 *Included studies evaluating vaccine effects on Opsonophagocytic Antibody Titer against serotype 6A*

Author, Year Country (Quality of evidence)	Vaccine(I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
Temple, 2013* Vietnam	PCV 10 PCV 13	% infants achieving OPA titer ≥ 1:8	66.9 (57.8,75.2)	100 (97,100)	80.34 (5.00, 1291.78) S

Author, Year Country (Quality of evidence)	Vaccine(I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
(Good)		OPA Geometric Mean Titer	118 (74,189)	3847 (3311, 4468)	-3729 (-4310.35, -3147.65) S
Vesikari, 2009[&] Finland (Intermediate)	PCV10 PCV7	% infants achieving OPA titer ≥ 1:8	58.0 (51.7, 64.1)	68.5 57.8, 78.0)	1.83 (1.34, 2.53) S
		OPA Geometric Mean Titer	40.9 (31.4, 53.3)	83.3 (51.6, 134.3)	-42.4 (-85.18, 0.38) NS
Kieninger, 2010 Germany (High)	PCV 13 PCV 7	% infants achieving OPA titer ≥ 1:8	96.0 (90.0, 98.9)	72.0 (61.8, 80.9)	0.14 (0.08, 0.25) S
		OPA Geometric Mean Titer	1228 (883, 1708)	122 (74, 202)	1106 (688.56, 1523.44) S
Yeh, 2010 USA (High)	PCV 13 PCV 7	% infants achieving OPA titer ≥ 1:8	100 (96.2,100)	77.7 (67.9,85.6)	0.01 (0.00, 0.15) S
		OPA Geometric Mean Titer	980 (783,1226)	100 (66,152)	880 (654.36, 1105.64) S
Bryant, 2010 (Moderate)	PCV 13 PCV 7	OPA Geometric Mean Titer	855.6 (485.3,1508.4)	28.6 (12.9,63.6)	827 (314.82, 1339.18) S

Note: *^Risk ratio computed for the proportion of infants achieving OPA threshold; Mean difference computed for OPA GMT (geometric mean titer); *Submitted by proponents; [&]Included in the FDA review;* **S**-*Significant results;* **NS**- *non-significant results*
For details, see Appendix A Table 9

Immunogenicity: Serotype 19A

Serotype 19A: IgG concentration

In the studies identified (n=15, *Table 4.11*), one good quality RCT by Pomat et al. directly compared PCV13 and PCV10 which showed that PCV13 significantly induced higher immune response when compared with PCV10 in terms of the proportion of infants achieving the set IgG concentration threshold and mean IgG concentration on serotype 19A at 4 months after the 3rd dose.[2] However, at 9 months after the 3rd dose, the proportion of infants who achieved the threshold between PCV10 and PCV13 did not differ significantly while the IgG mean concentration is still significantly higher in PCV13 than PCV10.

Bermal et al. (Philippines), Bermal et al. (Poland), and Wysocki et al. for PCV10 showed significant findings in mounting a stronger immune response against serotype 19A versus PCV7.[24, 25] However, one study, Vesikari et al., showed that use of PCV10 did not result in the induction of stronger immune response compared with PCV7 in terms of mean IgG concentration.[26]

Payton et al., Amdekar et al., Huang et al., Wechx et al., Kieninger et al., Snape et al., Yeh et al., and Bryant et al. which evaluated PCV13 showed significant findings in inducing stronger IgG response compared with PCV7 for serotype 19A in terms of the proportion of infants achieving the threshold. Meanwhile, Payton et al., Amdekar et al., Wechx et al., Kieninger et al., Snape et al., Yeh et al., Esposito et al., and Bryant et al. showed that PCV13 resulted in in higher mean IgG concentration compared to PCV7.[23, 27-35] One study by Esposito et al. comparing PCV13 with PCV7 had non-significant results for immunogenic response in terms of the proportion of infants achieving the threshold. On the other hand, the study by Huang et al. showed the same findings in terms of the mean IgG concentration against serotype 19A.[29, 34]

Table 4.11 *Included studies evaluating vaccine effects on IgG concentration for serotype 19A*

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
Pomat, 2018 Papua New Guinea (Good)	PCV 10 PCV 13	% achieving IgG conc. ≥ 0.35 μg/mL	4 months: 89.0% (82.9, 95.1) 9 months: 85.4% (78.5, 92.4)	4 month: 98.0% (95.4,99.5) 9 month: 92.9% (87.8,98.0)	4 months: 3.74 (1.09, 12.88) S 9 months: 2.04 (0.87, 4.79) NS
		IgG GMC	4 months: 0.76 (0.66,0.87) 9 months: 0.85 (0.73,1.00)	4 months: 3.63 (3.00,4.39) 9 months: 1.21 (0.99,1.47)	After 4 months: -2.87 (-3.57, -2.17) S After 9 months: -0.36 (- 0.64, -0.08) S
Bermal 2009 Philippines (Good)	PCV 10 PCV 7	% achieving IgG conc. ≥ 0.35 μg/mL	51.2 (45.3,57.2)	23.2 (15.1,32.9)	2.23 (1.52, 3.27) S
		IgG GMC	0.36 (0.31, 0.41)	0.18 (0.15, 0.22)	N/A
Bermal 2009 Poland (Good)	PCV 10 PCV 7	% achieving IgG conc. ≥ 0.35 μg/mL	43.7 (37.8,49.6)	11.5 (5.9,19.6)	3.81 (2.15, 6.75) S
		IgG GMC	0.29 (0.25,0.34)	0.12 (0.25,0.34)	N/A
Wysocki, 2009 Germany, Poland, Spain (Low)@	G1: PCV 10 +MenC-CRM G2- PCV 10 +MenC-TT	% achieving IgG conc. ≥ 0.35 μg/mL	(G1): 43.1 (35.5,51.0) (G2): 37.6 (30.3,45.2) (G3): 32.2 (25.2,39.7)	(G4): 12.7 (8.0,18.7)	G1: G4 3.34 (2.18, 5.11) S G2: G4 2.91 (1.89, 4.50) S

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
	G3- PCV 10 +Hib-MenC G4- PCV 7 +Hib-MenC				G3: G4 2.50 (1.60,3.91) S
		IgG GMC	(G1): 0.27 (0.22,0.32) (G2): 0.22 (0.19, 0.27) (G3): 0.18 (0.15, 0.22)	(G4): 0.12 (0.1,0.14)	N/A
Vesikari, 2009[&] Finland (Intermediate)	PCV10 PCV7	% achieving IgG conc. $\geq$ 0.35 µg/mL	8.2 (5.3, 12.1)	10.6 (5.2, 18.7)	1.03 (0.99. 1.07) NS
		IgG GMC	0.08 (0.07, 0.09)	0.11 (0.09, 0.13)	-0.03 (-0.05, -0.008) S
Dagan, 2013[#] (Intermediate)	PCV13 PCV7	IgG GMC	1.81	0.70	1.11
Payton, 2013 USA (Good)	PCV 13 PCV 7	% achieving IgG conc. $\geq$ 0.35 µg/mL	98.6	94.4	4.2 (1.1,8.7) S
		IgG GMC	1.91	1.38	1.38 (1.21,1.57) S
Amdekar, 2013 India (Low)	PCV 13 PCV 7	% achieving IgG conc. $\geq$ 0.35 µg/mL	99.5 (97.3,100.0)	84.7 (78.8,89.6)	14.8 (9.9, 20.7) S
		IgG GMC	2.76 (2.46,3.10)	0.74 (0.66,0.82)	3.75 (3.21, 4.38) S
Huang, 2012 Taiwan (High)	PCV 13 PCV 7	% achieving IgG conc. $\geq$ 0.35 µg/mL	100 (95.5, 100)	100 (95.6, 100)	1.06 (0.02,52.92) S
		IgG GMC	3.69 (3.20, 4.24)	2.46 (2.13, 2.84)	1.23 (0.60,1.86) NS
Wechx, 2012 Brazil	PCV 13 PCV 7	% achieving IgG conc. $\geq$ 0.35 µg/mL	99.4	98.7	0.51 (0.05, 5.53) S

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
(High)		IgG GMC	3.63 (3.22, 4.10)	1.83 (1.61, 2.09)	1.80 (1.30, 2.30) S
Kieninger, 2010 Germany (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 μg/mL	99.3 (97.5, 99.9)	79.2 (73.8, 83.9)	0.03 (0.01-0.14) S
		IgG GMC	3.26 (2.97, 3.59)	0.64 (0.58, 0.71)	2.62 (2.30, 2.94) S
Snape, 2010 UK (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 μg/mL	100.0 (96.5, 100.0)	100 (95.9, 100.0)	0.86 (0.02, 42.69) S
		IgG GMC	12.05 (10.01, 14.51)	5.32 (4.41, 6.42)	6.73 (4.27, 9.19) S
Yeh, 2010 USA (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 μg/mL	98.4 (96.0, 99.6)	86.6 (81.6, 90.6)	0.13 (0.05, 0.35) S
		IgG GMC	2.07 (1.87, 2.30)	0.89 (0.79, 0.99)	1.18 (0.94, 1.42) S
Esposito, 2010 Italy (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 μg/mL	100. (98.5, 100.0)	99.6 (97.7, 100.0)	0.4 (-1.1, 2.3) NS
		IgG GMC	9.81 (8.82, 10.92)	4.24 (3.85, 4.67)	2.31 (2.00, 2.67) S
Bryant, 2010 USA (Good)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 μg/mL	100.0 (96.15,100.0)	94.4 (88.19,97.91)	0.09 (0.01, 1.53) S
		IgG GMC	1.84 (1.57,2.16)	1.17 (1.00,1.38)	0.67 (0.32, 1.02) S

Note: *^Risk ratio is computed for the proportion of infants achieving IgG threshold; Mean Difference is computed for IgG GMC (geometric mean concentration); #Submitted by HTAC subcommittee on vaccines; &Included in the FDA review;* **S**-*Significant results;* **NS**- *non-significant results. @MenC-CRM (Meningitec) or MenC-TT (NeisVac-C) or Hib-MenC-TT (Menitorix) were N. meningetidis conjugate vaccines co-administered with PCV10 in the Wysocki et al.*

For details, see Appendix A Table 10

Serotype 19A: Opsonophagocytic Antibody Titer

Five studies that evaluated opsonophagocytic antibody titers for serotype 19A were identified (*Table 4.12*). A good quality RCT by Temple et al., which directly compared PCV13 and PCV10 showed that the use of PCV13 induced a significantly higher proportion of infants reaching the OPA titer threshold and mean OPA titer compared with PCV10.[3] The study by Vesikari et al. which compared PCV10 to PCV7 showed that PCV10 can induce a significantly higher proportion of infants achieving the set OPA threshold and higher mean OPA titer.[26] Kieninger et al., Yeh et al., and Bryant et al. illustrated that PCV13 has significantly higher geometric mean titer for the serotype of interest compared with PCV7.[31, 33, 35] Meanwhile in terms of the proportion of infants who achieved the threshold, Kieninger et al. showed non-significant findings.[31] On the other hand, Yeh et al. showed that the use of PCV13 significantly increased the proportion of infants achieving the set OPA threshold compared with PCV7.[33]

Table 4.12 *Included studies evaluating vaccine effects on Opsonophagocytic Antibody Titer against serotype 19A*

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
Temple, 2013* Vietnam (Good)	PCV 10 PCV 13	% infants achieving OPA titer ≥ 1:8	61.2 (51.9,69.9)	99.2 (95.4,100)	46.61 (6.53, 332.43) S
		OPA Geometric Mean Titer	25 (18,34)	587 (461,748)	-562 (-705.72, -418.28) S
Vesikari, 2009& Finland (Intermediate)	PCV10 PCV7	% infants achieving OPA titer ≥ 1:8	19.6 (15.0, 25.0)	3.4 (0.7, 9.5)	0.83 (0.77, 0.89) S
		OPA Geometric Mean Titer	8.6 (7.1, 10.5)	4.5 (3.9, 5.3)	4.1 (2.26, 5.94) S
Kieninger, 2010 Germany (High)	PCV 13 PCV 7	% infants achieving OPA titer ≥ 1:8	100 (96.2, 100)	17.0 (10.1, 26.2)	0.00 (0.00, 0.03) NS
		OPA Geometric Mean Titer	442 (361, 543)	7 (5, 9)	435 (343.98, 526.02) S
Yeh, 2010 USA (High)	PCV 13 PCV 7	% infants achieving OPA titer ≥ 1:8	91.4 (83.8,96.2)	16.3 (9.4,25.5)	0.10 (0.07, 0.16) S
		OPA Geometric Mean Titer	152 (105,220)	7 (5,8)	145 (87.48, 202.52) S
Bryant, 2010 (Moderate)	PCV 13 PCV 7	OPA Geometric Mean Titer	42.0 (20.1,87.8)	5.2 (3.8,7.1)	36.8 (2.91, 70.69) S

*Note: ^Risk ratio computed for the proportion of infants achieving OPA threshold; Mean difference computed for OPA GMT (geometric mean titer); *Submitted by proponents; &Included in the FDA review;* ***S****-Significant results;* ***NS****- non-significant results*
For details, see Appendix A Table 11

Immunogenicity: Serotype 3

Serotype 3: IgG concentration

In the studies identified (n=11, *Table 4.13*), Pomat et al. showed that PCV13 had a significantly higher proportion of children who achieved the set IgG concentration threshold and overall mean

IgG concentration against serotype 3 when compared with PCV10, four months after receiving the 3rd dose while after 9 months, PCV13 only had an advantage over PCV10 in terms of the proportion of infants achieving the threshold. [2] Payton et al., Amdekar et al., Huang et al., Wechx et al., Kieninger et al., Snape et al., Yeh et al., Esposito et al., and Bryant et al. consistently showed that PCV13 induced significantly stronger IgG response compared with PCV7 for serotype 3, in terms of the proportion of infants who achieved the threshold and overall mean IgG concentration. [27-35] Aside from the study of Pomat et al., there were no other identified studies that evaluated the effect induced by PCV10 on IgG concentration for serotype 3.

***Table 4.13** Included studies evaluating vaccine effects on IgG concentration for serotype 3*

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
Pomat, 2018 Papua New Guinea (Good)	PCV 10 PCV 13	% achieving IgG conc. ≥ 0.35 µg/mL	After 4 months: 45.0% (35.3,54.6) After 9 months: 50.5% (40.6,60.4)	After 4 months: 81.4% (73.8,88.9) After 9 months: 32.7% (23.4,41.9)	After 4 months: 2.96 (1.90, 4.59) S After 9 months: 0.74 (0.58, 0.93) S
		IgG GMC	After 4 months: 0.32 (0.27,0.39) After 9 months: 0.34 (0.28,0.42)	After 4 months: 0.70 (0.60,0.81) After 9 months: 0.29 (0.24,0.36)	After 4 months: -0.38 (-0.50, -0.26) S After 9 months: 0.05 (-0.04, 0.14) NS
Dagan, 2013# (Intermediate)	PCV13 PCV7	IgG GMC	0.97	0.04	0.93
Payton, 2013 USA (Good)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	73.3	3.0	70.3 (65.8, 73.6) S
		IgG GMC	0.56	0.04	14.49 (12.74, 16.48) S
Amdekar, 2013 India (Low)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	87.6 (82.1,91.8)	2.1 (0.6,5.4)	85.4 (79.7, 90.0) S
		IgG GMC	0.80 (0.72, 0.90)	0.05 (0.05,0.06)	15.34 (12.89, 18.25) S
Huang, 2012 Taiwan (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	97.5 (91.3, 99.7)	2.4 (0.3, 8.4)	0.03 (0.01, 0.10) S
		IgG GMC	1.20 (1.00, 1.45)	0.05 (0.04, 0.06)	1.15 (0.92, 1.38) S
Wechx, 2012 Brazil (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	87.1	4.4	0.13 (0.09, 0.20) S
		IgG GMC	0.77 (0.69, 0.86)	0.05 (0.04, 0.06)	0.75 (0.66, 0.84) S

Author, Year Country (Quality of evidence)	Vaccine (I/C)	Outcome measure	Treatment arm	Control arm	Risk ratio/Mean difference (95% CI)^
Kieninger, 2010 Germany (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	98.2 (95.9, 99.4)	6.3 (3.7, 9.8)	0.02(0.01, 0.04) S
		IgG GMC	1.55 (1.41, 1.72)	0.05 (0.04, 0.06)	1.50 (1.34, 1.66) S
Snape, 2010 UK (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	88.2 (80.4, 93.8)	6.6 (2.5, 13.8)	0.13 (0.07, 0.21) S
		IgG GMC	1.01 (0.83, 1.22)	0.07 (0.05, 0.09)	0.94 (0.74, 1.14) S
Yeh, 2010 USA (High)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	63.5 (57.1, 69.4)	4.6 (2.3, 8.0)	0.38 (0.32, 0.45) S
		IgG GMC	0.49 (0.43, 0.55)	0.04 (0.03,0.04)	0.45 (0.39, 0.51) S
Esposito, 2010 Italy (High)	PCV 13 PCV 7	% infants achieving IgG conc ≥ 0.35 µg/mL	93.9 (90.1, 96.5)	6.7 (3.9, 10.6)	87.2 (82.1, 91.2) S
		IgG GMC	1.22 (1.09, 1.35)	0.07 (0.06, 0.08)	16.83 (13.93, 20.35) S
Bryant, 2010 USA (Good)	PCV 13 PCV 7	% achieving IgG conc. ≥ 0.35 µg/mL	98.9 (94.21,99.97)	14.0 (8.06, 22.07)	0.01 (0.00, 0.09) S
		IgG GMC	1.33 (1.16, 1.54)	0.09 (0.07,0.12)	1.24 (1.05, 1.43) S

Note: ^Risk ratio is computed for the proportion of infants achieving IgG threshold; Mean Difference is computed for IgG GMC (geometric mean concentration); #Submitted by HTAC subcommittee on vaccines; &Included in the FDA review; ***S****-Significant results;* ***NS****- non-significant results*

For details, see Appendix A Table 12

Serotype 3: Opsonophagocytic Antibody Titer

Temple et al., Kieninger et al., Yeh et al., and Bryant et al. evaluated opsonophagocytic antibody titers for serotype 3 (*Table 4.14*). The results of these studies showed that compared with PCV10 and PCV7, the use of PCV13 resulted in a significantly higher proportion of infants achieving OPA titer of ≥1:8. PCV13 also induced a higher mean OPA titer compared with PCV10 and PCV7. [3, 31, 33, 35]

Table 4.14 *Included studies evaluating vaccine effects on opsonophagocytic antibody titer against serotype 3*

Author, Year Country (Quality of Evidence)	Vaccine (I/C)	Outcome measure	Treatment Arm	Control Arm	Risk Ratio/Mean Difference (95% CI)^
Temple, 2013* Vietnam (Good)	PCV10 PCV13	% infants achieving OPA titer ≥ 1:8	3.3 (0.9 to 8.2)	88.3 (81.2 , 93.5)	8.29 (5.06, 13.58) S
		OPA Geometric Mean Titer	4 (4 to 5)	54 (43, 68)	-50 (-632.51, -37.49) S
Kieninger, 2010 Germany (High)	PCV13 PCV7	% infants achieving OPA titer ≥ 1:8	99.0 (94.6, 100)	24.5 (16.2, 4.4)	0.01 (0.00, 0.04) S
		OPA Geometric Mean Titer	251 (206, 306)	6 (5, 7)	245 (194.99, 295.01) S
Yeh, 2010 USA (High)	PCV13 PCV7	% infants achieving OPA titer ≥ 1:8	96.8 (91.0, 99.3)	21.3 (13.5, 30.9)	0.04 (0.02, 0.09) S
		OPA Geometric Mean Titer	121 (92, 158)	7 (5, 9)	114 (80.94, 147.06) S
Bryant, 2010 (Moderate)	PCV 13 PCV 7	OPA Geometric Mean Titer	10.9 (7.8, 15.2)	4.1(3.9, 4.3)	6.8 (3.09, 10.51) S

*Note: ^Risk ratio computed for the proportion of infants achieving OPA threshold; Mean difference computed for OPA GMT(geometric mean titer); *Submitted by proponents;* ***S****-Significant results;* ***NS****- non-significant results*
For details, see Appendix A Table 13

Nasopharyngeal carriage The effectiveness of PCV in lowering nasopharyngeal carriage is indirect evidence of effectiveness through the reduction of transmission of *S. pneumoniae*. Evidence which evaluated the effect of PCV10 and PCV13 on nasopharyngeal carriage of *S. pneumoniae* showed that both vaccines are effective in decreasing carriage of their ten shared serotypes compared with 'no vaccination' or hepatitis B vaccine. On the other hand, serotype-specific studies showed that PCV13 use reflected a decreased carriage of serotypes 6A and 19A.

Vaccine effects on nasopharyngeal carriage of the ten shared serotypes

Five studies were identified which evaluated vaccine-type *S. pneumoniae* carriage (*Table 4.15*). The study by Saez Llorenz et al. showed that PCV10 had significantly lower nasopharyngeal carriage compared with hepatitis B vaccine.[17] On the other hand, Heinsbroek et al. showed that PCV13 was associated with significantly lower nasopharyngeal carriage compared with 'no vaccination'.[60] According to Bosch et al., Kaur et al., and Dagan et al., when PCV10 or PCV13 was compared with PCV7, both vaccines did not significantly lower nasopharyngeal carriage.[21-23]

Table 4.15 *Identified studies evaluating vaccine effects on nasopharyngeal carriage*

Author, Year Country (Quality of Evidence)	Study design	Vaccine (I/C)	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)
Saez Llorenz, 2017 Panama (Poor)	RCT	PCV 10 Hepatitis B vaccine	% colonization	11.7 (9.5, 14.1)	15.7 (13.2, 18.4)	0.74 (0.58, 0.96) S
Bosch, 2015 Netherlands (Poor)	Cohort	PCV 10 PCV 7	% colonization	11 months: 193/330 (59%) 2 yo: 211/330 (64%)	11 months: 173/330 (52%) 2 yo: 185/330 (56%)	11 months: 1.12 (0.97, 1.28) NS 2 yo: 1.46 (1.26, 1.68) S
Heinsbroek, 2018 Malawi (Poor)	Cohort	PCV 13 'no vaccination'	% colonization	22/44 (50.0%)	53/71 (74.7%)	0.67 (0.48, 0.93) S
Kaur, 2016 USA (Poor)	Cohort	PCV 13 PCV 7	% colonization	685/2044 (33.5%)	350/1072 (32.7%)	1.03 (0.92, 1.14) NS
Dagan, 2013# Israel (Intermediate)	RCT	PCV13 PCV7	New NP Acquisition	N/A	N/A	1.00 (0.96, 1.04) NS

Note: *N/A- not reported; #Submitted by HTAC subcommittee on vaccines;* ***S****-Significant results;* ***NS****- non-significant results*
For details, see Appendix A Table 14

Vaccine effects on nasopharyngeal carriage of serotypes 6A, 19A and 3

Saez Llorenz et al. showed that PCV10 did not significantly lower the nasopharyngeal carriage of serotypes 6A and 19A compared with the hepatitis B vaccine.[17] Meanwhile, Dagan et al., which compared PCV13 to PCV7 showed that PCV13 significantly reduced nasopharyngeal carriage of serotypes 6A and 19A but not serotype 3 *(Table 4.16)*. [23]

Table 4.16 *Studies evaluating vaccine effect on nasopharyngeal carriage against serotype 6A, 19A and 3*

Author, Year Country (Quality of Evidence)	Study Design	Vaccine (I/C)	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)
Saez Llorenz, 2017 Panama (Poor)	RCT	PCV 10 Hepatitis B vaccine	% Colonization **(6A)**	5.2 (3.8, 7.0)	5.0 (3.6, 6.7)	1.05 (0.68, 1.60) NS
			% Colonization **(19A)**	2.2 (1.3, 3.4)	1.1 (0.5, 2.2)	1.88 (0.84, 4.19) NS

Dagan, 2013# Israel (Intermediate)	RCT	PCV13 PCV7	New NP acquisition **(6A)**	63/881	106/873	0.58 (0.43, 0.78) S
			New NP acquisition **(19A)**	105/881	190/873	0.55 (0.44, 0.68) S
			New NP acquisition **(3)**	16/881	16/873	0.99 (0.48, 2.06) NS

*#Submitted by HTAC subcommittee on vaccines; **S**-Significant results; **NS**- non-significant results*
For details, see Appendix A Table 15

Two-dose effects This review focused on the effects of three doses of PCV since the NIP uses a 3+0 vaccination schedule. Two dose effects were presented as well to gauge possibilities in the actual setting (*Table 4.17*).

One RCT by Snape et al. which compared PCV13 to PCV7 showed that infants vaccinated with 2 doses of PCV13 resulted in a significantly higher proportion of infants reaching the IgG concentration of ≥0.35 ug/mL for serotype 3, 6A, and 19A.[32] Infants vaccinated with PCV13 had significantly higher mean IgG concentrations for serotype 6A and 3 while the mean IgG concentration for 19A induced by PCV13 and PCV7 were not significantly different. No studies on immunogenicity measured the effect of two doses of PCV10.

A poor-quality study on IPD conducted by Domingues et al. which compared PCV10 to 'no vaccination' showed that two doses of PCV10 significantly reduced overall IPD incidence.[6] Vesikari et al. showed that PVC10 did not significantly reduce the incidence of AOM compared to hepatitis B vaccine.[18]

Table 4.17 *Included studies evaluating the effect of PCV after 2 doses*

Study, Year Country (Quality of Evidence)	Vaccine (I/C)	Outcome	Outcome measure	Treatment Arm	Control Arm	Risk Ratio/Mean Difference (95% CI)^
Vesikari, 2016 (Good)	PCV 10 Hepatitis B vaccine	Acute Otitis media	Vaccine effectiveness in reducing the number of children reporting ≥1 AOM episode	327/917	485/1291	0.89 (0.80, 1.00) NS
Domingues, 2014*& Brazil (Poor)	PCV10 'no vaccination'	Vaccine type IPD	A. Cases for IPD B. Control for IPD	Cases: 34/316 (115) Control: 173/1219 (14%)	Cases: 129/1219 (41%) Control: 304/1219 (25%)	0.55 (0.39, 0.77) S
Snape, 2010 UK (High)	PCV13 PCV7	Immunogenicity 6A	% achieving IgG conc. ≥ 0.35 µg/mL	79.2 (70.3, 86.5)	12.0	0.24 (0.16,0.34) S

Study, Year Country (Quality of Evidence)	Vaccine (I/C)	Outcome	Outcome measure	Treatment Arm	Control Arm	Risk Ratio/Mean Difference (95% CI)^
					(6.4, 20.0)	
			IgG GMC	0.86 (0.68, 1.07)	0.14 (0.11, 0.16)	0.72 (0.52, 0.92) S
		Immunogenicity 19A	% achieving IgG conc. ≥ 0.35 μg/mL	92.7 (86.2, 96.8)	88.9 (81.0, 94.3)	0.65 (0.27, 1.56) S
			IgG GMC	1.9 (1.54, 2.34)	0.92 (0.77, 1.11)	0.98 (0.55, 1.41) NS
		Immunogenicity 3	% achieving IgG conc. ≥ 0.35 μg/mL	86.0 (77.9, 91.9)	2 (0.2, 6.9)	0.14 (0.09, 0.23) S
			IgG GMC	0.63 (0.56, 0.71)	0.04 (0.03 0.05)	0.59 (0.51, 0.67) S

Note: *^Risk ratio- % infants achieving IgG threshold, IPD, AOM; Mean difference- IgG GMC; &Included in the FDA review;* ***S****- Significant results;* ***NS****- non-significant results*
For details, see Appendix A Table 16.

4.4.3 Risk of bias assessment

Systematic reviews

For the quality assessment of the SRs, only domain 1, a non-critical domain (*review question included components of PICO*) achieved 100% compliance among all the studies. Domain 7 (*provide a reason for exclusion of studies*) and 16 (*reported potential sources of conflict of interest*) achieved a high level of compliance at 85.71%, both of which are critical domains. Domain 14, a non-critical domain, (*investigated and discussed heterogeneity*) also had relatively high compliance with 84.62% of the studies which complied. Domains 4 (*use of comprehensive literature search*) and 10 (*critical- indicated funding source of the included studies*) had the poorest compliance, with only 28.57% of the studies complying with these two domains. Of these two, only domain 4 is critical.

From the 14 SRs included, five were assessed for meta-analysis-specific domains (Domain 11, 12, and 15, all non-critical). Only domain 11 (*used appropriate statistical method for combination of results*) had a high degree of compliance at 80%. Compliance with domains 12 (*discussed implication of risk of bias assessment on the result of the meta-analysis*) and 15 (*reported publication bias*) was low at 40% and 16.67%, respectively.

Overall, two out of the 14 systematic reviews were of high quality, one of moderate quality, and 11 were of critically low quality (*Appendix B, Table 1*).

Individual studies

Randomized clinical trials

For the risk of bias assessment of randomized controlled trials, domain 1 (random sequence generation) and domain 6 (selective reporting) achieved a high degree of compliance at 94.74%. Majority of the domains achieved at least 50% compliance, except domain 7 (other sources of bias), with only 15.79% of studies being able to comply. The other source of bias identified is the sponsorship of the RCTs by the manufacturers of the vaccines under study. Out of the 19 RCTs included, seven were graded as high quality, nine were intermediate quality, and three were considered as low-quality evidence (*Appendix B, Table 2*).

Cohort studies

Overall, only four out of 14 cohort studies included were graded as having good quality evidence. The remaining 10 cohort studies were deemed to have poor-quality evidence mainly due to failure to comply with domain 5 (comparability of the cohorts in consideration) and 2 (selection of non-exposed cohorts) *(Appendix B, Table 3).*

Case-control

All case-control studies included were graded to have poor-quality evidence. This is due to failure to comply with domain 5 (comparability of the cases and the controls). This is because most of the studies were time-series, limiting the comparability of the cases and controls. All of the case-control studies complied with the rest of the domains except domain 8 (non-response rates), in which one out of the three studies did not comply (*Appendix B, Table 4*).

4.5. Conclusion

From the observational and time-series studies included in this review, the overall evidence showed that both PCV10 and PCV13 were effective in reducing the incidence of overall IPD and clinical pneumonia when compared with PCV7, other vaccines, or 'no vaccination'. In terms of reducing the burden of AOM and NP carriage, both PCV10 and PCV13 were effective compared with 'no vaccination' or hepatitis B vaccine.

RCTs which evaluated the effect of PCV10 on IPD, pneumonia, and AOM showed that PCV10 is efficacious in reducing the incidence of these pneumococcal infections compared with hepatitis B vaccine.

The body of evidence considered in this review did not show a clear significant difference in the vaccine impact on the overall IPD burden between PCV10 and PCV13 due to the three additional three serotypes 3, 6A, and 19A. There was also inconsistency in findings across studies with regard to the impact on pneumonia and AOM incidence caused by the three additional serotypes of PCV13. This may be attributed to inherent limitations/ weaknesses found in the studies as well as their heterogeneity (e.g., varying study designs, small sample sizes, different follow-up periods), as well as the probable differences in baseline risks across different settings and populations. It should also be noted that there may be varying patterns of serotype distribution across countries, including the Philippines.

5. COST UTILITY AND BUDGET IMPACT ANALYSES

5.1. Objectives

5.1.1. To determine whether either PCV represents good value for money in the Philippines in terms of preventing mortality and morbidity due to IPD, clinical pneumonia, and AOM for infants.
5.1.2. To determine the budgetary requirement of including either PCV10 or PCV13 on the Expanded Program on Immunization (EPI) and the Philippine Health Insurance Corporation (PhilHealth) benefits programs.

5.2. Research Questions

5.2.1 Does PCV represent good value for money in the Philippines for preventing mortality and morbidity due to IPD, clinical pneumonia, and AOM for infants?
5.2.2 What is the budget implication of using either PCV10 or PCV13 in EPI and PhilHealth benefits?

5.3. Methodology

5.3.1. Cost-utility analysis

This cost-utility analysis applied the reference case in the *Philippine HTA Methods Guide*. A Markov model was used to calculate and compare the costs and health outcomes of (a) PCV13 versus 'no vaccination' (b) PCV10 versus 'no vaccination' and (c) PCV10 versus PCV13. The population of interest was 90% of the birth cohort of the year 2020 who would receive three doses of either PCV vaccine in the same year. Furthermore, the government perspective was taken to gauge the costs associated with PCV, while measurement of health outcomes was through quality-adjusted life years (QALY) gained. A lifetime horizon with a discounting rate of 7% per annum was employed for both costs and outcomes.

Results were presented as incremental cost-effectiveness ratios (ICER)—the ratio of additional vaccination and treatment costs to additional QALYs.[61, 62]

Several scenarios were explored in this study. We used a base case scenario of 50% coverage without herd effects since it best reflects the current vaccination coverage that ranges from 30 to 60% across regions in the country. Literature suggests that herd effects can be achieved if at least 80% of the target population is vaccinated.[12] With this coverage, an additional scenario incorporating herd effects was also evaluated given that the ideal target vaccination coverage is 90% of the birth cohort.

The budgetary requirement of covering either PCV10 or PCV13 was also assessed for fiscal years 2020-2024 based on the governmental perspective (i.e., costs incurred by the NIP and treatment cost incurred by the PhilHealth).

Economic model

Markov model is one of the most common modeling approaches to estimate long-term costs and effects in economic research. In this reassessment, we used the economic model previously used in the DOH-led PCV assessment developed by Kulpeng et al.[36] The model was revalidated by clinical and economic experts, where minor modification was done to consider both mild and severe cases of AOM (*see Figure 5.1*).[36] A cycle length of one year for 99 cycles was applied to represent a lifetime horizon. The model applies the following key assumptions:

1. The infant would receive a complete three-dose schedule to achieve intended effects.
2. PCV10 is cross-reactive on serotype 19A, hence effective for clinical outcomes evaluated.

3. In the model, vaccine effectiveness (VE) was estimated using RCTs of PCV10 compared with hepatitis B vaccine as control, while the incremental effect of PCV13 was adjusted based on the additional serotype coverage for serotypes 3 and 6A. PCV10 and PCV13 effects on the rest of the serotypes were assumed equal.
4. PCV10 vaccine effectiveness on AOM against H. *influenzae* was not considered since the only clinical trial estimating the benefits of PCV10 on reducing at least one case of clinically diagnosed AOM against H. *influenzae* did not illustrate significant effects [RR: 0.84 (95% CI: 0.44, 1.58), P = 0.5526].[17]
5. The duration of PCV protection is five years, with or without herd immunity. Herd immunity is gained on the assumption that 80% of the target population is vaccinated.
6. Only one type of infection can occur per year, though more than one infection may occur in the time horizon assessed. Long-term sequelae could only occur once in patients aged <15 years.

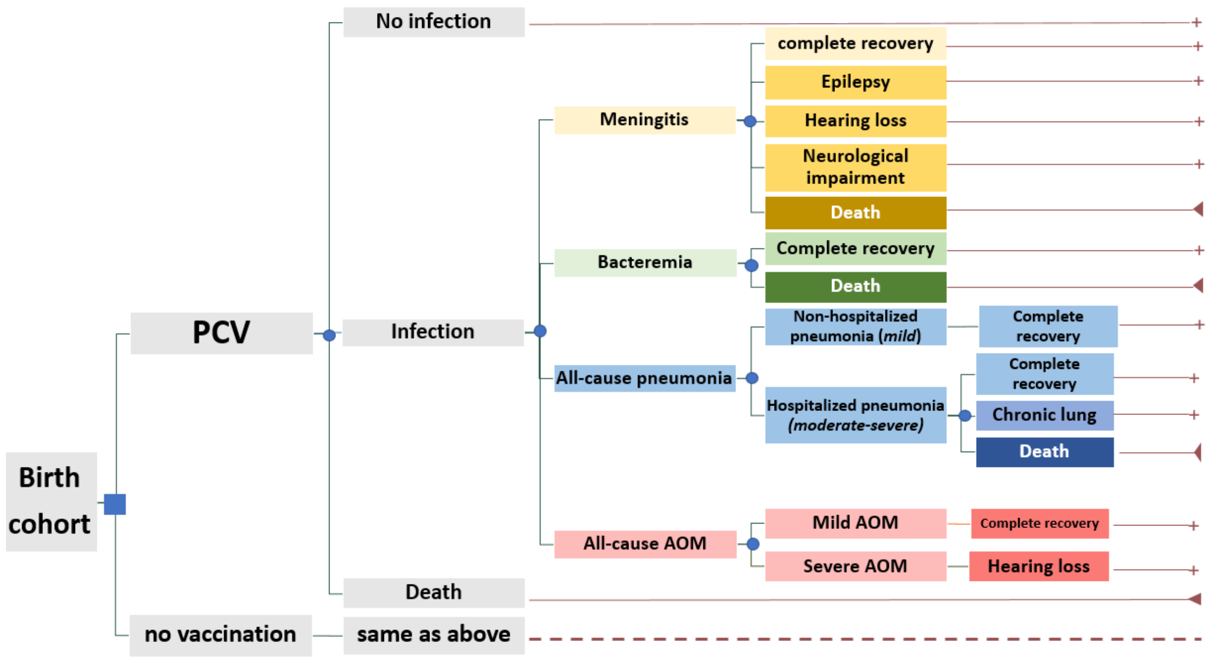

Figure 5.1. *The economic model used for assessing the health and economic impact of pneumococcal conjugate vaccine (PCV) vaccination compared with 'no vaccination'*

Epidemiologic parameters

This model was populated with input parameters found in *Table 5.2*. The epidemiologic, cost, and utility input parameters were validated by clinical and economic experts.

Incidence Philippine-specific data on the incidence of pneumococcal meningitis, bacteremia, and sepsis across all age groups were taken from anonymized insurance claims obtained from the PhilHealth. Incidence was derived from the ratio of the average hospital claims for 2017-2019 over the estimated population per age group (*Table 5.2*). Standard errors were computed based on the difference in incidence for 2017-2019.

Two incidence parameters were derived from surveillance studies. Hospitalized pneumonia incidence for children less than 5 years old was derived from a community survey in Biliran last June 2011-May 2012, where the incidence of severe-pneumonia-like episodes was considered as incidence for hospitalized pneumonia.[75] All-cause AOM incidence was derived from a local study that determined the prevalence of clinically diagnosed otitis media in the Philippine community setting.[61] According to global estimates, AOM occurs regularly in younger age groups.[62] With this, it was assumed that none of the cases were severe enough to require hospitalization in people aged 50 and above or to cause death. Thus, the incidence of AOM was assumed to be zero for individuals 12 years or older.

Transition probabilities We derived most of the transition probabilities from local studies.[40] Two parameters were derived from other countries since local data were not available: (a) China for necrotizing pneumonia; [67] (b) Indonesia for hearing loss after AOM.[68]

Serotype prevalence Data on the distribution of serotypes in IPD was taken from three laboratory-based surveillance of RITM from 2012 to 2019 (Appendix D). These surveillances collected isolates across all age groups, and it was confirmed that no overlap occurred among the laboratories. A total of 536 IPD isolates were collected with the following isolates collected per laboratory:

(a) *Antimicrobial Resistance Surveillance Reference Laboratory (ARSP)*—collected 385 *S. pneumoniae* isolates from 2012 to 2019, which are from blood or cerebrospinal fluid.
(b) *Acute Meningitis Encephalitis Surveillance of Philippine Integrated Disease Surveillance and Response (PIDSR)*—gathered 29 isolates from 2015 to 2018 from 9 sentinel hospitals across the country.
(c) *Department of Microbiology of RITM*—collected 122 isolates from 2012 to 2019 nationwide.

Vaccine-type IPD coverage of PCV10 and PCV13 was computed for different age groups (Appendix D). Standard errors were computed based on the difference in isolates among the three laboratories.

Vaccine effectiveness Vaccine effectiveness (VE) of PCV10 and PCV13 has been shown in various settings. Based on the rapid review conducted, only immunogenic studies (n=2) directly compared PCV13 and PCV10.[2, 3] Since these were surrogate outcomes, these studies cannot be used as references for vaccine efficacy.

Moreover, since there is a lack of evidence of efficacy data for the 3+0 schedule implemented by the NIP, we based VE of PCV10 on studies that used a 2-dose primary series plus a booster dose (2+1). Given that the Philippine FDA has acknowledged cross-reactivity of PCV10 against serotype 19A as an approved indication of use in the country, cross-reactivity for PCV10 on serotype 19A was incorporated in the base-case scenario, modeling the effects of the vaccine for the final clinical outcomes IPD, pneumonia, and AOM. We referred to the following RCTs for VE of PCV10 against the specific outcomes:

(a) ***IPD.*** 2013 Finnish Invasive Pneumococcal Disease (FinIP) vaccine trial for PCV10 Vaccine efficacy of PCV10 against vaccine-type IPD was assumed to be 92%.[4]
(b) ***Pneumonia.*** Since only one good quality RCT and one poor-quality cohort study were identified from the rapid review, the vaccine efficacy against pneumonia was based on a 2018 follow-up study to the FinIP trial for PCV10.[15]
(c) ***AOM.*** Two studies compared PCV10 versus hepatitis B vaccine in reducing clinically diagnosed AOM (C-AOM) post-vaccination. These two studies differed in the dosing schedule – 3+1 schedule; 2+1 schedule. [17, 18] Vaccine effectiveness of PCV10 against C-AOM in at least one episode resulted in an incidence rate ratio of 0.90 (95% CI: 0.83, 0.98). The result of the meta-analysis was the basis for the vaccine efficacy of PCV10 against AOM.

From the 2013 PCV assessment, the references for vaccine efficacy were updated based on the rapid review conducted. Given the lack of RCTs that assessed PCV13, vaccine efficacy related to its use was extrapolated using serotype coverage of PCV13 relative to PCV10, based on local seroprevalence data provided by RITM. Computations can be found in Appendix E.

Herd protection The possibility of acquiring herd immunity among the unvaccinated population was also tested. Herd protection was assumed to occur when the PCV vaccination coverage rate of 80% is achieved.[65] Herd effects among unvaccinated individuals on IPD infections were based on the results of a meta-analysis testing the effect of PCV13 in decreasing IPD incidence by Shiri et al.[71] The study concluded that population PCV programs will lead, on average, to substantial protection across the whole population within a decade. This was based on 2,420 observational studies that reported IPD changes following PCV introduction in unvaccinated populations, which cover 27 high-income and seven middle-income countries. From this study, herd immunity effects were adjusted using local serotype coverage. This study considered herd protection for pneumococcal meningitis, bacteremia/sepsis, and pneumonia across all age groups.

We extrapolated data from IPD to estimate herd effects on pneumonia cases among unvaccinated populations. It was assumed that pneumonia incidence decreases proportionally to the IPD fall computed for the respective age groups. Pneumonia incidence was computed by multiplying the incidence of pneumonia requiring hospitalization and the proportion of hospitalized patients due to *S. pneumoniae*. Meanwhile, the herd effect for AOM was not estimated.

Costs input In general, all costs and resource use inputs were obtained from either public sources available locally or international health economic literature, which could best reflect the Philippine setting. The costs taken into consideration were:

Vaccine implementation cost

(a) Acquisition cost. In 2020, single-dose (SDV) and multiple-dose vials (MDV) of PCV10 and PCV13 were offered to the Philippine government. Costs per dose of MDVs for both vaccines were significantly lower than those of the quoted price for the SDV at the time of the previous analysis (2014). The vaccine price offers submitted by the proponents were in USD and were converted to Philippine Peso (PHP) using the exchange rate on April 21, 2020 and were adjusted with 12% value-added tax (VAT).

During the appeals period of this assessment, vaccine manufacturers submitted new price quotations, which were then incorporated in the final analysis to determine the impact on the ICERs and the potential budget impact on the government.

(b) Vaccine wastage. We referred to the WHO recommendations on vaccines with a single dose presentation for vaccine wastage. An added cost of 5% based on vaccine price for each dose was incorporated. Using MDVs would result in 10% wastage according to the NIP.[67]

(c) Vaccine storage. The NIP was consulted to account for vaccine storage costs. For SDVs, an additional 8% based on vaccine price was considered to account for storage cost, while an additional 4% was considered to account for MDVs since the number of vials would be reduced.

Treatment cost

Insurance claims data from 2019 provided by PhilHealth were used to calculate the treatment cost of disease sequelae. The WHO ICD-10 codes were used as a reference to extract the total medical cost for each disease presentation. Moreover, actual costs from both government and private hospitals were considered, where utilization rates were computed by estimating the proportion of the number of claims in government and private facilities. Standard errors were computed based on the difference in costs per age group. We converted these cost values to 2020 values using the Philippine Consumer Price Index.[68]

The costs for non-hospitalized pneumonia and mild AOM cases were determined through an expert panel consultation. The only cost item considered was antibiotic treatment. Professional fees were excluded since, given a government perspective, it is assumed that the patient would go to Rural Health Units (RHUs) and therefore, would not incur professional fees. To update costs, we referred to the course of treatment in the National Antibiotic Guidelines. The cost was calculated using the ceiling prices for government bidding and procurement set by the DOH.[41, 69]

Utility values Due to the absence of local utility parameters, Thai values using the Health Utilities Index Mark 3 were adopted.[36]

Uncertainty analysis

Policy scenarios A vaccination coverage scenario of 50% was assessed to account for the current vaccination coverage of PCV13 in selected regions of the Philippines. This scenario also reflects the coverage if only the two poorest quintiles of the population were prioritized for vaccination. The base-case scenario or the "best estimate scenario" considered no herd effect using multiple-dose vial (MDV) since the NIP has expressed intent in implementing this preparation. The use of SDV was also evaluated in case of a short supply of MDV preparations.

The scenario of 90% vaccination coverage of the birth cohort was also assessed. This accounts for ideal vaccination coverage in the universal implementation of PCV. Based on the interview with DOH program managers, this is the current NIP coverage with other vaccines since it is estimated that 10% of the population goes to private facilities. In this given scenario, herd immunity was considered since a vaccination coverage rate of at least 80% is achieved.[65]

***Table 5.1**. Policy scenarios used in PCV economic evaluation*

Scenario	Vaccination coverage	Parameters applied
Scenario 1	50% coverage	MDV; without herd immunity
Scenario 2	50% coverage	SDV; without herd immunity
Scenario 3	90% coverage	MDV; with herd immunity
Scenario 4	90% coverage	SDV; with herd immunity

Probabilistic analysis Probabilistic sensitivity analysis was conducted through Monte Carlo simulation with 1,000 iterations using Microsoft Office Excel 2010. Cost-effectiveness acceptability curves were generated to illustrate the cost-effectiveness of interventions at different ICER thresholds.

One-way sensitivity analysis Changes in ICER values using MDV preparations and a policy scenario assuming no herd immunity as a reference were also identified to explore the robustness of results to variations in parameter uncertainties and key assumptions. This includes (1) discount rate at 3% and 10% per annum, (2) PCV10 including effectiveness on serotypes 6A and excluding serotype 19A, (3) exclusion of protection of serotype 3 for PCV13, (4) inclusion of herd immunity; (5) procurement cost using higher market prices and SDV price. The results from the one-way sensitivity analyses were shown through a tornado diagram, graphing sequentially the variables with the largest impact on the cost-utility results.

Table 5.2 *Input parameters used in the model*

Parameters	Age	Distribution	Mean	SE	References
Incidence					
Pneumococcal (pn) meningitis in age *G00.1, G00.2, G00.9, G03.8, G03.9*	0-4	Beta	0.00004	0.000002	PhilHealth, 2019
	5-9	Beta	0.00001	0.000000	PhilHealth, 2019
	10-24	Beta	0.00001	0.000001	PhilHealth, 2019
	15-24	Beta	0.00001	0.000000	PhilHealth, 2019
	25-34	Beta	0.00001	0.000001	PhilHealth, 2019
	35-44	Beta	0.00000	0.000000	PhilHealth, 2019
	55-64	Beta	0.00001	0.000000	PhilHealth, 2019
	> 65	Beta	0.00001	0.000000	PhilHealth, 2019
Bacteremia and sepsis in age *P36.1, P36.8, P36.9, A40.3, A40.8, A40.9, A41.8, A41.9*	0-4	Beta	0.00124	0.000090	PhilHealth, 2019
	5-19	Beta	0.00019	0.000018	PhilHealth, 2019
	20-49	Beta	0.00026	0.000023	PhilHealth, 2019
	50-64	Beta	0.00117	0.000091	PhilHealth, 2019
	> 65	Beta	0.00464	0.000339	PhilHealth, 2019
All-cause pneumonia by age *J12-J15, J18*	0-5	Beta	0.05220	0.000426	[75]
	6-18	Beta	0.00034	0.000022	PhilHealth, 2019
	19-49	Beta	0.00004	0.000003	PhilHealth, 2019
	> 50	Beta	0.00027	0.000026	PhilHealth, 2019
Acute otitis media in age	0-12	Beta	0.09570	0.019140	[61]
Transition probabilities					
Epilepsy after pn meningitis		Beta	0.0364	0.0013	Phil 2007-2010/ [71]
Hearing loss after pn meningitis		Beta	0.0218	0.0063	Phil 2007-2010/ [71]
Neurodevelopmental impairment after pn meningitis		Beta	0.0473	0.0384	Phil 2007-2010/ [71]
Death after pn meningitis		Beta	0.1290	0.0258	Phil 2007-2010/ [71]
Death after pn bacteremia and sepsis		Beta	0.4000	0.1477	[40]
Necrotizing pneumonia after pn pneumonia		Beta	0.2683	0.0537	China [63]
Proportion of hospitalized pneumonia due to *S. pneumoniae*		Beta	0.1047	0.0224	Phil 2010-2012, [72]
Death after hospitalized pneumonia		Beta	0.047	0.0704242	Phil 2008-2016/ [78]
Hearing loss after AOM		Beta	0.2000	0.0864	Indonesia [68]
Vaccine efficacy (Direct effects)					

Parameters	Age	Distribution	Mean	SE	References
PCV10 VE in IPD		Gamma	46.43%	10.71%	4
PCV10 VE in pneumonia		Beta	28.00%	7.14%	15
PCV10 VE in AOM		Beta	10.00%	3.83%	17, 18
PCV13 VE in IPD		Gamma	53.81%	10.71%	4
PCV13 VE in pneumonia		Beta	32.45%	7.14%	15
PCV13 VE in AOM		Beta	11.59%	3.83%	17, 18
Herd immunity effects					
PCV 10 Herd effects in IPD	5-18	Beta	10.82%	3.83%	71 RITM 2012-2019
	19-48	Beta	8.75%	4.85%	
	49-65	Beta	9.59%	3.06%	
	<65	Beta	10.03%	1.28%	
PCV 13 Herd effects in IPD	5-18	Beta	12.67%	3.83%	
	19-48	Beta	9.69%	4.85%	
	49-65	Beta	13.54%	3.06%	
	<65	Beta	14.15%	1.28%	
PCV 10 Herd effects in pneumonia	5-18	Beta	0.68%		RITM 2012-2019[72]
	19-48	Beta	0.55%		
	49-65	Beta	0.60%		
	<65	Beta	0.63%		
PCV 13 Herd effects in pneumonia	5-18	Beta	0.60%		
	19-48	Beta	0.63%		
	49-65	Beta	0.85%		
	<65	Beta	0.89%		
Costs input (in PHP)					
Bacterial meningitis in age	0-5	Gamma	91,264	4,717	PhilHealth 2019
	6-18	Gamma	76,948	5,038	PhilHealth 2019
	19-49	Gamma	96,557	5,309	PhilHealth 2019
	> 50	Gamma	120,715	12,427	PhilHealth 2019
All-cause Bacteremia and Sepsis in age	0-5	Gamma	54,715	485	PhilHealth 2019
	6-18	Gamma	67,820	1,046	PhilHealth 2019
	19-49	Gamma	95,754	1,039	PhilHealth 2019
	> 50	Gamma	152,746	884	PhilHealth 2019
Hospitalized pneumonia in age	0-5	Gamma	28,035	128	PhilHealth 2019
	6-18	Gamma	31,052	297	PhilHealth 2019
	19-49	Gamma	38,191	904	PhilHealth 2019
	> 50	Gamma	58,616	1,008	PhilHealth 2019
Non-hospitalized pneumonia in age	0-5	Fixed	106		Expert panel
	6-18	Fixed	211		Expert panel
	19-49	Fixed	376		Expert panel
	> 50	Fixed	376		Expert panel
Acute otitis media in age (hospitalized) *H65.1-H65.4, H65.9, H66.0-H66.3, H66.9*	0-5	Gamma	14,283	596	PhilHealth 2019

Parameters	Age	Distribution	Mean	SE	References
Acute otitis media by age (mild)	0-5	Fixed	106		[69]
Epilepsy in age *G40.0-G40.9*	0-14	Gamma	21,592	1,174	PhilHealth 2019
	15-59	Gamma	29,609	1,280	PhilHealth 2019
	> 60	Gamma	54,522	3,066	PhilHealth 2019
Hearing loss in age *RVS 69421 (0-59 yo)* *RVS 69502 (>60 yo)*	0-5	Gamma	42,153	11,433	PhilHealth 2017-2019
Neurodevelopmental disorder *F82, F89, F90.8*	0-14	Gamma	23,835	5,896	PhilHealth 2017-2019
	> 15	Gamma	17,193	5,385	PhilHealth 2017-2019
Chronic lung disorder *J44.0, J44.1, J44.8, J44.9*	0-14	Gamma	15,465	444	PhilHealth 2019
	15-59	Gamma	20,086	249	PhilHealth 2019
	> 60	Gamma	37,303	207	PhilHealth 2019
Utility parameters					
Meningitis		Beta	0.9638	0.0046	[36]
Bacteremia		Beta	0.9852	0.0025	[36]
Pneumonia		Beta	0.9910	0.0020	[36]
Acute otitis media		Beta	0.9984	0.0001	[36]
Epilepsy		Beta	0.6400	0.0738	[36]
Hearing Loss		Beta	0.5500	0.0554	[36]
Neurodevelopmental impairment-MMR		Beta	0.6900	0.0707	[36]
Neurodevelopmental impairment SMR		Beta	0.1000	0.1085	[36]
Neurodevelopmental impairments-MR+Epilepsy		Normal	0.0001	0.0943	[36]
Chronic lung disorder		Beta	0.5900	0.0575	[36]

5.3.2. Budget impact analysis

Currently, PCV is the most expensive vaccine in the NIP. For the year 2020, approximately PHP 4 billion of the total PHP 7.2 billion NIP budget was allocated for PCV alone. 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 with 'no vaccination' was determined for five fiscal years.

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. Using the predicted population report by the *Philippine Statistics Authority*, we computed for the total birth cohort vaccinated by multiplying the total population by 2.4%, which is the assumed total number of newborns as advised by the DOH NIP program managers. From this number, 90% is assumed vaccinated under the NIP as it is estimated that 10% of the population go to private facilities. Given these assumptions, the total number of infants likely to be vaccinated was predicted for the years 2020 to 2024. Vaccine wastage and storage, as well as other considerations such as PHP 2.50 for the syringe cost per dose, were also included in the analysis. Taxes, handling fees, and freight costs incurred through the UNICEF procurement were excluded since the national program is considering local bidding as a mode of procurement. Program cost (e.g., training, information-education-communication materials) was likewise excluded as suggested by the NIP since pneumococcal vaccination has been implemented since 2014.

5.4. Results

5.4.1. Cost-utility analysis

Incremental Cost-effectiveness Ratio ICERs illustrate that when compared with 'no vaccination', PCV10 and PCV13 were both very cost-effective even at lower ceiling ICER threshold values, in either MDV or SDV preparations. Whether using SDV or MDV, PCV13 was slightly dominant over PCV10 due to a higher QALY gain calculated for PCV13. However, it can be observed that the ICERs of both vaccines were very close when compared with 'no vaccination' even after incorporation of the revised price quotations. All ICER values generated are from probabilistic analysis (*Tables 5.3 and 5.4*).

Using MDV preparations, both PCV10 and PCV13 were cost-effective compared with 'no vaccination' (*Table 5.3*). The cost-utility analysis also showed very close ICER values for PCV10 or PCV13 when compared with 'no vaccination', with lower ICER values for PCV10. This may be the case since the quoted price for PCV13 is almost 2.5 USD higher than PCV10. The additional marginal benefit of PCV13 over PCV10 due to two additional serotypes may have been compensated by the greater price difference between the MDV preparations that resulted in close ICER values calculated between the two vaccines.

SDVs are more expensive than MDVs on a per-dose basis and have no price flexibility since floor prices of SDVs are effectively set by the Pan American Health Organization (PAHO). Still, SDVs for either vaccine were cost-effective for all coverage scenarios compared with 'no vaccination' (*Table 5.4*). When compared with the 'no vaccination' scenario, it can be observed that the difference in ICER values of PCV10 and PCV13 was wider in SDVs compared with MDVs. Moreover, negative ICERs were generated when ICERs of PCV10 are compared with PCV13 in both high and low coverage scenarios, owing to negative QALYs incurred between the two. This was the case since the quoted price of PCV13 is only a dollar more expensive compared with PCV10; the closeness of the price between the vaccines did not compensate for the lower QALYs of PCV10.

For either vaccine, achieving 90% coverage at which herd immunity could be assumed was cost-saving compared with 50% coverage where herd immunity was excluded. 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. Regions that had higher vaccine coverage may achieve the corresponding benefits for herd effects within a shorter time as compared with those regions with low coverage. Moreover, this could encourage implementers to prioritize higher vaccination coverage.

PCV10 resulted in lesser costs but also a lower number of deaths and episodes of IPD, pneumonia, and AOM averted when compared to PCV13 in the low-coverage scenario (50%). This was true despite the resulting ICERs having close values when both vaccines were compared with 'no vaccination', even after incorporating cross-reactivity with serotype 19A.

Table 5.3 ICER results for multi-dose vials (MDV)

	PCV10 versus 'no vaccination'				PCV13 versus 'no vaccination'				PCV10 versus PCV13			
	Inc. Cost	Inc. LY	Inc. QALYs	Cost/QALY PHP	Inc. Cost	Inc. LY	Inc. QALYs	Cost/QALY PHP	Inc. Cost	Inc. LY	Inc. QALYs	Cost/QALY PHP
Without herd immunity *(50% coverage; Scenario 1)*	126	0.0358	0.0429	2,947	350	0.0421	0.0504	6,932	-223	0.0063	-0.0075	29, 605
With herd immunity (90% coverage; Scenario 3)	-1,816	0.0685	0.0754	-24,080	-2,037	0.0804	0.0885	-23,006	221	0.0119	-0.0131	-16,837

Table 5.4. *ICER results for single-dose vial (SDV)*

	PCV10 versus 'no vaccination'				PCV13 versus 'no vaccination'				PCV10 versus PCV13			
	Inc. Cost	Inc. LY	Inc. QALYs	ICER/QALY PHP	Inc. Cost	Inc. LY	Inc. QALYs	ICER/QALY PHP	Inc. Cost	Inc. LY	Inc. QALYs	ICER/QALY PHP
Without herd immunity *(50% coverage; Scenario 2)*	996	0.0371	0.0441	22,606	966	0.0435	0.0517	18,667	29.74	0.0065	-0.0077	-3,860
With herd immunity *(90% coverage; Scenario 4)*	-948	0.0690	0.0767	-12,369	-1,418	0.0818	0.0898	-15,794	470	0.0119	-0.0131	-35,797

Disease cases averted with PCV10 and PCV13 In summary, universal infant vaccination with PCV would reduce both clinical and economic burden caused by *S. pneumoniae* infection. All clinical outcomes measured favor PCV13 showing higher episodes averted for IPD, pneumonia, and AOM as well higher deaths averted for IPD, with the highest difference in the episodes averted for pneumonia and AOM given that 90% birth cohort of 2.2 million infants would be vaccinated.

Results from the Markov model suggest 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 with PCV10 because of greater serotype coverage (*Figure 5.2*). This is also with the assumption that the government would pay for the vaccines.

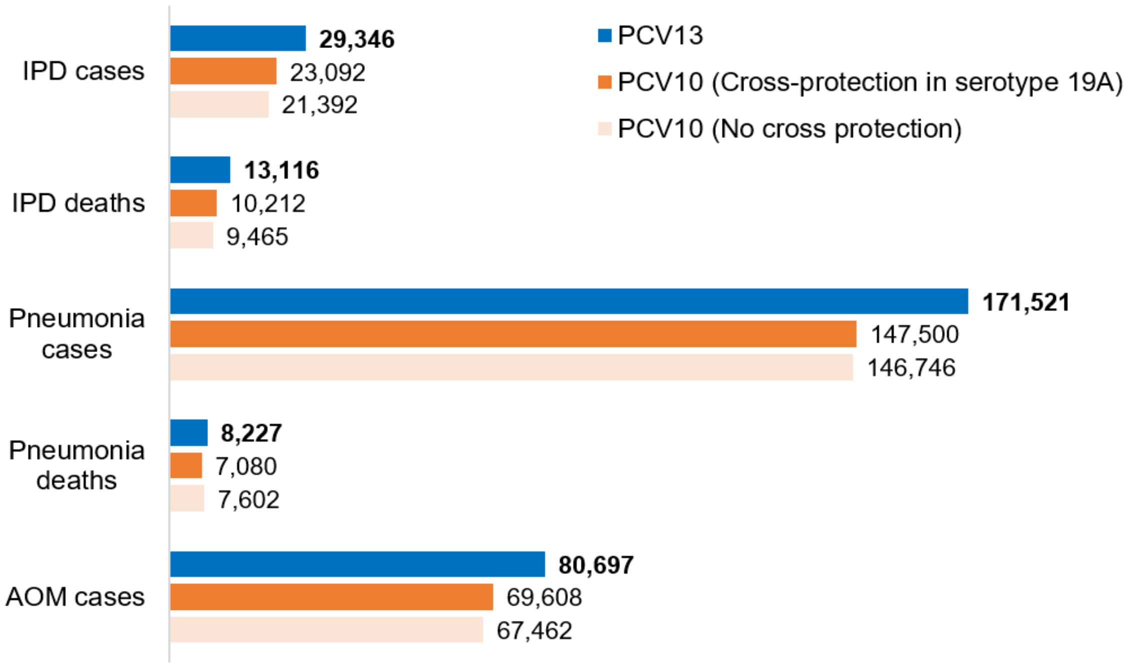

Figure 5.2 *Projected number of cases and deaths averted in PCV13 and PCV10 (inclusion/ exclusion of serotype 19A)*

Uncertainty analyses

Cost-effectiveness acceptability curve The cost-effectiveness acceptability curve (CEAC) showed that both PCV10 and PCV13 when compared with 'no vaccination' had a high probability of being cost-effective using either MDV or SDV preparations even at a lower willingness-to-pay threshold (*Figure 5.3*). 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 5.4)*. 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.

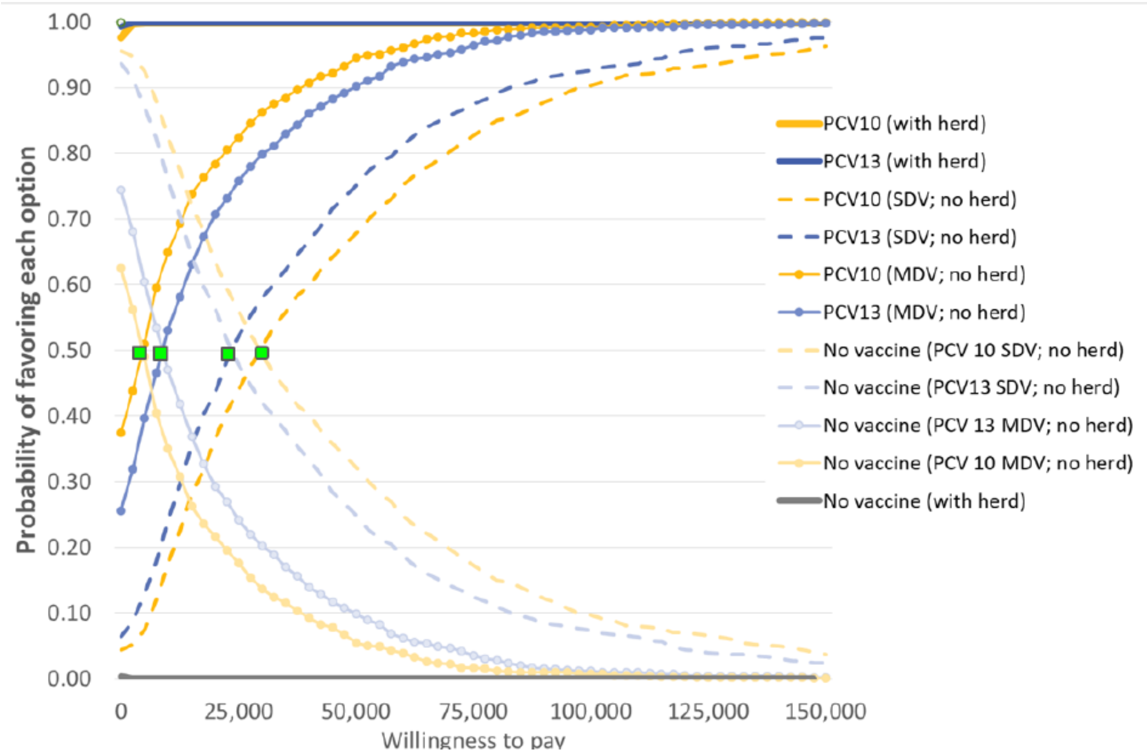

***Figure 5.3** Cost-effectiveness acceptability curve for PCV10 versus 'no vaccination', PCV13 versus 'no vaccination, multi-dose vials, or single-dose vials, with or without herd effects.*

Note: Green dots highlight where the compared interventions intersect

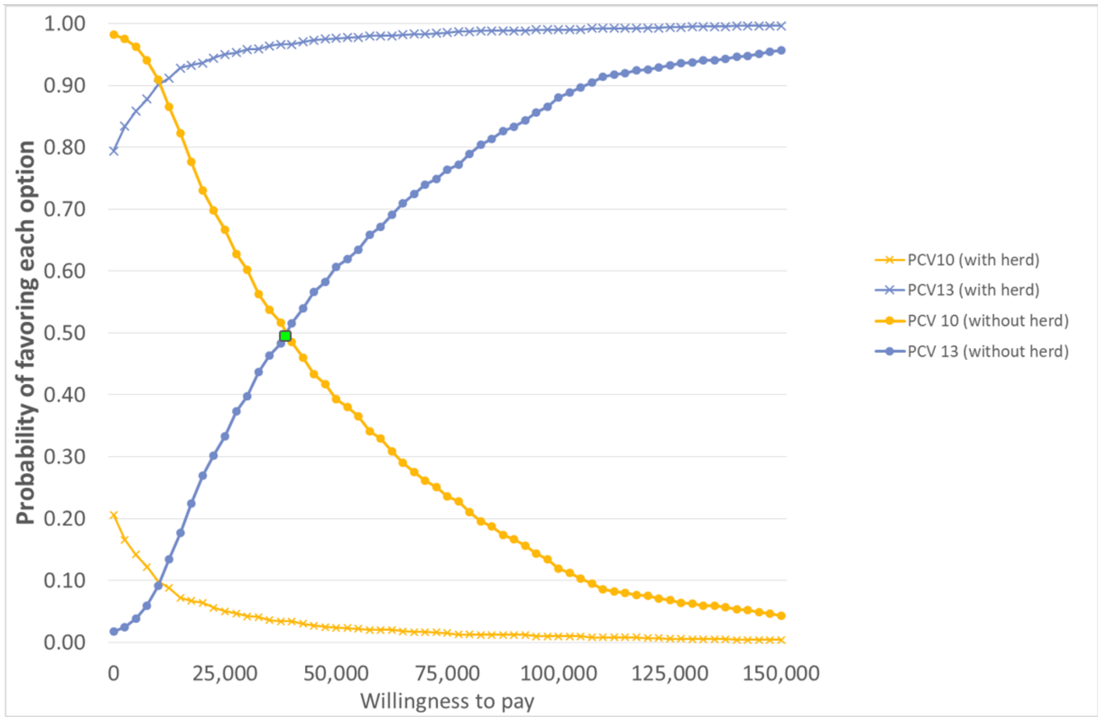

***Figure 5.4** Cost-effectiveness acceptability curve for PCV10 versus PCV 13 for **multidose vials**, with or without herd effects*
Note: Green dot highlights where the compared interventions intersect

One-way sensitivity analysis Results of one-way sensitivity analysis are in reference to deterministic ICER values on MDV without herd effects (PCV10 versus 'no vaccination': PHP 3,752 /QALY gained; PCV13: PHP 7,441 /QALY gained).

(a) Sensitivity analysis for PCV10. Parameters that influence ICER values by more than 10% for PCV10 is illustrated in the tornado diagram (*Figure 5.5*). The right-hand side is the increase in ICER value and (dark orange) and the left-hand side illustrates a decrease in ICER values (grey). A 3890% increase in ICER value would render PCV10 not cost-effective based on an implicit cost-effectiveness threshold.

Among all the parameters, the changes in procurement cost (i.e., market price, SDV) of PCV 10 had the greatest influence in ICER with up to 3304.20% change in ICER together with the following parameters:

(1) Vaccine efficacy against C-AOM [rate ratio: 0.90 (95% CI: 0.83, 0.98)] with change in ICER ranging from -442.65% to 689.85%, ranking second in ICER changes.
(2) Considering herd effects, lowering ICER value by 700.00%
(3) Discounting rate with a change in ICER ranging from -136.27% to 275.12%
(4) Vaccine efficacy against pneumonia with a change in ICER ranging from -89.11% to 211.04%
(5) Cost of hearing loss for less than five-year-old with a change in ICER ranging from -62.69% to 174.89%

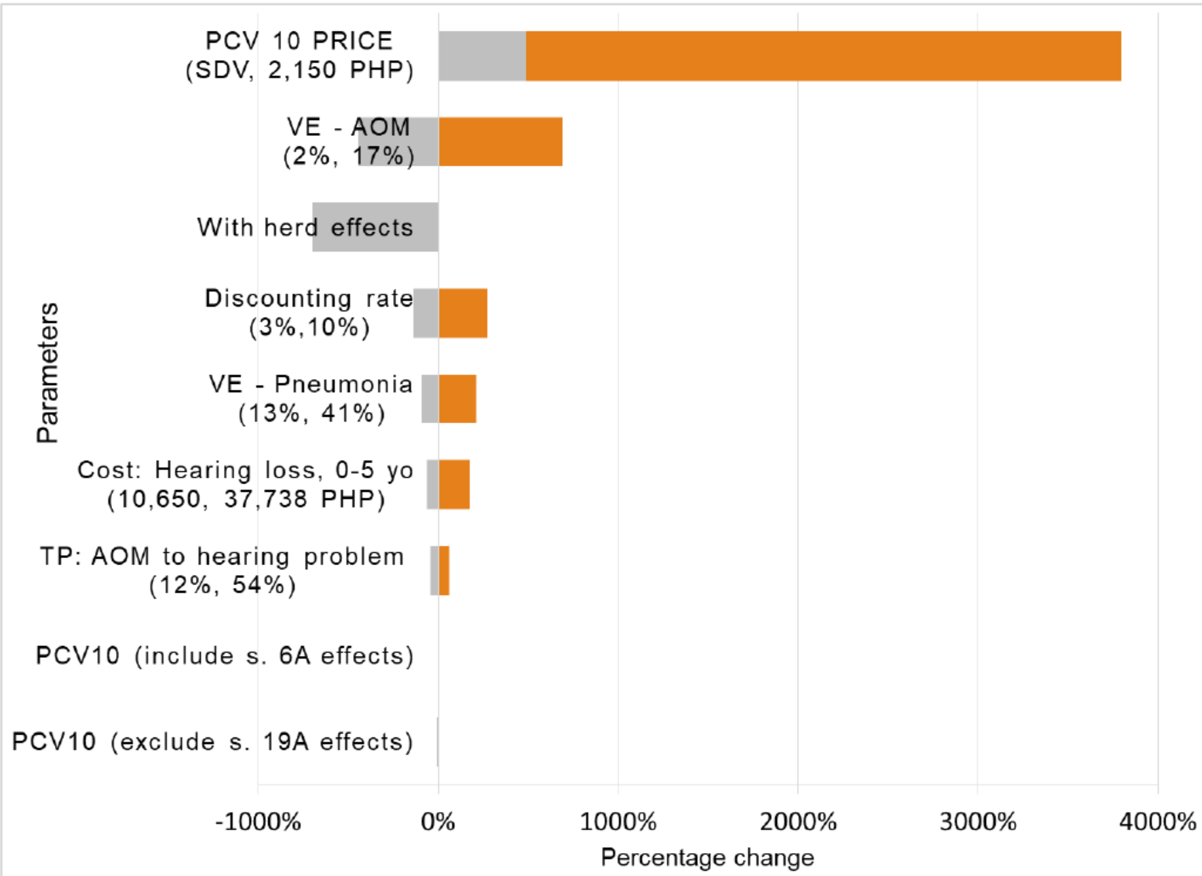

Figure 5.5 *Tornado diagram for changes in ICER values of PCV10 (TP - transition probability, VE - Vaccine efficacy)*

(b) Sensitivity analysis for PCV13. The right-hand side illustrates the increase in ICER value and (dark blue) and the left-hand side illustrates a decrease in ICER values (grey). A 2016% increase in

ICER value would render PCV13 not cost-effective based on an implicit cost-effectiveness threshold *(Figure 5.6).*

The ICER for PCV13 is most sensitive to the procurement cost (i.e., market price, SDV price) with up to 2534.92% change in ICER together with the following parameters:

(1) Vaccine efficacy against C-AOM [rate ratio: 0.90 (95% CI: 0.83, 0.98)] with change in ICER ranging from -272.00% to 321.76%, ranking second in ICER changes.
(2) Herd effects lowering ICER value by 409.00%
(3) Vaccine efficacy against pneumonia with a change in ICER ranging from -65.55% to 140.10%
(4) Discounting rate with a change in ICER ranging from -72.00% to 53.00%
(5) Transition probability of AOM proceeding to hearing loss with a change in ICER ranging from -45.29% to 50.64%

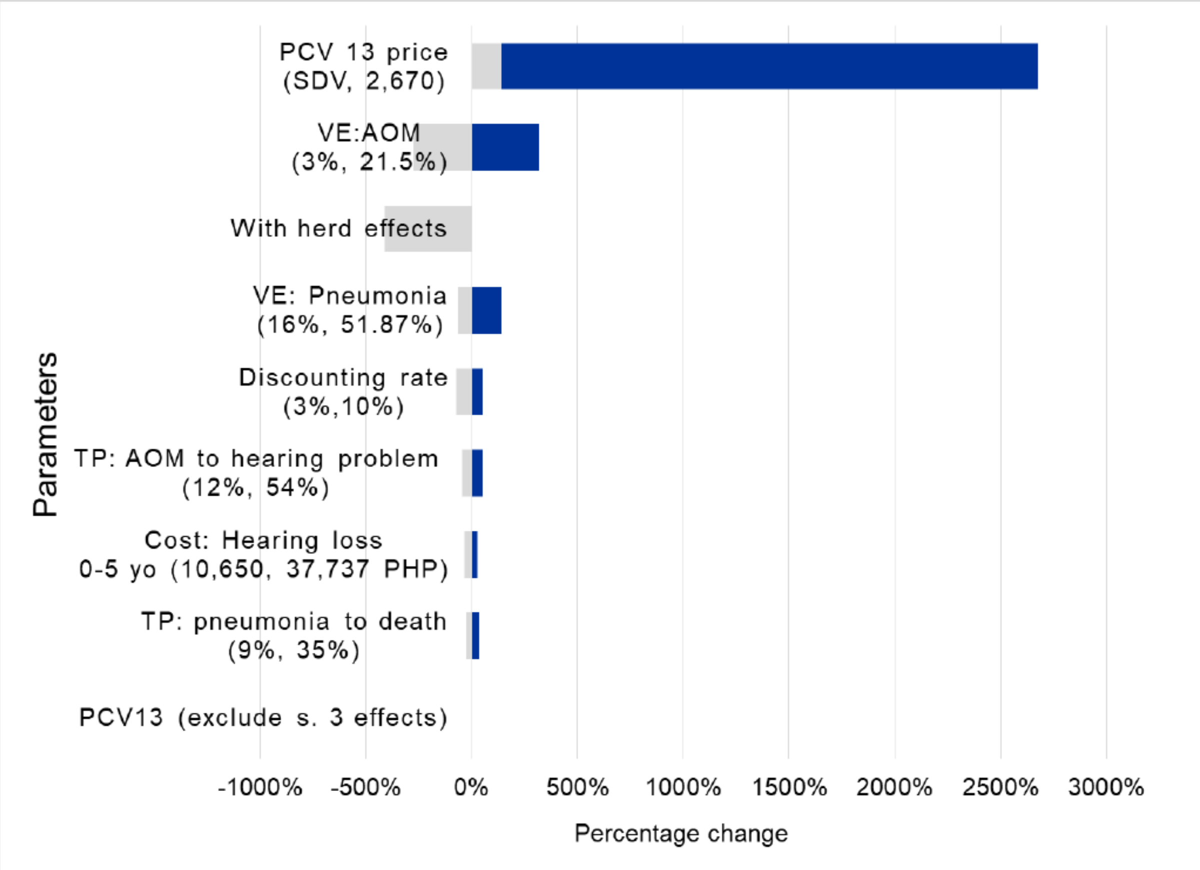

***Figure 5.6** Tornado diagram for changes in ICER values of PCV13 (TP - transition probability, VE -Vaccine efficacy)*

5.4.2. Budget impact analysis

The estimated budget needed for implementing PCV10 or PCV13 for the target birth cohort was also analyzed (*Table 5.5*). For the total vaccination cost to the NIP for 2020-2024, MDV using PCV13 was at PHP 25.01 billion, while for PCV10 it was at PHP 19.99 billion. Meanwhile, SDV use is estimated to cost PHP 30.15 billion for PCV10, while PCV13 would cost PHP 32.80 billion. PCV13 consistently showed a higher budget requirement than PCV10. Implementing PCV vaccination programs would avert cases of AOM, IPD, and pneumonia consequently leading to lower treatment costs which are assumed to be covered by the PhilHealth. If PCV13 would be implemented, treatment costs were estimated to be reduced by PHP 14.72 billion, while PCV10 implementation would reduce treatment cost by PHP 12.15 billion compared with 'no vaccination' for the fiscal years evaluated.

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 with purchasing PCV10 in MDV over five years.

The total budgetary impact for MDV use in PCV10 is at PHP 233.92 billion, while for PCV13 it is at PHP 237.96 billion. However, since vaccination implementation would drive the treatment costs lower versus 'no vaccination', the incremental budgetary requirement of PCV10 versus 'no vaccination' is at PHP 7.21 billion, while for PCV13 versus 'no vaccination' is estimated at PHP 11.25 billion. Since PCV10 costs 2.5 USD less than PCV13 in MDV preparations, significantly less budget is needed to achieve 90% coverage of the target birth cohort. This, however, results in potentially less QALYs gained and less IPD, pneumonia, AOM, and deaths averted compared to PCV13.

For 2020, PCV10 implementation requires an estimate of PHP 3.78 billion while PCV13 implementation requires PHP 4.88 billion to achieve 90% coverage of the birth cohort.

***Table 5.5** Budgetary impact of PCV10 and PCV13 compared with 'no vaccination' in billions PHP*

Year	Scenario 1 (MDV, 90% coverage)				Scenario 2 (SDV 90% coverage)				'No vaccination'
	PCV10		PCV13		PCV10		PCV13		
	Vaccination Cost	Treatment Cost	Vaccination Cost	Treatment Cost	Vaccination Cost	Treatment Cost	Vaccination Cost	Treatment Cost	Treatment Cost
2020	3.78	18.85	4.88	18.67	5.87	18.85	6.40	18.67	20.26
2021	3.83	33.02	4.94	32.68	6.00	33.02	6.48	32.68	34.86
2022	3.87	45.42	5.01	44.89	6.02	45.42	6.56	44.89	47.81
2023	3.91	54.82	5.06	54.10	6.09	54.82	6.64	54.10	57.77
2024	3.96	62.53	5.12	61.64	6.16	62.53	6.72	61.64	66.01
5 year Budget Impact	19.99	214.56	25.01	211.99	30.15	214.64	32.80	211.99	226.71
Total Budget Impact	**233.92**		**237.96**		**244.79**		**244.79**		**226.71**

5.5 Conclusion

The reassessment of existing PCV vaccines in the Philippines showed that both PCV10 and PCV13 are cost-effective especially with the use of multi-dose vials when compared with 'no vaccination'.

This study also shows that both PCV vaccines will incur a considerable budgetary impact to the Department of Health. Shifting from SDV to MDV preparations of the vaccines can result in significant savings since PCV10 has a lower incremental program cost (Php 7.21 billion) compared to PCV 13 (with an incremental program cost of 11.25 billion). Thus, PCV10 was deemed more affordable than PCV13.

6. ETHICAL AND SOCIAL IMPLICATIONS

6.1. Objective

To determine the ethical and social implications in immunizing infants with either PCV10 or PCV13

6.2. Research Question

What are the ethical and social implications in immunizing infants with either PCV10 or PCV13 to prevent mortality and morbidity due to IPD, clinical pneumonia, and AOM?

6.3. Methodology

To assess the ethical and social impact of using both PCV10 and PCV13 in the EPI, perspectives of patients, civil society organizations, and marginalized communities were gathered on the effect of PCV on equitable access, budget allocation, and public acceptability of vaccines.

An online-focused group discussion (FGD) was initially planned to gather the perception of patient groups and civil societies on social and ethical issues of use or non-use of PCV10 and PCV13. Due to logistical limitations, an online questionnaire was sent instead to five patient groups and three civil societies. Questions were developed using the pre-existing HTA submission forms for patient groups as a guide (Appendix G). The questions were also designed to determine relevant social determinants that affect access of infants to vaccination. A study by Glatman-Freedman examining the impact of social determinants in immunization programs was used as a reference.[74] Only social determinants identified for lower-income countries were used in the questionnaire.

Responses of marginalized community leaders were gathered through online messages and phone interviews. The questions given were derived from questions developed for the patient groups and civil societies and were simplified in an attempt to draw their social values to inform decision making rather than directly asking them to choose a vaccine product based on highly technical information which will be difficult to convey given the limitations in the methodology (Appendix F).

Questionnaires were administered in Tagalog for patient groups and civil societies, and leaders of marginalized communities. The questions were reviewed and approved by the ethics practitioner, anthropologist, and citizens' representative of the HTA Council Core Committee. Key points from the responses were summarized. Ranking questions were analyzed using Friedman's test to determine the mean rank of each option.

6.4. Results

6.4.1 Ethical and social implication data collection method

Two sets of questionnaires were developed to gather societal perspectives on the use of PCV10 and PCV13. One set was sent to patient groups and civil society organizations (CSOs) while the second set was sent or used as guide questions for phone interviews with leaders of the marginalized communities. This is to acknowledge the plurality of narratives of the Filipino people who are differentiated by socio-economic and cultural capitals.

Given that representatives of civil society organizations (CSO) and patient groups have been involved in the development of various health programs and policies in the past, it is acknowledged that they can understand the implications of use or non-use of a certain health technology if they are provided with sufficient context. Thus, the instrument used to gather their response was drafted to include information on the epidemiology of the disease being addressed, background information on the health technologies under assessment, the history of PCV implementation, and the budgetary and projected clinical implications in our country. This information was deemed necessary to enable them to form an opinion regarding the ethical and social implications of choosing one PCV product over another, given the important tradeoffs based on the best data available.

The set of questions for CSOs and patient groups aimed to give the participants an in-depth understanding of several things: First, the health problem being addressed by the vaccine is prevalent in our country. It also elaborated that one vaccine might provide better health outcomes due to better serotype coverage but is more expensive, and also a cheaper vaccine is available which may contribute to better vaccination coverage. They were also informed that that the vaccine takes up a significant amount of our national immunization program budget, which can be reallocated to other health programs. Although their responses were gathered through a questionnaire sent through email instead of a focused group discussion, the questions were varied as multiple choice, ranking, and open-ended questions to ensure that neutrality is maintained and participants could freely express their insights regarding the inquiry. However, a problem was encountered because the instrument used was in Tagalog. One representative from a patient group had expressed difficulty in conveying sentiments in that language.

A unique approach was used in gathering the perspective of leaders from marginalized communities. Participants were provided the basic operational framework of this inquiry: 1) there is a limited budget, 2) one vaccine has better coverage than the other has, but is more expensive, and 3) potential savings could contribute to other health program coverage. These are the health system realities parallel to what communities in the margins face: 1) not everyone gets vaccinated due to limited supply, 2) more are made vulnerable by the most basic diseases that could be addressed by both vaccines, 3) capacity and inclination for vaccine-related out-of-pocket expense in resource-poor households are low. The instrument was drafted based on the realities that were verified with anthropologists who have worked in these communities for decades.

Each community representative who took part in this consultation was sent a questionnaire that aimed to capture their worldview of health vulnerabilities and accessibility. By focusing on their social values associated with health, decision-makers may have a better means of understanding the predispositions of people for health technologies that may be introduced. For this specific case, their inclination towards vaccination was more important than aggregating their understanding of the statistical repercussion of choosing one technology over the other. Considering the gaps in the distribution of free vaccines in low-income communities, how they prioritize health threats and basic needs were more important sources of reflection.

There is no conclusive data about the potential differences in the effects of the vaccines in the communities that took part in the study. With the questions framed with inclusivity in mind, participants were provided multiple ways to express their experiences. Ranking, multiple options, localized contexts were used to ensure that no community's voice was silenced using a marginalizing general narrative which could be neatly packaged as the Filipino experience. This hegemonizing orientation must be tempered, if not eradicated, in understanding health vulnerabilities and resilience.

6.4.2 Patient group and civil society organization perspective

Four out of six respondents (1 out of 3 from patient groups and 3 out of 3 from civil society organizations) answered the questionnaire. Overall, concerned groups prioritize the number of cases prevented (mean rank = 1.55) when choosing a vaccine for implementation. This is followed by vaccination coverage (mean rank = 2.25). Last in their prioritization was the price of vaccine (mean rank = 3.00) and savings for possible re-allocation to other health programs (mean rank = 3.00). The respondents pointed out several advantages and disadvantages in their choice of PCV. (*Table 6.1*).

Table 6.1. *Perceived advantages, disadvantages, and acceptability of PCV10 and PCV13 to patient groups and civil societies.*

	PCV10	PCV13
Advantages	o Greater vaccination coverage which improves equity o Additional funds saved could cover other immunization programs that others need o The use of PCV10 will enable the health system to balance budget allocation against the needs of other urgent/essential health concerns of other sectors	o A higher degree of protection and more cases averted o Higher quality-adjusted life-years gained o More cost-saving
Disadvantages	o A lesser degree of protection/fewer cases averted o Equity issue may arise when a marginalized population acquires infection due to lesser protection	o Budget constraints will be felt in addressing new priorities, other vaccination programs, and/or other health services
Acceptability	o PCV10 is acceptable in terms of more equitable access to PCV o Less protection against 3 serotypes is acceptable for 1 civil society representative	o PCV13 is more acceptable in terms of its perceived advantage in health benefits o Financial and logistical measures should be done to ensure equitable access to the best vaccine available despite the higher price

From a patient group perspective, the best health technology should be given to the citizens, which to them is PCV13. However, given the budget impact of PCV13 and the budget allocation for PCV, they concluded that the budget allocation is insufficient to achieve universal coverage. Thus, PCV10 becomes more acceptable. Meanwhile, representatives from civil society organizations deemed PCV13 as the more acceptable option due to its perceived benefit in the number of pneumococcal infection cases and deaths averted. They recognized that the use of PCV13, which is the more expensive vaccine, may affect vaccination coverage negatively. A representative emphasized that measures should be done to ensure that the more clinically effective vaccine would be implemented without compromising coverage.

The groups recognized that the information gap in terms of safety and efficacy of the vaccines should be addressed, especially to the marginalized communities. This is to ensure the acceptability of vaccines which plays a role in achieving universal coverage. Hence, information dissemination on vaccination should be prioritized when introducing either PCV product.

No comments were made regarding the effect of the PCV budget on budget allocation to other vaccines implemented by the NIP or other health programs of the Department of Health. However, they emphasized that budget allocation ought to be based on accurate and relevant data such as the census of the total target population, including at-risk groups.

6.4.3 Leaders of marginalized communities' perspective

Out of the 26 leaders of the identified marginalized communities, eight (30.77%) were from highly urbanized areas in the National Capital Region, Region IV-A, and Region XI. Meanwhile, 18 of them were from communities the Cordillera Administrative Region (CAR) (n =1), Region III (n = 9), Region IV-A (n = 6), Region IV-B (n = 1) and Region VII (n = 1). Among these 18 communities, nine were from 1st class municipalities, six from 2nd class municipalities, two from 3rd class municipalities, and one from a 4th class municipality. Their experience with PCV vaccination cannot be ascertained, but all community leaders were briefed regarding PCV to help them in answering the questions provided.

Responses were received from 24 of the identified community leaders. In-depth phone interviews were only conducted with eight of the respondents. Answers of the remaining 16 respondents were received through online messages.

Table 6.2. *Summary of responses of marginalized community leaders*

Topic	Response
Priority in choosing vaccine product (n= 23)	1. Cases averted (56.52% ranked as top priority) 2. Greater vaccination coverage (30.43%) 3. Lower vaccine price (13.04%)
Preferred vaccine product (n= 24)	The vaccine which can prevent less disease but with a lower vaccine price would result to greater vaccination coverage (PCV10) (91.67%). Prevention of more disease but is more expensive, thus lower vaccination coverage (8.33%).
Limiting factors to equitable vaccine access (n= 22)	1. Limited knowledge of parents and guardians (mean rank = 2.22) 2. Vaccine price (mean rank = 2.95) 3. Insufficient support from government to ensure easier access to vaccines (mean rank = 3.05) 4. The distance of household to health facility (mean rank = 3.31) 5. Religious and personal beliefs (mean rank = 4.59) 6. Sex of infant (mean rank = 5.91)

A summary of responses of marginalized community leaders is provided in *Table 6.2*. When choosing a vaccine, leaders of marginalized communities prefer more cases averted followed by greater vaccination coverage and lastly, lower vaccine price, as reflected in mean ranks of the three independent decision criteria. However, when made to choose between a vaccine which can prevent more disease but is more expensive, thus lower vaccination coverage (PCV13) and a vaccine which can prevent less disease but with lower vaccine price leading to greater vaccination coverage (PCV10), 91.67% of the respondents chose the latter option. Based on this, it can be perceived that marginalized communities value protection for more infants over preventing the occurrence of more cases of the diseases. Indirectly, the stakeholders implied the importance of herd protection for their respective communities. Further, this is supported by the findings in a national study which suggests that Filipinos are willing to pay more to ensure that the vulnerable and indigent sectors can access quality health services.[75] This highlights the Filipinos' willingness to forego personal financial or health gain for equitable access to healthcare.

Six social determinants of vaccination applicable in the Philippine setting were identified from a study by Glatman-Freedman et al.[74] This includes financial factors, urban vs rural place of residence, parental education, program accessibility and governance, religious and minority groups, and gender-based inequity. These were then used to identify which social determinant significantly affects the access of marginalized communities to vaccines in our setting. Mean ranking showed that marginalized community leaders perceive that limited knowledge on vaccines is the leading cause of inequitable access to vaccines, followed by high vaccine price, insufficient support from the government, distance to health facilities, religious and personal beliefs, and lastly, sex of the infant.

Limited problems concerning equitable access to vaccines were observed due to the religious and personal beliefs of parents or guardians of infants. Meanwhile, no respondent identified sex of infant as a factor affecting access to vaccines.

Based on interviews with the community leaders, limited knowledge of parents regarding vaccines contributes to inequitable access to vaccines. Misconceptions about the safety and efficacy of vaccines should be addressed to secure the maximum acceptability of new vaccines such as PCV10 or PCV13 in regions not included in the prior PCV13 implementation.

Statements from respondents showed that there is a co-relationship between vaccine price, insufficient support of government to vaccination programs, and distance to health facilities in limiting equitable access to vaccines. The most-prevalent issues identified were insufficient vaccine supply, insufficient manpower and delayed delivery of vaccines especially to geographically isolated areas (GIDA). These shortcomings limit timely access of infants to free vaccination, therefore, passing the financial burden to the parents or guardians.

Based on the *2018 Official Poverty Statistics by the Philippine Statistics Authority*, the poverty threshold in our country is at PHP 10, 727. The market price for single-dose vials of PCV10 and PCV13 ranges from PHP 2, 150 to PHP 3,670 which is approximately 20-36% of the poverty threshold. This is still exclusive of professional fees for the physicians who administer the vaccine in the private setting. Without the free access to vaccination from the government and considering such high household financial impact of a single dose of PCV, impoverished families situated in GIDA might opt not to vaccinate their children which undermines the goal of universal healthcare.

In summary, it is important to consider which among the two, PCV10 and PCV13 could lead to maximum coverage and timely free vaccination in order to provide equitable access to this vaccine.

The representatives of patient groups and civil society organizations had a different response from the representative communities because of the difference in their socioeconomic status which affected the choices they made. As an institution that promotes social justice and equity, both voices were given equal importance and representation in this evaluation. They were gathered in the most inclusive process possible, and their orientations were upheld independent of each other.

6.5 Conclusion

Results of the interviews and survey on ethical and social impact assessment showed that patient group and leaders of marginalized communities generally prefer PCV10 over PCV13. This is because of its advantage in enabling more equitable access to vaccines. By allowing more vaccines to be purchased, greater proportion of the population can be covered resulting in better public health outcomes. Civil society organizations (CSOs), however, prefer PCV13 to PCV10 due to its perceived benefit in terms of clinical outcomes.

7. LEGAL IMPLICATIONS

7.1. Objective

To determine the legal implications in immunizing infants with either PCV10 or PCV13.

7.2. Research Question

What are the legal implications in immunizing infants with either PCV10 or PCV13 to prevent mortality and morbidity due to IPD, clinical pneumonia, and AOM?

7.3. Methodology

Assessment of legal implications focused on the impact of the result of the economic assessment of PCV on the bidding and procurement of the vaccine. Written and online meeting consultations with the DOH-Legal Service and the DOH-Central Office Bids and Awards Committee (COBAC) were conducted to determine the legality of open bidding for PCV to allow both PCV10 and PCV13 to take part, noting that PCV13 and PCV10 are two different products. This could only be the case if both vaccines are included in the Philippine National Formulary (PNF). The HTA Council experts were also consulted regarding other possible legal implications that may arise from the result of the assessment. To understand fully the legal opinions sent, the representative of the DOH Legal Service was invited to the HTA Council's deliberation to explain any information that needed clarifications.

7.4. Results

Government and legal references used in the review and responses by the DOH-Legal Service (LS) and the DOH- Central Office Bids and Awards Committee (COBAC) includes the *8th edition of the PNF*, *Republic Act 9184 or the Government Procurement Reform Act* and its revised *Implementing Rules and Regulations (IRR), and the DOH-Customized Procurement Manual: Volume 2 Manual of Procedures for the Procurement of Goods*. The DOH offices explained that the specification of a vaccine product for procurement should be used by the *DOH- Central Office Bids and Awards Committee (COBAC)* to determine the winning bidder.

According to the Government Procurement Reform Act (RA 9184), "*specifications for the procurement of Goods shall be based on relevant characteristics, functionality and/or performance requirements.*" To elaborate, in determining the technical specifications of the goods to procure, the Procurement Management Office (PMO) or end-user or implementing unit must consider the objectives of the project or the procurement at hand and identify the standards that should be met by the goods in terms of function, performance, environmental interface and/or design. Further, in-house experts who are part of the technical working group (TWG) or the PMO must likewise be tapped to provide technical advice.[76] The technical advice pertains to the type of product to procure, and its technical specifications needed for the bidding documents.

Moreover, the use of brand names is prohibited under the revised IRR of the Procurement Act as stipulated in the DOH Customized Procurement Manual, "*the use of brand names, or tailor-fitting the technical specifications to specific brand names, is prohibited. Specifications for the procurement of goods shall be based on relevant characteristics and/or performance requirements. Hence, a generic description of the product or service must be used*".[37, 76]

According to Section 10 of RA 9184, all government procurement shall be done through a competitive bidding process. However, according to Section 48 of RA 9184, alternative methods of procurement are permissible to promote economy and efficiency given that there is prior approval of the Head of the Procuring Entity or his duly authorized representative. Some valid justifications are when a specific good may only be provided by one or few sources, goods that require immediate purchase, a repeat order from a previous winning bidder, had two failed biddings, etc. Since PCVs are with patents and therefore sourced only to limited manufacturers, procuring through alternative methods may be permitted.[76]

The current specification for procurement of PCV is based on the monograph for PCV in the PNF. PCV is characterized as a 13-valent, 0.5 mL single-dose vial or 0.5mL prefilled syringe, suspension for intramuscular injection. [77] Given this specification, only the single-dose vial of PCV13 can participate in the bidding for PCV. The said specification may be changed to a 10-valent vaccine because of the assessment. However, changing the specification for bidding of PCV does not automatically entail the delisting of PCV13 in the formulary. The Health Technology Assessment Council (HTAC) may still decide to retain PCV13 in the formulary upon the inclusion of PCV10.

Two possible scenarios were foreseen during the assessment. First, HTAC may recommend a change in the specifications for procurement from a 13-valent vaccine to a minimum 10-valent vaccine, however, careful specification setting shall be done. This is to consider that there is another PCV10 product, *Pneumosil II* of Serum Institute of India, which is expected to receive a Certificate of Product Registration (CPR) from the Philippine FDA within the year. It is important to note that serotypes contained in *Pneumosil II* are different from that of the PCV10 considered in this assessment which is manufactured by GlaxoSmithKline. If competitive bidding between PCV10 and PCV13 is done, a possible product switch driven by fluctuating prices of vaccines every procurement cycle may occur, which is not advisable according to the *DOH Legal Service*. Fluctuation of prices may lead to inaccuracy in the approved budget for the contract (ABC). This makes procurement planning difficult.

Secondly, to prevent a vaccine product that did not undergo the HTA process from entering the bid, the serotypes contained in the vaccine may be specified. However, this may be deemed as tailor-fitting which is restricted in the DOH Manual of Procedures for Procurement of Goods.

According to the DOH Legal Service, Scenario 1 may be feasible given that the serotypes present in the vaccine are shown to be prevalent in our country and would be sufficient in addressing pneumococcal diseases in the country. In this case, PCV13, which covers three additional serotypes may also enter the bidding process. As for scenario 2, although at a glance, enumerating serotypes may seem to be tailor-fitting specifications, this particular health technology may be exempted given that evidence on the burden of disease correlates with specific serotypes. This procedure may also protect the government from procuring other products which did not undergo health technology assessment. Moreover, indirect product inclination due to specifying serotypes that would result in a sole manufacturer may be allowed given the substantial evidence that presents the actual needs of the country.

In summary, since the determination of the goods and services to be procured is for the end-user or implementing unit to determine, taking into considerations the needs and requirements of the procuring entity, the Council could recommend including in the procurement specifications the pneumococcal serotypes in PCV vaccines prevalent in the local setting to address the burden of the disease.

Lastly, it was recommended by a stakeholder during the public consultation that multiyear vaccine purchases may lead to a significant vaccine price reduction, thereby producing more savings for the government. However, several caveats were raised by the Council. It was noted that the NIP procures vaccines on a yearly contract. Although few legal concerns were identified, the confidence of the Council on recommending multi-year vaccine purchases is inhibited by the current poor surveillance of IPD in the country. The Council deemed that this may be considered in future purchases with the improvement of surveillance data in the country.

7.5 Conclusion

Both the DOH Legal Service and COBAC both articulated that the determination of the goods and services to be 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. A specific inclination to a certain PCV product is permissible according to the DOH-Legal Service given that the product is able to address the burden of disease in the country. Therefore, specifying pneumococcal serotypes in PCV prevalent in the Philippines may be exempted from the rules of tailor-fitting. Lastly, multiyear vaccine purchasing as suggested in the public consultation may be considered in future purchases with the improvement of surveillance data in the country.

8. HEALTH SYSTEMS IMPLICATIONS

8.1. Objective

To determine the health system implications in immunizing infants with either PCV10 or PCV13

8.2. Research Question

What are the health system implications in immunizing infants with either PCV10 or PCV13 to prevent mortality and morbidity due to IPD, clinical pneumonia, and AOM?

8.3. Methodology

8.3.1 Literature review on country experience in product switching

Literature searches on PubMed and Google Scholar were performed using the terms "PCV10," "PCV13," "switch," and each of their related terms to retrieve articles related to immunization programs that underwent product switch from PCV13 to PCV10. The search terms used can be found in *Table 8.1*. We did not apply restrictions on the type of review, language, and date. Narrative reviews focusing on the implications of switching from PCV13 to PCV10 on clinical, economic, as well as social, and ethical aspects were explored. Other factors that may arise due to the product switch was also taken into consideration. Additional published articles that specifically tackled the impact of product switching submitted post public consultation last June 11, 2020, were also incorporated in the narrative review.

Table 8.1. *List of databases and search terms used for product switching*

Databases	Search terms
PubMed Google Scholar	"PCV switch" and its similar terms "PCV13 to PCV10" and its similar terms "13 valent to 10 valent"

A total of 12 stakeholders answered the web-based survey for the health system impact assessment last May 7-14, 2020. The survey was developed based on the findings from the WHO review on the impact of new vaccine introduction on immunization and health systems.[78] The two-part survey detailed the impact of choosing: (1) between single-dose vial (SDV) or multi-dose vial (MDV) preparations, and (2) between PCV10 or PCV13 (Appendix H). The framework for the health system impact assessment is shown in *Table 8.2* where the target respondents for each of the domains are enumerated. Responses were summarized to determine the major factors that led to their responses.

Table 8.2. *The framework of health systems impact assessment of PCV and its target respondents per domain*

Survey domain	Scope/ objective of the domain	Target respondents
Service Delivery	Determine how the use of PCV will affect the delivery of safe, effective, and quality vaccines to those who need them when they need them.	○ DOH- National Immunization Program (NIP) ○ DOH- Central for Health Development (CHD) ○ Rural health unit (RHU) ○ Infectious disease and pediatrics practitioners ○ United Nations Children's Fund (UNICEF) ○ World Health Organization (WHO)

Survey domain	Scope/ objective of the domain	Target respondents
Health Manpower	Determine how the use of PCV will affect how the health workforce works to ensure responsive, fair, and efficient healthcare delivery.	○ DOH- National Immunization Program (NIP) ○ DOH- Central for Health Development (CHD) ○ Infectious disease and pediatrics practitioners ○ United Nations Children's Fund (UNICEF) ○ World Health Organization (WHO)
Information	Determine how the use of PCV will affect how generation, analysis, dissemination, and use of reliable data on diseases will be done.	○ DOH- Epidemiology Bureau (EB) ○ DOH- Central for Health Development (CHD) ○ Rural health unit (RHU) ○ Private primary clinics
Supply Management	Determine how the use of either preparation of PCV will affect equitable access to safe, effective, and quality vaccines.	○ DOH- National Immunization Program (NIP) ○ DOH- Procurement and Supply Chain Management Team (PSCMT) ○ Rural health unit ○ Private primary clinics ○ United Nations Children's Fund (UNICEF) ○ World Health Organization (WHO)
Financing and Sustainability	Determine how the use of PCV will affect the health financing system.	○ DOH- National Immunization Program (NIP) ○ Private primary clinics ○ United Nations Children's Fund (UNICEF)
Leadership and Governance	Determine how the use of PCV will affect strategic policy frameworks and institutions in place.	○ DOH- National Immunization Program (NIP) ○ DOH- Center for Health Development ○ National Immunization Technical Advisory Group (NITAG) ○ United Nations Children's Fund (UNICEF) ○ World Health Organization (WHO)

8.4 Results
8.4.1 Literature review

The systematic search conducted found six studies that tested the effect of switching from PCV13 to PCV10 in Indonesia, Belgium, Morocco, and Canada. The summary of findings from these studies is found in *Table 8.3*.

Suwantika et al. investigated the impact of switch options on economics from PCV13 single-dose vials to either PCV10 (single dose or multi-dose vial) or PCV13 multi-dose vials in Indonesia. Findings showed that switching into multi-dose of PCV10 with Gavi-AMC price in 2021 to 2024 resulted in the highest potential saving considering factors including vaccination coverage, vaccine price, and logistics. However, the potential averted incidence of IPD under one year of age would decrease from 246,164 to 105,587 due to the switch for the years 2019 to 2024. The study suggests that a more comprehensive economic evaluation study is required to investigate further the comparison of cost-effectiveness values among all PCVs.[84]

Morocco switched from PCV7 to PCV13 in October 2010 and again switched to PCV10 in July 2012. Results of the surveillance study by Diawara et al. found that the number of IPD cases among children less than 5 years of age did not significantly increase from the years 2013 to 2014. This may suggest that the switch to PCV10 will not lead to more IPD cases caused by the additional serotypes in PCV13.[85]

Desmet et al. presented a real-world case in Belgium when they switched from PCV13 to PCV10 in May 2016. Two years after the switch, the number of invasive pneumococcal disease (IPD) isolates received at the National Reference Centre originating from infants aged 0-2 years rose from 121 isolates in 2015 to 154 in 2017. Moreover, the number of serotype 19A IPD isolates, which is not contained by PCV10, had an increase from 2 to 21 isolates. The Belgian experience of re-emergence of a non-covered serotype after switching to a lower-valent PCV is an important consideration for policymakers when making programmatic shifts in childhood vaccination strategies. [81] Another study showed that the proportion of nasopharyngeal carriage non-vaccine serotype decreased (94.6%, 438/463 isolates in 2016 vs 89.7%, 599/668 in 2017 to 2018) while that of PCV13-non-PCV10 serotypes (3, 6A, 19A) increased (0.9%, 4/463 isolates in 2016 vs 7.8%, 52/668 in 2017–2018). Serotype 19A was the most frequently identified among the three PCV13-non-PCV10 serotypes before and after PCV10 introduction (87.9%, 58/66 isolates). Non-susceptibility of pneumococci against any of the tested antibiotics was stable over the study period (> 44%).[87]

Using the real-world prevalence of re-emergence of serotype 19A in Belgium, a re-analysis of modeling a switch from PCV13 to PCV10 in Canada revealed that the switch could cause an additional 726,531 cases of pneumococcal infection over 10 years using the country's historical trends of individual serotypes. [81] Moreover, the study also stated that despite a higher vaccine acquisition cost of PCV13, the net savings due to the lower disease incidence with continued PCV13 use would be greater than $500 million. However, these results should be interpreted cautiously since the two published studies that showed the product advantage of PCV13 were funded by the product manufacturer.

The *European Pediatric Association* reported that there was an observable increase in the cases of serotype 19 IPD in Belgium after the switch from PCV13 to PCV10. However, they also cited that PCV10 vaccination in Finland did not result in increased serotype 19 IPD cases. In Sweden, however, where PCV13 or PCV10 was implemented depending on the county, the incidence of 19A IPD did not differ among counties with PCV10 and those with PCV13. The study concluded that there is insufficient evidence to determine a correlation between the product switch and the magnitude of IPD cases per serotype. Rather, they emphasized the importance of several other epidemiologic factors pre-existing to PCV implementation such as innate serotype prevalence of *S. pneumoniae* and vaccination coverage to explain the rise in the IPD cases. Moreover, assessing the impact of PCVs should not be limited to IPD outcomes only. [83]

Table 8.3. *Summary of findings of studies included in the literature review on country experiences on PCV13 to PCV10 switch*

Author, Year	Country	Main findings
Suwantika et al., 2020	Indonesia	• Switching from PCV13 single-dose vials to PCV10 multi-dose vials produced the greatest cost savings in Indonesia considering factors including vaccination coverage, vaccine price, and logistics.

Author, Year	Country	Main findings
		• The switch will decrease the cases of IPD averted among under one of age from 246,164 to 105,587 due to the switch for 2019-2024.
Wouters et al., 2020	Belgium	• A rise in the nasopharyngeal carriage was seen on PCV13-non-PCV10 vaccine serotypes (3+6A+19A) (0.9%, 4 isolates/463 in 2016 vs 7.8%, 52/668) in 2017–2018 in Belgium after the product switch.
Wasserman et al., 2019	Canada	• Using the values derived by Desmet et al., the study projected 726,531 cases of disease over 10 years if the product switch from PCV13 to PCV10 will happen. • Despite a higher vaccine acquisition cost of PCV13, the net savings due to the lower disease incidence with continued PCV13 use would be greater than $500 million.
Levy et al., 2019	N/A	• Finland, who uses PCV10 in mass vaccination, did not result in increased serotype 19 IPD cases compared with other serotypes. • Sweden, where PCV13 or PCV10 was implemented depending on the counties, did not find a significant difference in the incidence of 19A IPD among counties with PCV10 and those with PCV13.
Desmet et al. 2018	Belgium	• A real country case of product switch from PCV13 to PCV10 revealed a rise in the number of IPD cases among 0-2 years old from 121 isolates in 2015 to 154 isolates in 2017. • The number of serotype 19A IPD isolates had an increase from 2 to 21 isolates from 2015 to 2017.
Diawara et al., 2015	Morocco	• The replacement to PCV10 (July 2012) from PCV13 did not find any significant increase in IPD cases among children 2-5 years old.

8.4.2 Health system stakeholder perspective

The Centers for Health Development and public and private practitioners comprised 58.3% (n=7) and 25% (n=3) of the total responses, respectively. The DOH Central Office had two respondents (16.7%). The summary of responses per domain for both Parts A and B are detailed in *Table 8.4*.

Table 8.4. *Characteristics and number of respondents per survey domain*

Domains (total respondents)	Survey Respondents [n,%]
1. Service Delivery (N=11)	DOH- National Immunization Program (NIP) (n=1, 11.1%) DOH- Central for Health Development (CHD) (n=7, 63.6%) Infectious disease and pediatrics practitioners (n=3, 27.3%)

2. Health Manpower (N=11)	DOH- NIP (n=1, 11.1%) DOH- CHD (n=7, 63.6%) Infectious disease and pediatrics practitioners (n=3, 27.3%)
3. Information (N=9)	DOH - (CHD) (n=7, 77.8%) Private primary clinics (n=2, 22.2%)
4. Supply Management (N=8)	DOH- NIP (n=6, 75%) Rural health unit and Private primary clinics (n=2, 25%)
5. Financing and Sustainability (N=9)	DOH- NIP (n=5, 55.6%) DOH- Health Policy Development and Planning Bureau (n=2, 22.2%) Private primary clinics (n=2, 22.2%)
6. Leadership and Governance (N=8)	DOH- NIP (n=1, 12.5%)) DOH- CHD (n=7, 87.5%))

Vaccine preparation The survey on the type of vaccine preparation contains five domains (service delivery, health manpower, supply management, financing and sustainability, leadership, and governance). The possibility of an increase in *Adverse Events Following Immunization (AEFI)* due to product contamination, logistical issues including inventory, storage, distribution and transportation, and balancing cost constraints and acceptability were highlighted as major concerns. Ensuring strict adherence to the Multi-Dose Vial Policy through effective training may help in building the confidence of health workers in administering MDVs. A nationwide situational analysis of logistical concerns per region or LGU level by the NIP and strengthening the information technology infrastructure for ordering and distribution may aid in the efficient implementation of the vaccination program. Lastly, improving operational efficiency through addressing the contextual concerns per region or LGU level will greatly expand vaccination acceptability and coverage nationwide.

The summary points of the responses are shown in *Table 8.5*. An in-depth discussion of each response is in the paragraphs following the table.

***Table 8.5** Summary table for vaccine preparation*

Domains	Single Dose Vials (SDVs)	Multi Dose Vials (MDVs)
1. Service Delivery	○ Reduction of possible contamination, lesser AEFI, better vaccine safety. ○ Easier tracking and logistics in terms of inventory, distribution, and utilization. ○ More supplies and cold chain capacity needed	○ Potential for contamination, increasing adverse events following immunization (AEFI). ○ Cost-effective for mass vaccinations ○ Less overall cold chain capacity required. ○ Ability to comply with strict multi-dose policy. (a potential cause of vaccine wastage) ○ Requires pooling of patients before vaccination
	Acceptability score: 4.6 (out of 5)	*Acceptability score: 3.9 (out of 5)*

Domains	Single Dose Vials (SDVs)	Multi Dose Vials (MDVs)
2. Health manpower	o Reorientation only o Fewer errors o Provide confidence in providing safe injections	o The required adherence to Multi-Dose Vial Policy may lead to decrease motivation and increase workload o The minor additional task of adding the date on the vial upon opening
	Acceptability score: 4.6 (out of 5)	*Acceptability score: 3.9 (out of 5)*
	o Some areas have health workers that are trained on both types of vaccines o Trained health workers will be motivated regardless of the vaccines	
3. Supply Manageme nt	o Greater cold chain capacity needed (upgrading) o Greater stock management and frequency of orders o Increased vial wastage	o Reduced required cold chain capacity o More difficult computation of orders and inventory o Potential to have greater vaccine waste o Unpredictability of demand
4. Financing and Sustainabili ty	o Increased costs due to an increased need for additional cold chain equipment and logistics o Less vaccine dose wastage, more vial wastage o More expensive but more predictable	o Reduced costs on cold chain equipment and logistics o Cheaper dose per vial o Higher vaccine wastage, less vial wastage o Cheaper but more unpredictable
	No effect on program promotion	
***5.** Leadershi p and Governance*	o *Improving operation efficiency due to ease of administration and safer vaccine preparation.* o *May have cost constraints and issues with logistics* o *Comparable to the private practice setting*	o *The operational efficiency of the NIP will increase when the demand for vaccination is high.* o *More cost-effective options in terms of considering procurement and storage.*

Domain 1: Service Delivery

A total of eleven respondents fit the stakeholder criteria to accomplish questions under Domain 1: Service Delivery.

(1) Advantages and disadvantages of vaccine preparations. The main advantage of SDVs is the reduction of possible contamination, lesser adverse events following immunization (AEFI), and thus having better vaccine safety. Moreover, since only one dose can be retrieved from the vial, in terms of program implementation, SDVs are easier for vaccine administration, there is also easier tracking and logistics in terms of inventory, distribution, and utilization. Also, the immediate use of the vial will make it less likely to be exposed to higher temperatures, resulting in less vaccine wastage. Its disadvantage is that there will be more vaccine vials, thus, the need for more cold chain storage capacity. However, a logistic problem faced when using SDVs is the innate bulk compared with MDVs. When inefficient logistics are operating, this may be a potential source of vaccine wastage.

The main advantages of MDVs include less overall cold chain storage capacity necessary for the health facilities and lower cost in logistics. Some respondents have mentioned that the vaccine preparation is cost-effective and more convenient for mass vaccinations. However, contrary to SDVs, MDVs have more potential for contamination, thereby increasing AEFI. Further, failure to comply with the strict multi—dose policy may be a potential cause of vaccine wastage. Based on the responses, pooling of patients must be performed before vaccine administration when using MDVs. According to one respondent, this may lead to vaccine wastage for those areas with only less than 4 infants who need vaccinations. However, it is important to note that MDVs of PCV can be stored for 28 days after opening. Thus, health workers should be properly oriented on good storage and labeling practices to ensure maximum utilization of MDVs.

(2) Acceptability for use by health workers of each vaccine preparation. Acceptability of SDVs to health workers was higher compared with MDVs (mean score of 4.6 vs 3.9 respectively). Stakeholders explained that SDVs are easy to administer and the importance of receiving the vaccine supersedes the importance of choosing the type of vaccine preparation to be used. According to the respondent from the NIP, almost all vaccine preparations in the program are in multi-dose preparations and s/he stated that parents are not particular with the preparation of the vaccine used. The private practitioner, on the other hand, stated that s/he had no experience in using MDVs.

(3) Rating the effect of the vaccine preparation on safe injection practices and improvement of quality of services. All respondents answered positively for SDVs (n=11; 100%) compared with 27.3% only for MDV (n=3) when it comes to safe injection practices and in improving the quality of services. The primary reason for their answer was the lower risk of contamination of SDVs. One interesting response was the client's uncertainty on the safety of previously opened vials.

Domain 2: Health Manpower

A total of eleven responses were obtained under Domain 2: Health Manpower. Questions in this domain involved the following topics: training requirements of health workers, the impact of implementation on health worker skills, motivation, and workload, and acceptability of the vaccine preparation by the health worker.

(1) Training requirements. SDVs do not seem to have a significant effect on the training requirements of the health workers (n=7; 63.4%). Furthermore, since almost all health workers have adequate experience in using SDVs, only reorientation on cold chain management will be needed. For MDVs, the majority expressed an increased effect on training requirements (n=6; 54.5%). Adherence to Multi-Dose Vial Policy will be a challenge faced in using MDVs. Additional training on sterility and aspiration techniques may be necessary. However, one notable response from the regional office has stated that their health workers were trained in using both SDVs and MDVs.

(2) Impact of implementation on health worker skills, motivation, and workload. Safe injection practices will be better observed in administering SDVs. Since there is only one dose per vial, fewer errors on aspirations may occur, thus, it may lead to less workload (positive n=5; 45.5%). Stakeholders have expressed that greater skills are needed for administering MDVs in terms of sterile techniques. More manpower will be needed for the training and observation of the Multi-Dose Vial Policy. Nevertheless, the respondents reacted positively to MDV (n=5; 45.5%).

Health worker motivation is perceived to increase for SDVs (n=4; 36.4%) due to the increased vaccination opportunities, improved vaccine safety, ease of vaccine administration, thus providing confidence to the health worker in providing safe injections. The same number of respondents chose no effect (n=4; 36.4%). They explained that the motivation of health workers does not depend on the vaccine preparations. For MDVs, discouragement due to increased workload and a possible decrease in confidence in providing safe injections may occur (decrease n=2; 18.2%). However, for those trained health workers, they will be more motivated (increase n=2; 18.2%). One interesting response was that the change from the usually given vaccine preparation which is SDV to MDV may confuse health workers.

Health staff workload for SDVs is perceived to increase (n=2; 18.2%) because of the time spent in storage, inventory, and disposal. However, some view that use of SDV results to a decrease in workload because of the ease of administration compared with MDVs may also happen (decrease n=3; 27.3%). However, for those respondents who stated that health workers were familiar with SDVs, there will be no perceived effect (n=4; 36.4%). It is important to note that health workers are already using SDVs. On the other hand, an increase in health staff workload is foreseen in implementing MDVs (n=4; 36.4%) due to the need to follow the Multi-Dose Vial Policy. An important response to note is that representatives from regional offices said that their health workers already have experience in using MDVs and only an additional minor task of adding the date on the vial upon opening should be performed.

(3) Acceptability of the vaccine preparation by the health worker. SDVs were rated an average of 4.6/5 compared with 3.9/5 for MDVs. The representative from private practice stated that SDVs have already been used for a long time, so using MDVs may be perceived as "*something new for private practitioners.*"

Domain 3: Supply Management

Eight responses were gathered for Domain 3, Supply Management. Questions were about the effect of the vaccine preparations on cold chain management and infrastructure, supply and use of safe injection equipment, forecasting, and stock management, and vaccine wastage.

(1) Effect of the vaccine preparations on cold chain management and infrastructure. For the respondents, SDVs have a negative impact on the cold chain management and infrastructure (n=7; 87.5%) because greater storage capacity will be needed for managing SDVs compared with MDVs (positive n=8; 100%).

*(2) Supply and use of safe injection equipment.*_An increase in the supply and use of safe injection equipment was gathered for both SDV (n=3; 37.5%) and MDV (n=4; 50%). For SDV, primarily there should be an increase in the cold chain equipment such as water packs, vaccine carriers, refrigerators, and cold rooms, therefore the need to upgrade the cold chain facility. Due to the current limited storage and the nature of the vaccine preparation, greater medical waste may be generated with SDV compared with MDV due to higher number of vials that needs to be disposed.

(3) Forecasting and stock management. A negative effect was perceived for SDV because of the greater stock management necessary, as well as the more frequent request for supply. The use of MDVs will save space, thus, more manageable cold chain requirements. However, according to some respondents, forecasting and computation for stocks for MDVs will be more difficult.

(4) Vaccine wastage. A decrease in wastage is associated with SDV use (n=6; 75%) while it will increase in MDV (n=8; 100%). In contrast to the stated response on medical wastes generated, since the entire vial contents will be administered fully for SDVs, it leads to less vaccine wastage. Improper handling of MDVs such as inexact or inaccurate aspiration of vaccine dose in MDV is a potential cause of vaccine wastage. Moreover, in the case of MDVs, there may be reluctance by some health workers to open MDVs for those *barangays* where only a few children need to be vaccinated. According to one response: "*…because some barangays have less than three babies that need to be vaccinated.*" A wastage factor of 1.05 and 1.18-1.33 for SDV and MDV, respectively, was mentioned by a respondent; however, no reference was attached.

Domain 4: Financing and Sustainability

Nine responses were gathered for this domain. Questions on this domain focused on the cost incurred on cold chain management, wastage, program promotion, and long-term sustainability of vaccination preparations.

(1) Cost incurred on cold chain management. An increase in the costs incurred on cold chain management of SDVs (n=8; 88.89%) is due to the increased need for additional cold chain equipment and logistics including transport and storage compared with MDVs (decrease n=8; 88.89%). To add, compared with MDVs, the cost per dose of SDVs will be higher.

(2) Wastage. When inquired about costs on wastage, the respondents viewed SDVs to have less wastage (SDV decrease n=6; 66.67%; MDV increase n=7; 77.78%). Since SDV contains the exact dose of the vaccine and has much reduced potential error in administration compared with MDVs, there may be less wastage. Therefore, the primary factor for the rise in the cost of wastage in MDVs is due to errors in vaccine administration. One specific argument stated that vaccine wastage is higher in MDV than SDV, however, this is compensated by the lower vaccine cost per dose in MDV versus SDV.

(3) Program promotion. The stakeholders answered mostly no effect on costs of program promotion for both SDV and MDV (n=6; 66.67% and n=5; 55.56% respectively). They have explained that *"program promotion should be based on the content effectiveness of a protective vaccine and not due to preparation."*

(4) Long-term sustainability of vaccination preparations. Lastly, in terms of uncertainties about the long-term sustainability of using SDVs and MDVs, stakeholders have discussed that both vaccine preparations have their respective problems in storage and inventory. Procuring SDVs may have implications on the limited storage capacity and adequacy of supply, while MDVs may tend to be over or understocked if inventory and forecasting will not be managed well. Although the unit cost of SDV is more expensive compared with MDV, the latter is said to be *"problematic when immunization demand is infrequent or unpredictable. Losing expired doses leads to additional costs and when vaccines are in short supply, depletes vaccine availability. Multi-dose vaccine vials present potential safety problems as well".*

Domain 5: Leadership and Governance

A total of eight responses were gathered for this domain. Questions were about the stakeholder's perception on the effect of operational efficiency of the vaccination program, effect on authority and prestige of the EPI and the NITAG, and primary differences in the monitoring of SDVs and MDVs.

(1) *Perception of the effect of the operational efficiency of the vaccination program.* Respondents perceived that the operational efficiency of the NIP will increase by using MDVs (Yes n=7; 87.5%) especially when the demand for vaccination is high. It is generally accepted as the more cost-effective option in terms of considering procurement and storage. However, some have raised that MDVs may be problematic for areas with infrequent or unpredictable immunization populations that may lead to difficult procurement or vaccine wastage of overstocks. When inquired about SDVs, there was a 50-50 response. The major factors for their corresponding answers for improving operation efficiency include the ease of administration and safer vaccine preparation. However, for those who answered negatively, cost constraints were pinpointed as the primary reason along with logistical factors that are necessary.

(2) Effect on authority and prestige of the EPI and the NITAG. SDVs were perceived to be the better option since the private sector also provides this type of vaccine preparation (Yes n=3; 37.5%). According to one response: "(Health Care Providers) may equate presentation of vaccines as like those with private doctors." In contrast, the use of MDVs may decrease the confidence of the caregivers in the health care providers due to potential safety concerns and AEFIs (No n=5;

62.5%). However, stakeholders have mentioned also that the majority of the vaccines available in their regional offices are in MDV preparations. Furthermore, one respondent commented that "*authority and prestige are not identified by the vaccine preparation.*"

*(3) Primary differences in the monitoring of vaccine preparations.*_A pressing difference in performance monitoring of SDVs and MDVs lies with complying with the Multi-Dose Vial Policy which includes proper handling and storage, consumption monitoring, and overall safety of the program.

PCV vaccine types The survey on the type of vaccine preparation contains six domains (service delivery, health manpower, information management, supply management, financing and sustainability, leadership, and governance). Overall, PCV10 is deemed less acceptable than PCV13 due to its perceived "incomplete protection". However, regardless of the type of PCV to be provided by the NIP, a greater focus on implementing higher vaccination coverage nationwide, coupled with ensuring vaccination acceptance for the parents of the infants to be vaccinated, should be done.

The summary points of the responses are shown in *Table 8.6*. An in-depth discussion of each response is in the paragraphs following the table.

Table 8.6. *Summary Table for PCV vaccine types*

<table>
<tr><th>Domains</th><th>PCV10</th><th>PCV13</th></tr>
<tr><td rowspan="3">1. Service Delivery</td><td>•PCV10 is cheaper than PCV13
•Perceived "incomplete protection"</td><td>• Viewed as protective against serotypes found in the country
• NIP emphasized that PCV13 is already being used. DOH-CAR used PCV 13 only.</td></tr>
<tr><td>Acceptability score: 3.5 (out of 5)</td><td>Acceptability score: 4.4 (out of 5)</td></tr>
<tr><td colspan="2">Parents are willing to vaccinate their children as long as it will be free of charge (esp. low-income groups)</td></tr>
<tr><td rowspan="3">2. Health manpower</td><td>Perceived "new" vaccine would require orientation</td><td>Training for vaccination will remain the same</td></tr>
<tr><td>Acceptability score: 3.3 (out of 5)</td><td>Acceptability score: 4.4 (out of 5)</td></tr>
<tr><td colspan="2">No perceived impact on health worker skills, health worker motivation, and health staff workload</td></tr>
<tr><td>2. Information Management</td><td colspan="2">No perceived effect: surveillance system of the government will always have to track Vaccine-Preventable Diseases (VPD)</td></tr>
<tr><td>3. Supply Management</td><td colspan="2">No effect on cold chain management and infrastructure, supply and use of safe injection equipment, forecasting, and stock management, and vaccine wastage.</td></tr>
<tr><td>4. Financing and Sustainability</td><td>"New" vaccine may incur additional costs of program promotion to explain the difference of the "new" vaccine to the usual vaccine used in immunization programs</td><td>DOH-CAR has specifically mentioned that current program promotion for PCV13 has not been a challenge and was successful in their region.</td></tr>
</table>

	Major factors include: (1) availability of funds to purchase vaccines and consistency of vaccine supply, (2) changes in the procurement protocol of DOH/government, (3) possibility of using other vaccine formulation to include more serotypes to provide broader protection in the future backed up by updated information and serotype distribution with the advancement of infrastructure in conducting surveillance of cases.	
6. Leadership and Governance	The focus should be on effectiveness and coverage rather than prestige	PCV13 will also improve the reputation of EPI and NITAG by providing the same vaccine given in the private setting.
	Careful surveillance of pneumococcal disease caused by the three serotypes (3,6,19A) found in PCV13 and not in PCV10	

Domain 1: Service Delivery

A total of eleven respondents accomplished the questions found in Domain 1. Questions rated were about the acceptability for use of each vaccine preparation by health workers, the effect of the vaccine preparation on safe injection practices and improvement of quality of services, and accessibility of various kinds of populations.

(1) Advantages and disadvantages of vaccine products. Respondents have mentioned that the main advantage of PCV10 compared with PCV13 is its cheaper vaccine price and procurement cost. Primary problems with PCV10 that was stated was the perceived "incomplete protection" compared with PCV13. Another problem lies with the response of DOH-CAR where they only have experience in using PCV13. The NIP emphasized that PCV13 is already being used in the immunization program, thereby, continued use will be beneficial for the program. However, the vaccine is more expensive than PCV10 which may have implications on the sustained availability of sufficient budget.

(2) Acceptability for use by health workers of each vaccine product. Acceptability of PCV13 to health workers was higher compared with PCV10 (mean score of 4.4 vs 3.5 respectively). Stakeholders explained that it will be more beneficial to administer the vaccine that may provide better protection. Regardless of the type of PCV used, parents are willing to submit their child for vaccination because it benefits their child as long as it will be free of charge.

(3) Rating the effect of the vaccine product on safe injection practices and improvement of quality of services. On the effect of vaccine preparations on the use of safe injection practices and improvement of quality of services, the majority of the respondents replied that no effect will be observed (PCV10 n=6; 54.5%; PCV13 n=6; 54.5%). They mentioned that *"the safe injection practices and improvement of quality of services are not affected by the content of the vaccine."*

(4) Accessibility to various types of populations. Regardless of the type of PCV, stakeholders answered that low-income groups may experience barriers to accessing the vaccines. If a cheaper vaccine will be procured, there may be a higher chance for these populations to have access to the vaccine, thus, government efforts should prioritize reaching these marginalized sectors.

Domain 2: Health Manpower

Eleven responses were obtained under Domain 2: Health Manpower which focused on training requirements of health workers, the impact of implementation on health worker skills, motivation, and workload. Acceptability of the vaccine preparation by the health worker was also rated.

(1) Training requirements. Stakeholders reported that the type of PCV has no effect on training requirements of health workers since the training for vaccination will remain the same (PCV10 n=6; 54.5%; PCV13 n=9; 81.9%). However, some respondents stated that there might be an increase in training requirements for PCV10 (n=3; 27.3%), due to the perception that it is a new vaccine, thus, orientation is needed. As mentioned, this is because PCV13 is presently used in the immunization program.

(2) Impact of implementation on health worker skills, motivation, and workload. Their answers showed no effect on the impact on health worker skills, health worker motivation, and health staff workload (*Table 8.7*).

Table 8.7. *Perceived effect of PCV products on components of health workforce domain*

	PCV10	PCV13
Health worker skills	No effect n=6; 54.5%	No effect n=8; 72.7%
Health worker motivation	No effect n=5; 45.5%	No effect n=7; 63.6%
Health staff workload	No effect n=8; 72.7%	No effect n=9; 81.9%

(3) Acceptability of the vaccine preparation by the health worker. PCV10 was rated an average score of 3.3/5 compared with a score of 4.4/5 for PCV13. Again, the perceived better protection offered by PCV13 was stated as the major reason for the higher rating.

Domain 3: Information Management

Nine responses were gathered for Domain 3: Information Management. Questions focused on the effect of implementing PCV on the current disease surveillance systems and awareness and reporting of AEFI.

(1) Effect on current disease surveillance systems and awareness and reporting of Adverse Events following Immunization (AEFI). Similar to the results in the previous domain, stakeholders agreed that no difference will be observed in disease surveillance, regardless of the type of PCV product. The surveillance system of the government will always have to track Vaccine-Preventable Diseases (VPD). [Effect on disease surveillance systems: No Effect n=5; 55.6%; Effect on awareness and reporting of AEFI No effect n=4; 44.4%, *Table 8.8*].

Table 8.8 *Perceived effect of PCV products on components of the information management domain.*

	PCV10	PCV13
Effect on disease surveillance systems	No effect n=5; 55.6%	No effect n=4; 44.4%
Effect on awareness and reporting of AEFI	No effect n=4; 44.4%	No effect n=5; 55.6%

Domain 4: Supply Management

Eight responses were gathered for Domain 4: Supply Management. Questions were about the effect of the vaccine preparations on cold chain management and infrastructure, supply and use of safe injection equipment, forecasting and stock management, and vaccine wastage. In general, stakeholders believed that the type of vaccine product does not affect these factors (*Table 8.9*).

Table 8.9 *Perceived effect of PCV products on components of the supply management domain.*

	PCV10	PCV13
Cold chain management and infrastructure	No effect n=6; 75%	No effect n=6; 75%
Supply and use of safe injection equipment	No effect n=5; 62.5%	No effect n=6; 75%
Forecasting and stock management	No effect n=5; 62.5%	No effect n=7; 87.5%
Wastage	No effect n=5; 62.5%	No effect n=6; 75%

Domain 5: Financing and Sustainability

Nine responses for Domain 5: Financing and Sustainability were gathered. Questions on this domain dealt with the cost incurred on program promotion, and long-term sustainability of vaccination preparations.

(1) Program promotion. PCV10, perceived as a "new" vaccine, may incur additional costs of program promotion to explain the difference of the "new" vaccine to the previous vaccine used in immunization programs (increase n=3; 33.3%). As for PCV13, since it was already previously implemented by the NIP, no other effects are perceived (n=4; 44.4%). DOH-CAR has specifically mentioned that current program promotion for PCV13 has not been a challenge and was successful in their region.

(2) Long-term sustainability of vaccination products. Issues raised on long term sustainability were: (1) availability of funds to purchase vaccines and consistency of vaccine supply, (2) changes in the procurement protocol of the DOH/government, (3) possibility of using other vaccine formulation to include more serotypes to provide broader protection in the future. This must be supported by updated information based on stronger surveillance studies.

Domain 6: Leadership and Governance

A total of eight responses were gathered for Domain 6: Leadership and Governance. Questions in this domain on the effect of the type of PCV product on the operational efficiency of the vaccination program, effect on authority and prestige of the EPI and the NITAG, differences in coordination with other government agencies, and primary differences in the monitoring of vaccine preparations.

(1) *Perception of the effect of the operational efficiency of the vaccination program*. More respondents favored PCV13 to improve operational efficiency (Yes n=4; 57.1%) because it is already included in routine immunization and because it contains a higher number of serotypes compared with PCV10.

(2) Effect on authority and prestige of EPI and NITAG. PCV13 will also improve the reputation of EPI and NITAG (Yes n=4; 57.1%) by implementing a vaccine that is perceived to provide better protection. However, one respondent stated that the focus should be on effectiveness and coverage rather than prestige.

(3) Coordination with other government agencies. Easier coordination with other government agencies is also viewed by using PCV13 (Positive n=4; 57.1%) because of the better quality of vaccine provided by the NIP.

(4) Primary differences in the monitoring of vaccine products. Although disease surveillance in health systems will not be largely affected by implementing either PCV10 or PCV13, careful surveillance of pneumococcal disease caused by the three serotypes (3,6,19A) found in PCV13 and not in PCV10 is crucial.

8.5. Conclusion

Results of the health systems impact assessment showed that generally, SDVs are rated as more acceptable than MDVs, especially in private settings where the experience on vaccination is drawn heavily from SDV use. Both types of vaccine preparations have their respective advantages and disadvantages on their use, therefore, balancing this with the available budget may be used as a factor in deciding what type of vaccine preparation should be procured.

PCV13 has an advantage when it comes to the confidence of health workers and public perception on quality of service from the NIP and the NITAG compared with PCV10 as it was perceived to give "incomplete protection". Implementation of PCV10 will also have to be supplemented by adequate orientation for the health workers. Equally important is the appropriate and effective communication among mothers to prevent resistance from the possible product switch, which may result in poor vaccination compliance.

9. LIMITATIONS

Clinical assessment A rapid review was conducted which meant that certain steps of a systematic review were abbreviated, and the search only included published studies in the English language. Second, due to the heterogeneity of methodological design and differences in clinical characteristics of the population included in the studies, only descriptive comparisons could be made. Studies on IPD and all-cause pneumonia could not be pooled since most were time-series population studies that are inherently heterogeneous in design. Moreover, a risk of bias assessment tool may be sought to capture the domains of a time series design.

Economic assessment The results of the economic assessment heavily relied on the input parameters used. Although the best data available was used in the assessment, the limitations of the following input parameters should be noted:

The existing national surveillance systems on existing pneumococcal serotypes in the Philippines at the RITM have limitations in terms of the passive nature of data collection and the lack of representativeness due to the limited coverage of sentinel sites. Thus, there is limitation with regards to the strength and conclusiveness of evidence on serotype prevalence and distribution in the country which could guide decision-makers on the appropriateness of existing PCV vaccines based on our serotype profile. The impact of implementing PCV vaccination over the past years cannot be determined as well due to this limitation on epidemiologic surveillance.

In this analysis, the computations on VE based on serotype distribution and coverage was based on the passive surveillance data in the Philippines. With regards costing, the dataset was based on PhilHealth's actual claims and its use underestimated the actual cost of treatment since claims data does not fully capture the actual treatment costs incurred by patients. Likewise, most of the incidence data were based on the PhilHealth claims which are prone to either overestimation because of upcoding or underestimation of disease incidence due to cases that are not claimed. Lastly, utility parameters were adapted from Thailand as we have no local utility data. Moreover, utility values were derived from the adult population instead of the pediatric population which is the target population in this assessment. Despite these limitations, we tested all parameters in the sensitivity analysis and found it not to affect our conclusion.

ELSHI assessment This report recognizes the limitations in the methodology since the data collection methods relied heavily on online correspondence instead of the preferred personal interviews, discussions, and consultations because of logistical barriers. Face-to-face focus group discussion with patient groups, civil societies, and leaders of marginalized communities and face-to-face consultations with internal and external stakeholders were improbable because of the pandemic situation. These face-to-face meetings would have yielded more substantive inputs and more concrete explanations could have been gathered. Second, the sample size and response rate for the health systems impact survey was low, which may indicate that the responses may not capture other concerns relevant to other health systems stakeholders. For future research, surveys may be distributed by the NIP to facilitate compliance for every CHD. Despite this, we still consider the findings reliable especially in our ethical and social assessment since its result is aligned with a national social values survey.[75]

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10. RELEVANT ATTACHMENTS

PCV Reassessment Capsule Protocol

Title **(Policy question)**	Should the DOH- Expanded Program on Immunization switch from using PCV13 to PCV10 in immunizing infants under five (5) years as prevention for invasive and non-invasive pneumococcal diseases?
Protocol Information	• Ceria-Pereña, J.A.; Briones, J.R.; Obmaña, S.M.; Genuino, A.J.; Guerrero, A.M.; Cabaluna, I.G.; Saniel, M.; Lazaro, J.E.; Roldan-Castor, M.A. • hta.philippines@gmail.com
Background	*Streptococcus pneumoniae* causes a spectrum of diseases ranging from non-invasive diseases such as acute otitis media and pneumonia up to severe and possibly fatal invasive diseases such as meningitis, bacteremia, and sepsis. *S. pneumoniae* infections in general are responsible for approximately 294,000 deaths in children under 5 years in 2015.[1] In the Philippines, pneumonia remains to be in the top ten causes of mortality, accounting for 23.4 deaths per 100 000 Filipinos.[2] An array of antibiotics is commonly used in the Philippines to treat pneumonia in children 2-59 months old. This includes Cefuroxime, Azithromycin, and Co-amoxiclav.[3] Based on the clinical practice guidelines developed by the Pediatric Infectious Diseases Society of the Philippines, *S. pneumoniae*-confirmed meningitis in children is treated with Penicillin for 10-14 days. Alternative treatment for pneumococcal meningitis includes Chloramphenicol and Ceftriaxone.[4] However, due to the development of resistance to the antibiotics used for pneumococcal infections, pneumococcal vaccination is needed to avert significant childhood mortality. This is supported by the notable reduction in the local burden of pneumonia which was as high as 42.7 deaths per 100 000 Filipinos[5] and an estimated 735 000 deaths in HIV-uninfected children worldwide in 2000, before the introduction of pneumococcal conjugate vaccines (PCV) in national immunization programs (NIP) worldwide.[1, 5] Currently, DOH NIP implements the single-dose vial preparation of PCV13 (Prevenar 13) as part of the Expanded Program on Immunization (EPI) in a 3+0 dosing schedule. From 2014 to 2018, PCV13 was implemented in all regions except in the National Capital

	Region, IVA, and IVB. In 2019, the NIP initiated a country-wide implementation of PCV13 vaccination. In light of the plan to expand the vaccination coverage, the presence of new clinical evidence on PCV10 and PCV13, updated price offer, and availability of cheaper multi-dose vial preparation, a re-assessment of the cost-effectiveness of these vaccines is necessary.
Research Questions	● What is the clinical efficacy/ effectiveness of PCV10 compared to PCV13 in preventing mortality and morbidity due to invasive pneumococcal disease (IPD), clinical pneumonia, and acute otitis media (AOM) in children under 5 years old? ● Which pneumococcal conjugate vaccine represents good value for money in the Philippines for preventing mortality and morbidity due to IPD, clinical pneumonia, and AOM of children under 5 years old? ● What are the budget implications of the Pneumococcal Conjugate Vaccine (PCV) in the Expanded Program on Immunization (EPI)? ● Are there any ethical, legal, social, and organizational implications for a possible switch of use PCV13 to PCV10 in the Philippines in preventing mortality and morbidity due to IPD, clinical pneumonia, and AOM in children under 5 years old?
Methods	**Assessment of Clinical efficacy/ effectiveness** A rapid review shall be performed to assess the clinical treatment effect of the vaccines in preventing mortality and morbidity due to invasive pneumococcal disease (IPD), clinical pneumonia, and acute otitis media (AOM) in children under 5 years old. A systematic search on Medline, CENTRAL, and Prospero will be searched. Relevant articles will be screened in accordance with PRISMA guidelines. Titles and abstracts will be screened and the full text will be retrieved if a decision could not be made based on available title and abstract. For the inclusion criteria, systematic reviews on PCV 10 and 13 among children less than 5 years of age will be identified. Studies for inclusion shall have any of the following outcomes: invasive pneumococcal disease (IPD), pneumonia, acute otitis media (AOM), pneumococcal nasopharyngeal (NP) carriage, pneumococcal serotype-specific immunogenicity, and indirect effects. Serotype-specific studies per outcome, (e.g. studies which assessed efficacy on 3, 6A, 19A only) will be also considered.

The included systematic review will be assessed for its quality using AMSTAR 2. AMSTAR-2 consists of critical (7 items) and non-critical domains (9 items). The confidence of the review's results will be graded "high confidence" if the SR complied with all critical and non-critical domains or only one non-critical domain was violated. The confidence will be graded as "moderate" if the authors complied with all critical domains but more than one non-critical domain was violated. If at least one critical domain is violated (with or without non-critical domain), the confidence of the review was graded as "low" and "critically low", respectively. One author will independently assess the quality of each study and discrepancies will be solved by discussion. Moreover, only results with high confidence will be considered for extraction and will be hand searched for relevant individual studies.

Systematic reviews will be hand searched for individual studies based on the same inclusion criteria above and duplicates among systematic reviews will be removed. We will include prospective or retrospective observational cohort, case-control, or randomized controlled trials (RCTs). These studies will be assessed for its quality through the risk of bias tools. For randomized control trials, Cochrane Collaboration's risk of bias v1 will be used. Meanwhile, the Newcastle - Ottawa quality assessment scale will be used for case-control/ cohort studies. Studies with scores of 1–3, 4–6 and7–9 were considered as low, intermediate and high quality, respectively. Only high-quality studies will be considered for data extraction.

Economic evaluation and Budget Impact Analysis

The economic evaluation for the reassessment of PCV10 and PCV13 will be a cost-utility analysis using a decision-analytic Markov model to calculate and compare the costs and utilities of using PCV13 vs PCV10. The model cohorts will be Filipino children under 5 years old who enter the model at the age of 6 weeks, after administration of the first dose of PCV. The analysis will be modeled over a lifetime horizon from a health systems perspective, with a discounting rate of 7% annually for both costs and outcomes. The incremental cost-effectiveness ratio (ICER) will be calculated and will be measured as Philippine Peso (PHP) per Life Year (LY) or Quality-adjusted life year (QALY) gained. A cost-effectiveness threshold of Php 150,000/QALY gained shall be used to determine the cost-effectiveness of the interventions. The study will employ four (4) policy scenarios: 100% coverage using single-dose vials, 100% coverage using multiple-dose vials, 50% coverage using single-dose vials, and 50% coverage using multiple-dose vials. Policy scenarios using 50% vaccination coverage shall account for the actual vaccination coverage of PCV13 in the Philippines.

Model overview

The Markov model from the previous PCV assessment by Haasis, et.al. (2015) will be used and will be populated with updated input parameters (see figure 1).[7] A cycle length of one (1) year will be run for 99 cycles to represent the lifetime horizon. The model assumed that only one infection could occur per year.

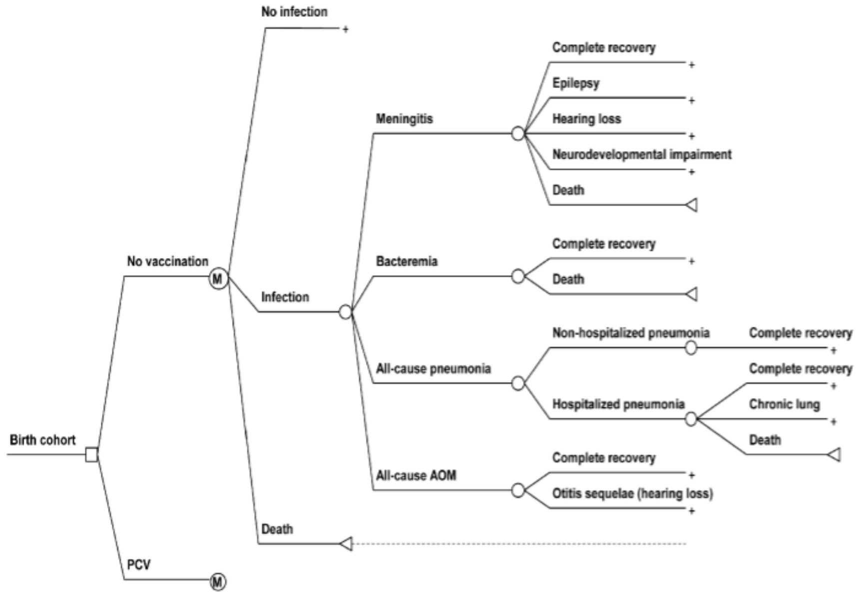

Figure 1. Markov model used for assessing the health and economic impact of pneumococcal conjugate vaccine (PCV) vaccination compared to "no vaccination". The structure of the PCV node was omitted in the figure, as it is identical to the "no vaccination" node.

The input parameters will be validated with local infectious disease experts, health economists, and national immunization program officers. Updated input parameters and their corresponding reference are as follows:

Input Parameter	Updated Reference
Epidemiologic data	Philippine Health Insurance Corporation (PhilHealth) claims, DOH- Epidemiology Bureau data
Local serotype prevalence data	Data from Research Institute for Tropical Medicine (2012-2019)
Clinical efficacy data	A systematic search on 2016-present PCV10 and PCV13 studies (to check updates on the WHO PRIME report)

Vaccination coverage rates	Expanded Immunization Program PCV13 vaccination coverage data (2018)
Utility data	Kulpeng et al (2013)
Vaccine cost	Price offer from companies, DOH Expanded Program on Immunization (EPI) (2019)
Treatment Cost	PhilHealth fee-for-service 2013 adjusted to 2020 costs through CPI, PhilHealth case rates
Budget impact estimates	DOH EPI vaccine utilization, projected total birth cohort

Both one-way and probabilistic sensitivity analyses (PSA) using second-order Monte Carlo simulation replicated for 1,000 times shall be performed to handle parametric uncertainties. The following distributions shall be assigned for the input parameters: beta distribution for transition probabilities, vaccine efficacy for pneumonia and AOM, and utility parameters; and, gamma distribution for vaccine efficacy for IPD and cost parameters. The PSA results shall be illustrated as incremental cost-effectiveness planes and cost-effectiveness acceptability curves.

For budget impact analysis, a 5-year budget impact shall be calculated in implementing PCV 10 versus PCV 13.

Assessment of ethical, legal, social, and organizational implications

Literature review on ethical, legal, social, and organizational implications assessment shall be conducted.

Social implications assessment will focus on identifying the marginalized population which will be affected by the possible switch of use from PCV13 to PCV10. Epidemiologic profile of patients whose isolates underwent *S. pneumoniae* serotyping will be determined based on age, geographic area, and socioeconomic status. This is to identify possible inequity as a result of removing vaccination coverage for PCV13-non-PCV10 serotypes.

Possible ethical implications of switching will be consulted with an ethicist. Further ethical assessment will be conducted as needed.

Consultation with legal experts and DOH Legal Service shall be done to gain context on legal implications of the possible switch in PCV

	used in the Philippines. Relevant health policies in place shall be taken into consideration. Organizational implications, i.e. impact on procurement, supply chain management, feasibility, and other programmatic concerns will be assessed through focus group discussion with program managers and private healthcare providers.
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	Vaccines Represent Good Value for Money in a Lower-Middle Income Country? A Cost-Utility Analysis in the Philippines. *PLoSONE 10*(7):e0131156. DOI:10.1371/journal.pone.0131156
About the Article	● Contributions of Authors The protocol for the reassessment was developed by SMO, JRB, JACP, AJG, and IGC.JACP and SMO manage the collection of epidemiologic data. JRB conducts cost adjustments from 2012 to 2020. JRB and ITC manage the systematic review for efficacy data of PCV. MS, JEL, and MARC identified data gaps and possible references for data inputs. They are also overseeing the general direction of the re-assessment along with AMG and AJG. ● Declarations of Interest The authors declare no competing interests. ● Sources of Support The authors acknowledge the contribution of experts from the Pediatric Infectious Disease Society of the Philippines, Philippine Society for Microbiology and Infectious Diseases, Philippine National Immunization Council, and Dr. Aleli Kraft (Professor, University of the Philippines School of Economics) for the validation of input parameters for the economic model. The authors also recognize the contribution of the Philippine Health Insurance Corporation, DOH National Program on Immunization, DOH Epidemiology Bureau, Research Institute for Tropical Medicine, and Dr. Maria Rosario Capeding in providing necessary data for the study. The authors would also like to thank Dr. Maria Carinnes Alejandria (Assistant Professor, Department of Sociology, University of Santo Tomas) for her guidance on the ethical and social component of the assessment.

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12. APPENDICES

APPENDIX A: Characteristics of Included Studies

Table 1. Characteristics of included systematic reviews

Author, Year	Corresponding author email	Conflict of interest	Search engines	Last search	Population	Intervention	Comparator	Outcome	Type of studies	Number of studies	Appraisal tool
Berman-Rosa, 2020	c.quach@umontreal.ca	None	Medline EMBASE Cumulative Index to Nursing and Allied Health Literature Web of Science Cochrane	July 2018	healthy children < or equal to 5 years	PCV10/13	Not specified	IPD	RCT	2	DistillerSR
									Cohort	1	DistillerSR
									Case-Control Studies	9	DistillerSR
								Acute Otitis Media (AOM) NP Carriage	RCT	3	DistillerSR
									RCT	2	DistillerSR
									Cohort	1	DistillerSR
Fortanier, 2019	rdamoiseaux@hotmail.com	none	CENTRAL, MEDLINE, Embase, CINAHL (EBSCO), LILVAS, Web of Science , ClinicalTrials.gov, www.who.int/trialsearch, google.com	March 2019	Children aged up to 12 years.	PCV 7, PCV 10, PCV 13	Placebo, control vaccine	AOM	RCT	11	Cochrane risk of bias tool
McGirr, 2019	ashleigh.a.mcgirr@gsk.com	GSK	Medline, EMBASE, CENTRAL	May 17 2017	children aged less than 5 years	PCV10/PCV13	Recombinant HepB and Hep A (RCT on PCV10)	IPD	RCT	1	RoB 2
									Indirect Cohort	4	NOS
									Case-Control	6	NOS
Choe, 2019	ychoe@hallym.ac.kr	None	PubMed EMBASE	April 8, 2019	healthy infants < 6 months	PCV7/10/13	Not specified	anti-pneumococcal antibody responses	RCT	69	not performed
		Pfizer	Medline	June 1 2017		PCV10/PCV13	not specified	IPD	Time Series	17	Not performed

Author, Year	Corresponding author email	Conflict of interest	Search engines	Last search	Population	Intervention	Comparator	Outcome	Type of studies	Number of studies	Appraisal tool
Tin Tin Htar, 2019	Myint.TinTinHtar@pfizer.com				children and adults (indirect effect)				Retrospective Studies	1	
								Pneumonia	Time Series	4	
									Retrospective Studies	1	
								Otitis Media	Time Series	3	
									Cross-Sectional	1	
								NP Carriage	Prospective Studies	2	
									Cross-Sectional	4	
									Time Series	1	
Alicinio, 2017	chiara.paganino @edu.unige.it	GSK, Pfizer	PubMed SciElo LILACS	December 15, 2016	Children aged under 5 years	PCV10/13	not specified	Community-Acquired Pneumonia	Time Series	6	modified Ramsey et al Criteria
									pre-post observational studies	6	(NIH) Checklist
Sings, 2017	heathersings@pfizer,com	Pfizer	PubMed EMBASE Cochrane	August 14, 2017	infants and children <5 years of age	PCV13	Not specified	IPD	Matched case-control	2	NOS
									Indirect cohort	3	NOS
									Unmatched case-control	1	NOS
Ciapponi, 2016	aciapponi@iecs.org.ar	NONE (PAHO funded)	CENTRAL, MEDLINE, EMBASE, LILACS	April 19, 2015	Children ≤5	PCV10	PCV7	Immunogenicity	RCT	3	RoB 2
									pre/ post observational studies	1	EPOQ Quality Criteria
de Oleivera, 2016	oliveirl@paho.org	NONE (PAHO funded)	MEDLINE (PubMed), Scopus, Web of Science, LILACS, CENTRAL	January 2016	Children ≤5 in LAC	PCV10/13	not specified	IPD	Interrupted Time Series	2	modified Ramsey et al Criteria
									Case-Control	1	Newcastle Ottawa Scale
									pre/ post observational studies	1	NIH checklist

Author, Year	Corresponding author email	Conflict of interest	Search engines	Last search	Population	Intervention	Comparator	Outcome	Type of studies	Number of studies	Appraisal tool
								Meningitis	Case Control	1	Newcastle Ottawa Scale
									pre/ post observational studies	4	NIH Checklist
								Pneumococcal Pneumonia	Interrupted Time Series	5	modified Ramsey et al Criteria
									Cohort	1	Newcastle Ottawa Scale
									Case-Control	1	Newcastle Ottawa Scale
									pre/ post observational studies	6	NIH Checlist
Duan, 2016	duankai63@163.com	NONE	PUBMED-Medline, OVID-Medline, EMBASE, CENTRAL CNKI	May 2015	Pre-term infants	PCV7/10/13	not specified	Immunogenicity	observational studies (not specified)	2	NOS
Moreira, 2016	marta.x.moreira@gsk.com	GSK FUNDED	PubMed EMBASE SciELO	February 2016	all age groups	PCV10	not applicable	IPD	Matched case-control	1	not performed
									Interrupted Time/Time Series	2	
									Retrospective Studies	2	
									Indirect Cohort	1	
								Pneumococcal Pneumonia	Observational Cross-Sectional Study	1	

Author, Year	Corresponding author email	Conflict of interest	Search engines	Last search	Population	Intervention	Comparator	Outcome	Type of studies	Number of studies	Appraisal tool
									with Retrospective DAta		
									Descriptive Study with Ecological Analysis	1	
Ruiz Aragon, 2013	jesusm.ruiz.ext@juntadeandalucia.es, reducido@hotmail.com	DID NOT DECLARE	Medline, EMBASE CENTAL, Science Citation Index, NICE	January 2013	infants	PCV13	PCV7	Immunogenicity	RCT	9	Critical Appraisal Skill Program (CASP) and Jadad Scale
Sucher, 2011	asucher@regis.edu	NONE	Medline	September 2011	pediatric patients	PCV13	PCV7	Immunogenicity	RCT	5	not performed

Table 2. Characteristics of included studies with meta-analysis

Author	Intervention	Comparator	Outcome and Subgroups	Type of studies pooled	No. of studies	No. of participants	Statistical method	Effect size (OR/RR)	Heterogeneity (I^2%)
Alicinio, 2017	PCV10/13	not specified	Clinical Pneumonia in <24 months				random effects	0.83 [0.78, 0.89]	99
			PCV10 vs No Vaccine	Before After	2	n.d	random effects	0.84 [0.78, 0.9]	65
				Interrupted Time Series	1	n.d			
			PCV13 vs PCV7	Before After	1	n.d		0.83 [0.82.0.84]	0
				Interrupted Time/ Time Series	3	n.d			
			PCV10 vs PCV7	Time Series	1	n.d		1.03 [0.82. 1.3]	n/a
			PCV13 vs No Vaccine	Before After	1	n.d		0.71 [0.7, 0.72]	n/a
			Clinical Pneumonia in 24-59 months				random effects	0.91 [0.86, 0.95]	96
			PCV13 vs PCV7	Interrupted Time Series	2	n.d	random effects	0.89 [0.8, 0.99]	78
				Before After	1	n.d			
			PCV10 vs No Vaccine	Before Aftet	1	n.d		0.93 [0.92, 0.93]	n/a

Author	Intervention	Comparator	Outcome and Subgroups	Type of studies pooled	No. of studies	No. of participants	Statistical method	Effect size (OR/RR)	Heterogeneity (I^2%)
			An X-ray confirmed Pneumonia <24 months				random effects	0.69 [0.65, 0.74]	63
			PCV10 vs No Vaccine	Before after	2	n.d	random effects	0.71 [0.55, 0.91]	26
			PCV13 vs No Vaccine	BEfore after	1	n.d		0.68 [0.59, 0.78]	43
				Interrupted Time Series	1	n.d			
			PCV13 vs PCV7	Interrupted/ Time Series	2	n.d		0.67 [0.62, 0.72]	0
			An X-ray confirmed Pneumonia 24-59 months				random effects	0.76 [0.67, 0.88]	87
			PCV10 vs No Vaccine	Before After	2	n.d	random effects	0.88 [0.87, 0.89	0
			PCV13 vs No Vaccine	Interrupted Time Series	1	n.d		0.74 [0.67, 0.81]	0
				Before After	1	n.d			
			PCV13 vs PCV7	Interrupted Time/ Time series	2	n.d		0.70 [0.64, 0.77]	0
Ruiz Aragon, 2013	PCV13	PCV7	Immunogenicity after Infant series (Primary series)						
			Serotype 3	RCT	6	2148	random effects	0.85 [0.76, 0.93]	94
			Serotype 6A	RCT	6	2146		0.53 [0.42, 0.64]	91
			Serotype 19A	RCT	6	2148		0.15 [0.02, 0.28]	98
			Immunogenicity after Toddler dose (Booster dose)						
			Serotype 3	RCT	4	1494	random effects	0.63 [0.26, 0.99]	99
			Serotype 6A	RCT	4	1492		0.12 [0.05,0.19]	83
			Serotype 19A	RCT	4	1492		0.01 [-0.01, 0.02]	29
Choe, 2019	PCV7/10/13	Not specified	PCV7	RCT	6	945	random effects	2.60 [2.45, 2.76]	98.30
			PCV10	RCT	8	1597		2.30 [2.21, 2.39]	97.7
			PCV13	RCT	8	2425		1.60 [1.54, 1.65]	97.7
Sings, 2017	PCV13	Not specified	Serotype 3	case-control	4	146	random-effects	63.5 [37.3, 89.7]	15.7

Table 3. Characteristics of included studies with overall invasive pneumococcal disease (IPD) outcome

Note: All studies performed the isolation of *S. pneumoniae* by culture from blood or CSF for endpoint determination and data source were from national surveillance of specified countries

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Study type	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
PCV 13/10 versus PCV 7												
Naucler, 2017	Sweden	≤48 months	PCV 13 PCV 10 PCV 7	2+1 (3, 5, and 12 months BD)	**PCV 13** counties: 96.2% **PCV 10** counties: 96.5% **PCV 7** (all counties for 2008): 95%	Cohort	Post PCV 13/10: 2013-2016 Post PCV 7: 2007-2009	IPD incidence/ 100,000 (95% CI) A. PCV 13 cohort B: PCV 10 cohort	A. 10.8 (10.3,11.5) (N = 1219) B. 14.4 (13.6,15.3) (N = 1169)	A. 13.2 (11.8,14.7) (N = 332) B. 17.7 (16.0,19.7) (N = 344)	A. 0.79 (0.70,0.89) B. 0.76 (0.67,0.86)	Government
PCV 13 versus PCV 7												
Varon, 2015	France	6-24 months	PCV13 PCV7	3+1 (2, 3, 4, months (12-15 months, BD))	PCV 13: >92% PCV 7: ≥86%	Cohort	Post PCV 13: 2012/2013 Post-PCV7: 2008/2009	IPD incidence	181/343 (52.8)	388/581 (66.8)	0.79 (0.70,0.89)	Pfizer
Jayasinghe, 2020	Australia	≤48 months	PCV 13 PCV 7	3+0 (2,4, 6 months)	PCV 13: 92% PCV 7: 90%	Cohort	Post PCV 7: 2007-2008 Post PCV 13: 2014	Incidence rate ratio (IRR) - All serotypes: A: less than 2 yo B: 2-4 yo **Adjusted annual case counts in parenthesis*	A: 6.0 (1336) B: 6.6 (1350)	11.3 (2156.7)	*PCV 13 vs no vaccine* 0.53 (0.50,0.57) *PCV 13 vs PCV 7*	Government

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Study type	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
											0.58 (0.54,0.62)	
Waight 2015	United Kingdom	≤48 months	PCV 13 PCV 7	2+ 1 (2,4, 12 months)	PCV13: >90% PCV7: > 90%	Cohort	PCV13: 2013-2014 PCV7: 2008-2010	IPD Incidence per 100 000 A: <2 yo, Overall B. <2 yo, vaccine type C. 2-4 yo, Overall D. 2-4 yo, vaccine type	A: 12·03 B: 1·43 C: 4·08 D: 0·46	A: 22·22 B: 12·67 C: 7·77 D: 4·98	A (Ratio): 0·54 (0·42, 0·69) B (Ratio): 0·11 (0·06, 0·22) C (Ratio): 0·52 (0·37, 0·74) D (Ratio): 0·09 (0·04, 0·25)	Government, Pfizer, GSK
Moore, 2016	USA	2–59 months	PCV 13 (1809) PCV 7 (1760)	3+1 (unspecified months)	N/A	Case control	2010-2014	A. Cases of IPD (Proportion) B. Control groups for IPD (Proportion)	A. 259/722 (36%) B. 1150/2991 (38%)	A. 343/722 (48%) B. 1417/2991 (47%)	VE: 86% (95%CI: 75.5, 92.3%)	Government
Domingues, 2014	Brazil	>2 months (Median age: 13.3 months)	PCV 10 No vaccine	2, 4, 6 months (12 months BD)	N/A	Case control	PCV 10: March-Sept. 2010 Follow up: Dec. 2012	A. Cases of IPD B. Control groups for IPD	A. 48/316 (15%) B. 129/316 (41%)	A. 221/1219 (18%) B. 304/1219 (25%)	VE: 83.8% (95%CI: 65.9, 92.3%)	Government, US CDC, PAHO (COI with GSK and Pfizer)
PCV 10 versus no vaccine												
Jokinen, 2015	Finland	3-42 months	PCV 10 'no vaccination'	2+1 (3,5, and 12 months BD)	PCV 10: 95%	Cohort	PCV 10: 2010-2013 No vaccine: 2004-2008	IPD incidence/100,000 person-years	12.9	62.9	0.21 (0.15,0.28)	GSK
Brandileone, 2018	Brazil	2 months-4 years	PCV10	3+1 (2,4,6,12-18 months)	PCV10: 81-94%	Cohort	Pre PCV10: 2005-2099	IPD incidence	28/247	1041/1313	0.14 (0.10, 0.20)	Government

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Study type	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
			'no vaccination'				Late PCV10: 2014-2015					
Rinta-Kokko, 2018	Finland	3- 78 months	PCV10 'no vaccination'	2+1 (3,5 months (12 months BD))	PCV10: up to 60%	Cohort	Pre PCV: 2002-2008 Post PCV10: 2010-2016	IPD incidence	23/114	391/520	0.27 (0.19, 0.39)	GSK

Table 4. Characteristics of included studies with serotype-specific invasive pneumococcal disease (IPD) outcome

Note: All studies performed the isolation of *S. pneumoniae* by culture from blood or CSF for endpoint determination and data source were from national surveillance of specified countries

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Study type	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
SEROTYPE 6A												
Van der Linden 2016	Germany	< 24 months	PCV 13 (221) PCV7 (125)	3+1 (2,3, 4 months (11-14 months BD))	PCV13: 58.3% PCV7: 33%	Case control	July 2010-June 2015	A: Cases for 3 doses B: Control for 3 doses C: Cases for 4 doses D: Control for 4 doses (vaccinated: unvaccinated)	A: 0:4 B: 74:20 C: 0:0 D: 33:16	A: 0:4 B: 38:27 C: 0:1 D: 11:19	NA	Pfizer
Naucler, 2017	Sweden	< 48 months	PCV 13 PCV 10 PCV 7	2+1 (3, 5 months (12 months BD))	PCV 13 counties: 96.2% PCV 10 counties: 96.5% PCV 7 (all counties for 2008): 95%	Cohort	Post PCV 13/10: 2013-2016 Post PCV 7: 2007-2009	IPD incidence/ 100,000 A. PCV 13 cohort B: PCV 10 cohort	A. 0.1 (0.0,0.2) B. 0.2 (0.1, 0.3)	A. 0.5 (0.3,0.9) B. 1.1 (0.7, 1.7)	A:0.19 (0.08, 0.48) B. 0.15 (0.08, 0.30)	Government

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Study type	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
Jokinen, 2015	Finland	3-42 months	PCV 10 'no vaccination'	2+1 (3,5months (12 months BD))	PCV 10: 95%	Cohort	PCV 10: 2010-2013 No vaccine: 2004-2008	IPD Incidence/100,000 person-years	0	2.2	0.00 (0.00,1.92)	GSK
Varon, 2015	France	6-24 months	PCV13 PCV7	3+1 (2, 3, 4, months (12-15 months, BD))	PCV 13: >92% PCV 7: ≥86%	Cohort	Post PCV 13 (2012/2013) Post-PCV7 (2008/2009)	Incidence of IPD	1/181	3/388	0.595 (0.22,1.57)	Pfizer
Brandileone, 2018	Brazil	2 months – 4 years	PCV10 'no vaccination'	3+1 (2,4,6,12-18 months)	PCV10: 81-94%	Cohort	Pre PCV: 2005-2009 Late PCV10: 2014-2015	IPD incidence	4/247	51/1313	0.42 (0.15, 1.14)	Government
Rinta-Kokko, 2018	Finland	3- 78 months	PCV10 'no vaccination'	2+1 (3,5 months (12 months BD))	PCV10: up to 60%	Cohort	Pre PCV: 2002-2008 Post PCV10: 2010-2016	IPD Incidence/ 100,000			95% (75, 100)	GSK
SEROTYPE 19A												
Naucler, 2017	Sweden	≤ 48 months	PCV 13 PCV 10 PCV 7	2+1 (3, 5 months) and 12 months BD))	PCV 13 counties: 96.2% PCV 10 counties: 96.5% PCV 7 (all counties for 2008): 95%	Cohort	Post PCV 13/10: 2013-2016 Post PCV 7: 2007-2009	IPD incidence/ 100,000 A. PCV 13 cohort B: PCV 10 cohort	A. 0.5 (0.4,0.7) B. 1.8 (1.6,2.2)	A. 0.5 (0.2, 1.0) B. 0.2 (0.1,0.9)	A. 1.06 (0.48, 2.34) B. 7.74 (1.83, 32.8)	Government

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Study type	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
Varon, 2015	France	6-24 months	PCV13 PCV7	3+1 (2, 3, 4, months (12-15 months, BD))	PCV 13: >92% PCV 7: ≥86%	Cohort	Post PCV 13 (2012/2013) Post-PCV7 (2008/2009)	IPD incidence	16/181 (8.8)	128/388 (33)	0.27 (0.16, 0.44)	Pfizer
Jokinen, 2015	Finland	3-42 months	PCV 10 'no vaccination'	2+1 (3,5 months (12 months BD))	PCV 10: 95%	Cohort	PCV 10: 2010-2013 No vaccine: 2004-2008	IPD Incidence/100,000 person-years	2.1	5.5	0.38 (0.14,0.87)	GSK
Brandileone, 2018	Brazil	2 months – 4 years	PCV10 'no vaccination'	3+1 (2,4,6,12-18 months)	PCV10: 81-94%	Cohort	Pre PCV: 2005-2009 Late PCV10: 2014-2015	IPD incidence	75/247	42/1313	9.49 (6.67, 13.50)	Government
Rinta-Kokko, 2018	Finland	3- 78 months	PCV10 'no vaccination'	2+1 (3,5 months (12 months BD))	PCV10: up to 60%	Cohort	Pre PCV: 2002-2008 Post PCV10: 2010-2016	IPD Incidence/ 100,000			26% (-13, 51)	GSK
Serotype 3												
Naucler, 2017	Sweden	< 48 months	PCV 13 PCV 10 PCV 7	2+1 (3, 5 months) and 12 months BD))	PCV 13 counties: 96.2% PCV 10 counties: 96.5% PCV 7 (all counties for 2008): 95%	Cohort	Post PCV 13/10: 2013-2016 Post PCV 7: 2007-2009	IPD incidence/ 100,000 A. PCV 13 cohort B: PCV 10 cohort	A. 1.1 (0.7, 1.7) B. 2.0 (1.7, 2.4)	A. 1.6 (1.4, 1.9) B. 1.4 (0.9, 2.1)	A. 1.42 (0.91, 2.22) B. 1.41 (0.88, 2.28)	Government

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Study type	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
Varon 2015	France	6-24 months	PCV13 PCV7	3+1 (2, 3, 4, months (12-15 months, BD))	PCV 13: >92% PCV 7: ≥86%	Cohort	post PCV 13 (2012/2013) post-PCV7 (2008/2009)	IPD incidence	5/181 (2.8)	18/388 (4.6)	0.60 (0.22, 1.58)	Pfizer
Jokinen, 2015	Finland	3-42 months	PCV 10 'no vaccination'	2+1 (3,5 months (12 months BD))	PCV 10: 95%	Cohort	PCV 10: 2010-2013 No vaccine: 2004-2008	IPD Incidence/100,000 person-years	2.1	0.5	4.20 (0.96, 25.17)	GSK
Brandileone, 2018	Brazil	2 months – 4 years	PCV10 'no vaccination'	3+1 (2,4,6,12-18 months)	PCV10: 81-94%	Cohort	Pre PCV: 2005-2009 Late PCV10: 2014-2015	IPD incidence	34/247	19/1313	9.51 (5.51, 16.40)	Government

Table 5. Characteristics of included studies with overall pneumonia outcome

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Endpoint determination	Study type	Data source	Study period	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI))	Funding
PCV13														
Becker-Dreps, 2014	Nicaragua	12-59 months	PCV13 No vaccine	3+1 (2,4,6 (12-24 BD)	PCV 13 in less than 12 months: 63% (2011), 97% (2012)	Hospital-diagnosed pneumonia	Cohort	Public hospital databases	Pre-PCV13: 2008-2010 Post-PCV13: 2011-2012	Incidence rate/1000 person-years in infants aged: A: Hospital-diagnosed pneumonia in <12	N/A	N/A	A: 0.67 (0.59, 0.75) B: 0.74 (0.67, 0.81) C: 0.73 (0.66, 0.81)	Pfizer

										months (716/1578) B: Hospital-diagnosed pneumonia in 12-23 months (296/602) C: Hospital-diagnosed pneumonia in 24-59 months (n.d.)				
PCV10														
Kilpi, 2018	Finland	Less than 7 months/ 7-11 months	PCV10 Hepatitis B vaccines **n at outcomes measure*	2+1	N/A		A: Hospital-diagnosed pneumonia B: Hospital-treated primary pneumonia C: Radiologically confirmed pneumonia	RCT	National Care Register	Follow-up after 1st dose (mean): 24 months	Incidence rate per 1000 person-years of: A: Hospital-diagnosed pneumonia: (195/271), (88, 65) B: Hospital treated primary pneumonia: (85/123), (33, 19) C: Radiologically	A: 9.9, 10.1 B: 4.3, 3.8 C: 4.9, 5.2	A:13.3, 15.1 B: 6.0, 4.4 C: 6.8, 9.0	A. Before 7 months of enrollment: 0.72 (0.59, 0.87) After 7 months of enrollment: 0.68 (0.48, 0.97) B.

											confirmed pneumonia: (97/130), (45,39) Note: *(before 7 months of age group)/ (7-11 months age group)			After 7 months of enrollment: 0.69 (0.52, 0.91) before 7 months of enrollment: 0.87 (0.49, 1.60) C. Before 7 months of enrollment: 0.71 (0.51 , 0.99) After 7 months of enrollment: 0.68 (0.47, 0.89)

Table 6. Characteristics of included studies with overall Acute Otitis Media (AOM) Outcome

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Endpoint determination	Study type	Follow up	Outcome measure	Intervention outcome	Comparator outcome	Risk Ratio (95% CI)	Funding source

Vesikari, 2016	Finland	1.5-6 months	PCV 10: (942) Hepa A/B vacc:(1,329)	2+1	N/A for RCTs	all-cause AOM	RCT	Follow up: 18 months	≥1 AOM episode	589/942	892/1329	0.93 (0.84, 1.03)	GSK
Saez Llorens, 2017	Panama	≤40 months	PCV10 Hepatitis B Vaccine	3+1	N/A for RCTs	Vaccine type C-AOM	RCT	Follow up period: 4 years (2007-2011)	≥1 AOM episode	6/3010	18/2979	0.83 (0.70, 0.98)	GSK
Pichichero, 2018	USA	6-36 months	PCV13 PCV7	3+0	100%	Clinically diagnose and Middle Ear Tympanocentesis	Cohort	30 months	AOM incidence	53/223	89/284	0.75 (0.58, 1.04)	Pfizer
Kawai, 2018	USA	0-4 yrs old	PCV13 'no vaccination'	3+1	≥3 doses: 93%	Clinically diagnosed AOM	Cohort	Follow up: 2 years	AOM incidence A. <2 yo B. 2-4 yo	A.826/1000 B.153/1000	A. 596/1000 B. 265/1000	A. 0.49 (0.41, 0.58) B. 0.63 (0.52, 0.77)	Not reported

Table 7. Characteristics of included studies with serotype-specific Acute Otitis Media (AOM) Outcome

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Endpoint determination	Study type	Follow up	Outcome measure	Intervention outcome	Comparator outcome	Risk Ratio (95% CI)	Funding source
Pichichero, 2018	USA	6-36 months	PCV13 PCV7	3+0	100%	Clinically diagnose and Middle Ear Tympanocentesis	Cohort	30 months	AOM incidence (6A)	0/53	6/89	0.12 (0.00, 2.23)	Pfizer
									AOM incidence (19A)	2/53	36/89	0.09 (0.02, 0.37)	
									AOM incidence (3)	2/53	4/89	0.83 (0.16, 4.43)	

Table 8. Characteristics of included studies with serotype 6A immunogenicity outcome measured through IgG concentration
Note: Endpoint of all studies is through IgG determination via ELISA; % responders is the proportion of infants with ≥ 0.35 ug/mL response

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
PCV 10 versus PCV 13										
Pomat 2018	PNG	1 month	**Dose 3**: PCV 10 (109) PCV 13 (102) **Dose 4**: PCV10 (103) PCV13 (98)	3+0 (1,2,3 months)	1 and 6 months after primary series	A. 4 month Dose 3: > 0.35 ug/mL (% Responders) B. 4 month Dose 3: GMC C. 9 month Dose 3: > 0.35 ug/mL (% Responders) D. 9 month Dose 3: GMC	A: 35.8 (26.5, 45.1) B: 0.24 (0.21, 0.29) C: 37.9 (28.36, 40.75) D: 0.26 (0.22, 0.30)	A: 77.5 (69.3, 85.6) B: 0.85 (0.69, 1.04) C: 64.3. (54.8, 73.8.) D: 0.49 (0.41, 0.60)	After 4 months: A: 2.85 (1.94, 4.19) B: -0.61 (-0.79, -0.43) C:: 1.74 (1.28, 2.36) D: -0.23 (-0.33,-0.13)	Government/ NGO
PCV 13 versus PCV 7										
Dagan, 2013	Israel	2 months	PCV13 (890) PCV7 (889)	3+1 (2,4,6,12 months)	1 month after infant and booster dose	IgG GMC after 3rd dose	2.53	0.36	2.17	Pfizer
Huang 2012	Taiwan	2 months	**Dose 3**: PCV 13 (80) PCV7 (83) **Dose 4**: PCV13 (79) PCV7 (84)	3+ 1 (2, 4, 6 months (15 months BD))	1-1.5 months after 3rd, 4th dose	A. Dose 3: % Responders B. Dose 3: GMC C. Dose 4: GMC	A: 100 (95.5, 100) B: 4.57 (3.92, 5.34) C: 11.55(9.66, 13.81)	A: 77.1 (66.6, 85.6) B: 0.79 (0.63, 0.99) C: 3.79 (3.01, 4.76)	A: 0.03 (0.00, 0.44) B: 3.78 (2.95, 4.61)	Wyeth
Wechx 2012	Brazil	1 month	PCV 13(156) PCV 7 (152-158)	3+1 (2 , 4, 6 months (12 months BD))	1-1.5 months after 3rd, 4th dose	A. Dose 3: % Responders B. Dose 3: GMC C. Dose 4: GMC	A: 97.4 B: 3.52 (3.06, 4.04) C: 8.96 (7.8, 10.28)	A: 52.6 B: 0.39 (0.32, 0.46) C: 1.84 (1.52, 2.24)	A: 0.05 (0.02, 0.14) B: 3.13 (2.64, 3.62)	Wyeth
Kieninger 2010	Germany	2 months	**Dose 3**: PCV13 (285) PCV7 (279) **Dose 4**: PCV13	3+1 (2 months, 3 months, 4 months (11-12	1 month after 3rd, 4th dose	A. Dose 3: % Responders B. Dose 3: GMC C. Dose 4: GMC	A: 91.9 (88.1, 94.8) B: 1.33 (1.18, 1.49) C: 5.88 (5.24, 6.59)	A: 31.6 (26.1, 37.5) B: 0.33 (0.20, 0.26) C: 1.74 (1.51, 2.01)	A: 0.12 (0.08, 0.18) B: 1.10 (0.94, 1.26)	Pfizer

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
			(279) PCV7 (268)	months BD))						
Snape 2010	United Kingdom	1.5-3.5 months	**Dose 2**: PCV13 (106) PCV7 (100) **Dose 3**: PCV13 (102) PCV7 (91)	2+1 (2 months, 4 months (12 months BD))	1 month after 3rd	A. Dose 3: % Responders D. Dose 3: GMC	A: 98.0 (92.9, 99.8) B: 6.27 (5.12, 7.69)	A: 71.7 (64.4, 80.6) B: 0.87 (0.64, 1.18)	A: 0.07 (0.02, 0.29) B: 5.40 (4.09, 6.71)	Wyeth
Yeh 2010	USA	2 months	**Dose 3**: PCV13 (252) PCV7 (252) **Dose 4**: PCV13 (239) PCV7 (223)	3+1 (2, 4, 6, and 12-15 months BD))	1 month after 3rd, 4th dose	A: Dose 3 Percent responders B: Dose 3 GMC C. Dose 4 GMC	A: 96 (92.8, 98.1) B. 2.19 (1.93, 2.48), C: 8.20 (7.30, 9.20)	A: 42.5 (36.2, 49) B: 0.25 (0.21, 0.29) C: 1.87 (1.60, 2.19)	A: 0.07 (0.04, 0.14) B: 1.94 (1.66, 2.22)	Wyeth
PCV 13 versus PCV 7										
Esposito 2010	Italy	3 months	PCV13 (303) PCV7 (303)	2+1 (3, 5, months (11 months BD))	1 month after 2nd, 3rd dose	A. Dose 3 % Responders B. Dose 3 GMC	A: 99.6 (97.7, 100.0) B:6.78 (6.04, 7.61)	A: 86.4 (81.5, 90.5) B: 1.42 (1.21, 1.66)	A 13.2 (9.1, 18.1) B. 4.77 (5.79, 13.93)	Wyeth
Payton 2013	USA	2 months	PCV13 (1216) PCV7 (159)	3+1 (2, 4, 6 months (12 months BD)	1 month after 3rd, 4th dose	A. Dose 3: % Responders B. Dose 3: GMC C. Dose 4: GMC	A: 97.3 B: 2.21 C: 7.11	A: 40.3 B: 0.28 C: 1.66	A. 57.0 (49.2, 64.5) B 7.82 (6.75, 9.07) C 4.29 (3.73, 4.93)	Wyeth
Bryant 2010	USA	2-3 months	**% responders**: PCV13 (94) PCV7 (107) **GMC:** PCV13	3+0 (2, 4, 6 months)	1 month after 3rd dose	A. Dose 3: % Responders B. Dose 3: GMC	A: 96.8 (90.86, 99.33) B: 2.29 (1.86, 2.82)	A: 34.0 (25.04, 43.80) B: 0.27 (0.22, 0 33)	A: 0.05 (0.02, 0.15) B: 2.02 (1.54, 2.50)	Wyeth

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
			(102) PCV 7 (113)							
Amdekar 2013	India	1.5 months	**Dose 3**: PCV13 (206) PCV7 (196) : PCV13 (193) PCV7 (196)	3+ 1 6, 10, and 14 weeks (12 months BD))	1 month after 3rd, 4th dose	A. Dose 3: % Responders B. Dose 3: GMC C. Dose 4: % Responders D. Dose 4: GMC	A: 90.0 (84.9, 93.8) B: 1.44 (1.25, 1.66) C: 100.0 (98.1, 100.0) D: 8.13 (7.11, 9.28)	A: 36.1 (29.3, 43.4) B: 0.28 (0.25, 0.31) C: 92.8 (88.2, 96.0) D: 1.87 (1.62, 2.17)	A 53.9 (45.4, 61.7) B 5.19 (4.33, 6.23) C 7.2 (4.0, 11.8) D 4.34 (3.56, 5.28)	Pfizer
PCV 10 versus PCV 7										
Bermal 2009	Philippines	1-3 months	PCV 10 (285) PCV 7 (95)	3+0 (6, 10, and 14 weeks of age)	1 month after 3rd dose	A: Dose 3 % Responders B: Dose 3 GMC	A: 45.6 (39.7, 51.6) B: 0.30 (0.26, 0.35)	A: 37.9 (28.1, 48.4) B: 0.23 (0.18, 0.30)	A.1.20 (0.90,1.60) B.NA	GSK
Bermal 2009	Poland	1-3 months	PCV 10 (285) PCV 7 (96)	3+0 (2, 4,6 months)	1 month after 3rd dose	A: Dose 3 % Responders B: Dose 3 GMC	A:30.9 (25.6, 36.6) B: .17 (0.15, 0.20)	A: 39.6 (29.7, 50.1) B: 0.26 (0.20, 0.33)	A.0.78 (0.58,1.06) B.NA	GSK
PCV 10 versus PCV 7										
Wysocki, 2009	Germany, Poland, Spain	2-18 months	G1- PCV 10 +MenC-CRM (169) G2- PCV 10 +MenC-TT (175) G3- PCV 10 +Hib-MenC	3+1 (2, 4, 6 months (11–18 months BD))	1 month after 3rd, 4th dose	A. Dose 3: % Responders B. Dose 3: GMC	A (G1): 41.3 (33.8, 49.2) A (G2): 33.3 (26.9, 35.9) A (G3): 28.5 (21.9, 35.9) B (G1): 0.24 (0.19, 0.29)	A (G4):43.4 (35.7, 51.3) B (G4):.24 (0.19, 0.29) C (G4): 88.8 (82.7, 93.3) D (G4) : 1.91 (1.5, 2.44)	G1:G4 0.95 (0.74, 1.22) G2:G4 0.76 (0.58,1.00)	GSK

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
			(173) G4- PCV 7 +Hib-MenC (170)				B (G2): 0.18 (0.15, 0.22) B (G3): 0.16 (0.13, 0.19) C (G1):72.4 (64.7, 79.3) C (G2): 68.4 (60.4 , 75.7) C (G3): 69.8 (62.0, 76.8) D (G1): 0.9 (0.72, 1.12) D (G2): 0.74 (0.58, 0.94) D (G3): 0.67 (0.53, 0.84)		G3:G4 0.65 (0.49, 0.87)	
Vesikari, 2009	Finland	6-12 weeks	PCV10 (1108) PCV7 (376)	3+1 (2,3,4 months, 12-18 months BD)	1 month after 3rd, 4th dose	A. Dose 3: % Responders B. Dose 3: GMC	A. 9.7 (6.5, 13.8) B. 0.07 (0.06, 0.08)	A. 19.4 (11.9, 28.9) B. 19.4 (11.9, 28.9)	A. 1.12 (1.06, 1.18) B. -19.33 (-27.83, -10.83)	GSK

^Risk ratio is computed for % responders; Mean difference is computed for GMC

Table 9. Characteristics of included studies with serotype 6A immunogenicity outcome measured through the Opsonophagocytic antibody titer.
Note: % responders is the proportion of infants with OPA Titer ≥ 1:8

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measured	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
PCV 10 versus PCV 13										
Temple 2013	Vietnam	2 months	PCV 10 (121) PCV 13 (120)	2+1 (2, 4 months,9.5 months BD)	1 month after booster dose	A: Dose 3 % Responders (Opsonisation index >8) B:Dose 3 Geometric Mean Opsonisation Index	A:66.9 (57.8, 75.2) B:118 (74, 189)	A: 100 (97, 100) B. 3847 (3311, 4468)	A: 80.34 (5.00, 1291.78) B: -3729 (-4310.35, -3147.65)	Government Bill & Melinda Gates Foundation
PCV 13 versus PCV 7										
Kieninger 2010	Germany	2 months	PCV 13 (100) PCV7 (100)	3+1 (2,3, 4 months (11-12 months BD))	1 month after primary series and booster dose	A: Dose 3: %Responder (OPA Titer > 1:8) B: Dose 3: OPA GMT C: Dose 4: %Responder (OPA Titer > 1:8) D: Dose 4: OPA GMT	A: 96.0 (90.0, 98.9) B: 1228 (883, 1708) C: 99.0 (94.4, 100) D: 2502 (1916, 3266)	A: 72.0 (61.8, 80.9) B: 122 (74, 202) C: 92.5 (85.1, 96.9) D: 501 (341, 736)	A: 0.14 (0.08, 0.25) B: 1106 (688.56, 1523.44)	Pfizer
Bryant 2010	USA	2-3 months	PCV 13 (121) PCV 7 (126)	3+0 (2, 4, 6 months)	1 month after primary series	A:Dose 3 OPA GMT	A: 855.6 (485.3, 1508.4)	A: 28.6 (12.9, 63.6)	827 (314.82, 1339.18)	Wyeth
Yeh 2010	USA	2 months	**Dose 3**: PCV13 (252) PCV7 (252) **Dose 4**: PCV13 (239) PCV7 (223)	3+1 (2, 4, 6, and 12-15 months BD))	1 month after primary series and booster dose	A: Dose 3: %Responder (OPA Titer > 1:8) B Dose 3: OPA GMT C: Dose 4: %Responder (OPA Titer > 1:8) D. Dose 4: OPA GMT	A: 100 (96.2, 100) B. 980 (783, 1226) C: 98.9 (94.1, 100) D: 2242 (1707, 2945)	A: 77.7 (67.9, 85.6) B: 100 (66, 152) C: 94.8 (88.3, 98.3) D. 539 (375, 774)	A: 0.01 (0.00, 0.15) B: 880 (654.36, 1105.64)	Wyeth
PCV10 versus PCV7										
Vesikari, 2009	Finland	6-12 weeks	PCV10 (1108) PCV7 (376)	3+1 (2,3,4 months, 12-18 months BD)	1 month after 3rd, 4th dose	A: Dose 3: %Responder (OPA	A. 58.0 (51.7, 64.1) B. 40.9 (31.4, 53.3)	A. 68.5 57.8, 78.0) B. 83.3 (51.6, 134.3)	A. 1.83 (1.34, 2.53) B. -42.4 (-85.18, 0.38)	GSK

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measured	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
PCV 10 versus PCV 13										
						Titer > 1:8) B: Dose 3: OPA GMT				

^Risk ratio is computed for % responders; Mean difference is computed for GMT

Table 10. Characteristics of included studies with serotype 19A immunogenicity outcome IgG concentration
Note: The endpoint of all studies is through IgG determination via ELISA; % responders is the proportion of samples with ≥ 0.35 ug/mL response. Check the follow-up period in Table 7.

Author, Year	Country	Population	Vaccine	Dosing schedule	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
PCV 10 versus PCV 13									
Pomat 2018	PNG	1 month	**Dose 3**: PCV 10 (109) PCV 13 (102) **Dose 4**: PCV10 (103) PCV13 (98)	3+0 (1,2,3 months)	A. 4 month Dose 3: > 0.35 ug/mL B. 4 month Dose 3: GMC C. 9 month Dose 3: > 0.35 ug/mL D. 9 month Dose 3: GMC	A: 89.0% (82.9, 95.1) B: 0.76 (0.66, 0.87) C: 85.4% (78.5, 92.4) D: 0.85 (0.73, 1.00)	A: 98.0% (95.4, 99.5) B: 3.63 (3.00, 4.39) C: 92.9% (87.8, 98.0) D: 1.21 (0.99, 1.47)	A:3.74 (1.09, 12.88) B: -2.87 (-3.57 , -2.17) C:2.04 (0.87, 4.79) D:-0.36 (- 0.64, -0.08)	Government /NGO
PCV 13 versus PCV 7									
Dagan, 2013	Israel	2 months	PCV13 (890) PCV7 (889)	3+1 (2,4,6,12 months)	IgG GMC after 3rd dose	1.81	0.70	1.11	Pfizer
Huang 2012	Taiwan	2 months	**Dose 3**: PCV 13 (80) PCV7 (83 **Dose 4**: PCV13 (79) PCV7 (84)	3+1 (2,4,6 months (15 months BD))	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A: 100 (95.5, 100) B: 3.69 (3.20, 4.24) C. 8.82 (7.45, 10.43)	A: 100 (95.6, 100) B. 2.46 (2.13, 2.84) C: 1.98 (1.69, 2.32)	A:1.06 (0.02, 52.92) B:1.23 (0.60, 1.86)	Wyeth
Wechx 2012	Brazil	1 month	PCV 13(156) PCV 7 (152-158)	3+1 (2 months, 4 months, 6 months (12 months BD)	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A: 99.4 B: 3.63 (3.22, 4.10) C: 8.91 (7.92, 10.03)	A: 98.7 B: 1.83 (1.61, 2.09) C :3.59 (3.13, 4.11)	A: 0.51(0.05, 5.53) B:1.80 (1.30, 2.30)	Wyeth
Kieninger 2010	Germany	2 months	**Dose 3**: PCV13 (285) PCV7 (279) **Dose 4**: PCV13 (279) PCV7 (268)	3+1 (2 months, 3 months, 4 months (11-12 months BD))	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A: 99.3 (97.5, 99.9) B: 3.26 (2.97, 3.59) C: 9.58 (8.68, 10.58)	A: 79.2 (73.8, 83.9) B: 0.64 (0.58, 0.71) C: 3.79 (3.40, 4.21)	A: 0.03 (0.01, 0.14) B: 2.62 (2.30, 2.94)	Pfizer

Author, Year	Country	Population	Vaccine	Dosing schedule	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
Snape 2010	UK	1.5-3.5 months	**Dose 3:** PCV13 (110) PCV7 (99) **Dose 4:** PCV13 (103) PCV7 (88)	2+1 (2 months, 4 months (12 months BD)	A. Dose 3 % Responders B. Dose 3 GMC	A: 100.0 (96.5, 100.0) B: 12.05 (10.01, 14.51)	A: 100 (95.9, 100.0) B: 5.32 (4.41, 6.42)	A:0.86 (0.02, 42.69) B: 6.73 (4.27, 9.19)	Wyeth
Yeh 2010	USA	2 months	**Dose 3**: PCV13 (252) PCV7 (252) **Dose 4**: PCV13 (239) PCV7 (223)	3+1 (2, 4, 6 months (12-15 months BD)	A: Dose 3 % Responders B: Dose 3 GMC C. Dose 4 GMC	A: 98.4 (96.0, 99.6) B: 2.07 (1.87, 2.30) C: 8.55 (7.64, 9.56)	A: 86.6 (81.6, 90.6) B: 0.89 (0.79, 0.99) C: 3.54 (3.15, 3.98)	A:0.13 (0.05, 0.35) B: 1.18 (0.94, 1.42)	Wyeth
PCV 13 versus PCV 7									
Esposito 2010	Italy	3 months	PCV13 (303) PCV7 (303)	2+1 (3, 5, (11 monthBD))	A: Dose 2 % Responders B: Dose 2 GMC C. Dose 3 % Responders D. Dose 3 GMC	A: 98.5 (96.1, 99.6) B: 2.87 (2.55, 3.24) C: 100.0 (98.5, 100.0) D: 9.81 (8.82, 10.92)	C: 99.6 (97.7, 100.0) D: 4.24 (3.85, 4.67)	C 0.4 (-1.1, 2.3) D 2.31 (2.00, 2.67)	Wyeth
Payton 2013	USA	2 months	PCV13 (1214) PCV7 (161)	3+1 (2, 4, 6 months (12 months BD))	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A: 98.6 B: 1.91 C:8.44	A: 94.4 B: 1.38 C: 4.56	A 4.2 (1.1, 8.7) B. 1.38 (1.21, 1.57) C 1.85 (1.62, 2.11)	Wyeth
Bryant 2010	USA	2-3 months	**% responders**: PCV13 (94) PCV7 (107) **GMC:** PCV13 (102) PCV 7 (113)	3+0 (2 months, 4 months, 6 months)	A: Dose 3 % Responders B. Dose 3 GMC	A:100.0 (96.15, 100.0) B:1.84 (1.57, 2.16)	A: 94.4 (88.19, 97.91) B: 1.17 (1.00, 1.38)	A: 0.09 (0.01, 1.53) B: 0.67 (0.32, 1.02)	Wyeth
Amdekar 2013	India	1.5 months	**Dose 3**: PCV13 (206) PCV7 (196) Dose 4: PCV13 (193) PCV7 (196)	3+1 (6, 10, and 14 weeks of age (12 months BD))	A. Dose 3: Percent responders B. Dose 3: GMC C. Dose 4: Percent responders D. Dose 4: GMC	A: 99.5 (97.3–100.0) B: 2.76 (2.46–3.10) C: 100.0 (98.1–100.0) D: 14.12 (12.45–16.01)	A: 84.7 (78.8–89.6) B: 0.74 (0.66–0.82) C: 98.5 (95.5–99.7) D: 3.56 (3.14–4.05)	A 14.8 (9.9, 20.7) B 3.75 (3.21, 4.38) C 1.5 (−0.4, 4.5) D 3.96 (3.31, 4.74)	Pfizer
PCV 10 versus PCV 7									
Bermal 2009	Philippines	1-3 months	PCV 10 (285) PCV 7 (95)	3+0 (6, 10, and 14 weeks of age)	A: Dose 3 % Responders B: Dose 3 GMC	A: 51.2 (45.3, 57.2) B:0.36 (0.31, 0.41)	A: 23.2 (15.1, 32.9) B: 0.18 (0.15, 0.22)	A.2.23 (1.52, 3.27) B.NA	GSK
Bermal 2009	Poland	1-3months	PCV 10 (284) PCV 7 (96)	3+0 (2, 4, and 6 months of age)	A: Dose 3 % Responders B: Dose 3 GMC	A: 43.7 (37.8, 49.6) B: 0.29 (0.25, 0.34)	A: 11.5 (5.9, 19.6) B: 0.12 (0.25, 0.34)	A.3.81 (2.15, 6.75)	GSK

Author, Year	Country	Population	Vaccine	Dosing schedule	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
								B.NA	
Wysocki, 2009	Germany, Poland, Spain	2-18 months	G1: PCV 10 +MenC-CRM (169) G4: PCV 7 +Hib-MenC (170)	3+1 (2, 4, 6 months (11–18 months BD))	A. Dose 3: % Responders B. Dose 3: GMC C: Dose 4: % Responders D: Dose 4 GMC	A (G1): 43.1 (35.5, 51.0) A (G2) 37.6 (30.3, 45.2) A (G3) 32.2 (25.2, 39.7) B (G1) 0.27 (0.22, 0.32) B (G2) 0.22 (0.19, 0.27) B (G3) 0.18 (0.15, 0.22) C (G1): 80.9 (73.9, 86.7) C (G2): 76.5 (68.9, 82.9) C (G3): 71.3 (63.6, 78.1) D (G1): 1.19 (0.96, 1.47) D (G2): 1.12 (0.89, 1.42) D (G3): 0.75 (0.6, 0.94)	A (G4) 12.7 (8.0, 18.7) B (G4) 0.12 (0.1, 0.14) C (G4) 44.1 (36.0, 52.4) D (G4): 0.35 (0.29, 0.42)	G1: G4 3.34 (2.18, 5.11) G2: G4 2.91 (1.89, 4.50) G3: G4 2.50 (1.60,3.91)	GSK
Vesikari, 2009	Finland	6-12 weeks	PCV10 (1108) PCV7 (376)	3+1 (2,3,4 months, 12-18 months BD)	1 month after 3rd, 4th dose	A. 8.2 (5.3, 12.1) B. 0.08 (0.07, 0.09)	A. 10.6 (5.2, 18.7) B. 0.11 (0.09, 0.13)	A.1.03 (0.99. 1.07) B. -0.03 (-0.05, -0.008)	GSK

^Risk ratio- % responder; Mean difference- GMC

Table 11. Characteristics of included studies with serotype 19A immunogenicity outcome measured through the Opsonophagocytic antibody titer.
Note: % responders is the proportion of infants with OPA Titer ≥ 1:8

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measured	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
Temple 2013	Vietnam	2 months	PCV 10 (121)	2+1 (2, 4 months (	1 month after	A: Dose 3 % Responders (Opsonisation index >8)	A: 61.2 (51.9, 69.9) B: 25 (18, 34)	A: 99.2 (95.4, 100)	A: 46.61 (6.53, 332.43) B: -562 (-705.72,-418.28)	Government Bill &

			PCV 13 (120)	9.5 months BD))	booster dose	B: Geometric Mean Opsonisation Index		B: 587 (461, 748)		Melinda Gates Foundation
Kieninger 2010	Germany	2 months	PCV 13 (100) PCV7 (100)	3+1 (2,3, 4 months (11-12 months BD))	1 month after primary series and booster dose	A: Dose 3: %Responder (OPA Titer > 1:8) B: Dose 3: OPA GMT C: Dose 4: %Responder (OPA Titer > 1:8) D: Dose 4: OPA GMT	A: 100 (96.2, 100 B: 442 (361, 543) C:100 (96.3, 100) D:1349 (1089, 1672)	A: 17.0 (10.1, 26.2) B: 7 (5, 9) C: 68.1 (57.5, 77.5) D:59 (37, 94)	A:0.00 (0.00, 0.03) B: 435 (343.98, 526.02)	Pfizer
Bryant 2010	USA	2-3 months	PCV 13 (121) PCV 7 (126)	3+0 (2, 4, 6 months)	1 month after primary series	A:Dose 3 OPA GMT	A: 42.0 (20.1, 87.8)	A: 5.2 (3.8, 7.1)	36.8 (2.91, 70.69)	Wyeth
Yeh 2010	USA	2 months	**Dose 3**: PCV13 (252) PCV7 (252) **Dose 4**: PCV13 (239) PCV7 (223)	3+1 (2, 4, 6, and 12-15 months BD))	1 month after primary series and booster dose	A: Dose 3: %Responder (OPA Titer > 1:8) B Dose 3: OPA GMT C: Dose 4: %Responder (OPA Titer > 1:8) D. Dose 4: OPA GMT	A: 91.4 (83.8, 96.2) B. 152 (105, 220) C: 97.8 (92.3, 99.7) D: 1024 (774, 1355)	A: 16.3 (9.4, 25.5) B: 7 (5, 8) C: 53.2 (42.6, 63.6) D. 268 (164, 436)	A: 0.10 (0.07, 0.16) B: 145 (87.48, 202.52)	Wyeth
Vesikari, 2009	Finland	6-12 weeks	PCV10 (1108) PCV7 (376)	3+1 (2,3,4 months, 12-18 months BD)	1 month after 3rd, 4th dose	A: Dose 3: %Responder (OPA Titer > 1:8) B Dose 3: OPA GMT	A. 19.6 (15.0, 25.0) B. 8.6 (7.1, 10.5)	A. 3.4 (0.7, 9.5) B. 4.5 (3.9, 5.3)	A. 0.83 (0.77, 0.89) B. 4.1 (2.26, 5.94)	GSK

^Risk ratio- % responder; Mean difference- GMC

Table 12. Characteristics of included studies with serotype 3 immunogenicity outcome IgG concentration
Note: The endpoint of all studies is through IgG determination via ELISA; % responders is the proportion of samples with ≥ 0.35 ug/mL response. Check the follow-up period in Table 7.

Author, Year	Country	Population	Vaccine	Dosing schedule	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/Mean Difference (95% CI)^	Funding
PCV 10 versus PCV 13									
Pomat 2018	PNG	1 month	**Dose 3**: PCV 10 (109) PCV 13 (102) **Dose 4**: PCV10 (103) PCV13 (98)	3+0 (1,2,3 months)	A. 4 month Dose 3: > 0.35 ug/mL B. 4 month Dose 3: GMC C. 9 month Dose 3: > 0.35 ug/mL D. 9 month Dose 3: GMC	A: 45.0% (35.3, 54.6) B: 0.32 (0.27, 0.39) C: 50.5% (40.6, 60.4) D: 0.34 (0.28, 0.42)	A: 81.4% (73.8, 88.9) B: 0.70 (0.60, 0.81) C: 32.7% (23.4, 41.9) D: 0.29 (0.24, 0.36)	A: 2.96 (1.90, 4.59) B: -0.38 (-0.50, -0.26) C:0.74 (0.58, 0.93) D:0.05 (-0.04, 0.14)	Government/NGO
PCV 13 versus PCV 7									
Dagan 2013	Israel	2 months	**PCV13 (890)** **PCV7 (889)**	3+1 (2,4,6,12 months)	IgG GMC	0.97	0.04	0.93	Pfizer
Huang 2012	Taiwain	2 months	**Dose 3**: PCV 13 (80) PCV7 (83) **Dose 4**: PCV13 (79) PCV7 (84)	3+1 (2,4,6 months (15 months BD))	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A: 97.5 (91.3, 99.7) B: 1.20 (1.00, 1.45) C: 1.29 (1.09, 1.53)	A: 2.4 (0.3, 8.4) B: 0.05 (0.04, 0.06) C: 0.12 (0.09, 0.16)	A: 0.03 (0.01, 0.10) B: 1.15 (0.92, 1.38)	Wyeth
Wechx 2012	Brazil	1 month	PCV 13(156) PCV 7 (152-158)	3+1 (2,4,6 months (12 months BD))	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A:87.1 B: 0.77 (0.69, 0.86) C: 0.85 (0.75, 0.96)	A: 4.4 B: 0.05 (0.04, 0.06) C: 0.07 (0.06, 0.08)	A: 0.13 (0.09, 0.20) B: 0.75 (0.66, 0.84)	Wyeth
Kieninger 2010	Germany	2 months	**Dose 3**: PCV13 (285) PCV7 (279) **Dose 4**: PCV13 (279) PCV7 (268)	3+1 (2,3,4 months (11-12 months BD0)	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A: 98.2 (95.9, 99.4) B: 1.55 (1.41, 1.72) C: 1.02 (0.92, 1.13)	A: 6.3 (3.7, 9.8) B: 0.05 (0.04, 0.06) C: 0.07 (0.06, 0.08)	A: 0.02(0.01, 0.04) B: 1.50 (1.34, 1.66)	Pfizer

Author, Year	Country	Population	Vaccine	Dosing schedule	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/Mean Difference (95% CI)^	Funding
Snape 2010	UK	1.5-3.5 months	**Dose 2**: PCV13 (107) PCV7 (102) **Dose 3**: PCV13 (102) PCV7 (91)	2+1 (2,4 months (12 months BD))	A. Dose 3 % Responders B. Dose 3 GMC	A: 88.2 (80.4 93.8) B: 1.01 (0.83, 1.22)	A: 6.6 (2.5, 13.8) B: 0.07 (0.05, 0.09)	A: 0.13 (0.07, 0.21) B: 0.94 (0.74, 1.14)	Wyeth
Yeh 2010	USA	2 months	**Dose 3**: PCV13 (252) PCV7 (252) **Dose 4**: PCV13 (239) PCV7 (223)	3+1 (2, 4, 6, and 12-15 months BD))	A: Dose 3 % Responders B: Dose 3 GMC C. Dose 4 GMC	A: 63.5 (57.1, 69.4) B: 0.49 (0.43, 0.55) C: 0.94 (0.83,1.05)	A: 4.6 (2.3, 8.0) B: 0.04 (0.03, 0.04) C: 0.07 (0.05, 0.08)	A: 0.38 (0.32, 0.45) B: 0.45 (0.39, 0.51)	Wyeth
Esposito 2010	Italy	3 months	PCV13 (303) PCV7 (303)	2+1 (3, 5, 11 month)	A: Dose 2 % Responders B: Dose 2 GMC C. Dose 3 % Responders D. Dose 3 GMC	A: 92.8 (89.0, 95.6) B: 1.15 (1.04, 1.28) C: 93.9 (90.1, 96.5) D: 1.22 (1.09, 1.35)	C: 6.7 (3.9, 10.6) D: 0.07 (0.06, 0.08)	C 87.2 (82.1, 91.2) D 16.83 (13.93, 20.35)	Wyeth
Payton 2013	USA	2 months	PCV13 (1193) PCV7 (164)	3+1 (2, 4, 6 months (12 months BD))	A: Dose 3 % Responders B. Dose 3 GMC C. Dose 4 GMC	A: 73.3 B: 0.56 C: 0.75	A: 3.0 B: 0.04 C: 0.07	A 70.3 (65.8, 73.6) B 14.49 (12.74, 16.48) C 11.57 (10.05, 13.31)	Wyeth
Bryant 2010	USA	2-3 months	**% responders**: PCV13 (94) PCV7 (107) **GMC:** PCV13 (102) PCV 7 (113)	3+0 (2,4,6 months)	A: Dose 3 % Responders B. Dose 3 GMC	A: 98.9 (94.21, 99.97) B: 1.33 (1.16, 1.54)	A: 14.0 (8.06, 22.07) B:0.09 (0.07, 0.12)	A: 0.01 (0.00, 0.09) B: 1.24 (1.05, 1.43)	Wyeth

Author, Year	Country	Population	Vaccine	Dosing schedule	Outcome measure	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/Mean Difference (95% CI)^	Funding
Amdekar 2013	India	1.5 months	**Dose 3**: PCV13 (206) PCV7 (196) Dose 4: PCV13 (193) PCV7 (196)	3+1 (6, 10, and 14 weeks of age, 12 months BD))	A. Dose 3: % Responders B. Dose 3: GMC C. Dose 4: % Responders D. Dose 4: GMC	A: 87.6 (82.1, 91.8) B: 0.80 (0.72, 0.90) C: 90.2 (85.1, 94.0) D: 0.91 (0.81, 1.03)	A: 2.1 (0.6, 5.4) B: 0.05 (0.05, 0.06) C: 12.9 (8.5, 18.4) D: 0.09 (0.08, 0.11)	A 85.4 (79.7, 90.0) B 15.34 (12.89, 18.25) C 77.3 (70.2, 83.2) D 9.78 (7.75, 12.35)	Pfizer

^Risk ratio- % responder; Mean difference- GMC

Table 13. Characteristics of included studies with serotype 3 immunogenicity outcome measured through the Opsonophagocytic antibody titer.
Note: % responders is the proportion of infants with OPA Titer ≥ 1:8

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measured	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio/ Mean Difference (95% CI)^	Funding
PCV 10 versus PCV 13										
Temple 2013	Vietnam	2 months	PCV 10 (121) PCV 13 (120)	2+1 (2, 4 months (9.5 months BD))	1 month after booster dose	A: Dose 3 % Responders (Opsonisation index >8) B : Geometric Mean Opsonisation Index	A: 3.3 (0.9, 8.2) B: 4 (4, 5)	A: 88.3 (81.2, 93.5) B:54 (43, 68)	A: 8.29 (5.06, 13.58) B: -50 (-632.51, -37.49)	Government Bill & Melinda Gates Foundation
PCV 13 versus PCV 10										
Kieninger 2010	Germany	2 months	PCV 13 (100) PCV7 (100)	3+1 (2,3, 4 months (11-12 months BD))	1 month after primary series and booster dose	A: Dose 3: %Responder (OPA Titer > 1:8) B: Dose 3: OPA GMT C: Dose 4: %Responder (OPA Titer > 1:8) D: Dose 4: OPA GMT	A: 99.0 (94.6, 100) B: 251 (206, 306) C: 98.0 (92.8, 99.8) D: 188 (153, 231)	A: (24.5 16.2, 4.4) B: 6 (5, 7) C: 35.8 (26.2, 46.3) D: 8 (6, 10)	A: 0.01 (0.00, 0.04) B: 245 (194.99, 295.01)	Pfizer

Bryant 2010	USA	2-3 months	PCV 13 (121) PCV 7 (126)	3+0 (2, 4, 6 months)	1 month after primary series	A:Dose 3 OPA GMT	A: 10.9 (7.8, 15.2)	A: 4.1(3.9, 4.3)	A: 6.8 (3.09, 10.51)	Wyeth
Yeh 2010	USA	2 months	**Dose 3**: PCV13 (252) PCV7 (252) **Dose 4**: PCV13 (239) PCV7 (223)	3+1 (2, 4, 6, and 12-15 months BD))	1 month after primary series and booster dose	A: Dose 3: %Responder (OPA Titer > 1:8) B Dose 3: OPA GMT C: Dose 4: %Responder (OPA Titer > 1:8) D. Dose 4: OPA GMT	A: 96.8 (91.0, 99.3) B. 121 (92, 158) C: 97.8 (92.3, 99.7) D: 380 (300, 482)	A: 21.3 (13.5, 30.9) B: 7 (5, 9) C: 43.8 (33.6, 54.3) D. 12 (9, 16)	A: 0.04 (0.02, 0.09) B: 114 (80.94, 147.06)	Wyeth

^Risk ratio- % responder; Mean difference- GMT

Table 14. Characteristics of included studies with overall nasopharyngeal carriage outcome

Author, Year	Country	Population	Vaccine	Dosing schedule	Vaccine coverage	Endpoint determination	Study type	Data source	Study period/Follow-up	Outcome measure	Treatment Arm	Control Arm	Risk Ratio (95% CI)	Funding
Saez Llorenz, 2017	Panama	2 months	PCV10 (627) Hep B (639)	3+1 (2,4,6, (15-18 months BD))	N/A	Serotypes of *S. pneumoniae* isolated through Nasopharyngeal colonization	RCT	N/A	1, 6-9 months after primary series, before booster dose, 1,3,9 months after the booster dose	% colonization	9.7 (7.5, 12.3)	13.5 (10.9, 16.4)	0.74 (0.58, 0.96)	GSK
Heinsbroek, 2018	Malawi	4.5 months, 1-4 years old	PCV 13 No vaccine	3+0 (6, 10, 14 weeks)	PCV 13 (2014): 89%	Serotypes of *S. pneumoniae* isolated through Nasopharyngeal colonization	Cohort	HDSS Records/ Local data	Prevaccination: 2009-2011 PCV 13: 2014 Exposed: 18 weeks	A. *S. pneumoniae* carriage (all serotypes), 18 weeks B. *S.*	A. 22/44 (50.0%) B. n.d.	A. 53/71 (74.7%) B. 72/103 (70.0%)	0.67 (0.48, 0.93)	not indicated

										pneumoniae carriage (all serotypes), 1-4 years				
Kaur 2016	USA	6 months	PCV 13 (685) PCV 7 (350)	3+1 (2, 4, and 6 months (15 months BD))	N/A	Serotypes of *S. pneumoniae* isolated through Nasopharyngeal colonization	Cohort	Laboratory data	PCV7 period (Jul 2006-Sept 2010) PCV13 period (Oct 2010-Sept 2015)	*S. pneumoniae* carriage (all serotypes)	685/2044 (33.5%)	350/1072 (32.7%)	1.03 (0.92, 1.14)	Pfizer and NIH
Bosch 2015	Netherlands	11-24 months	PCV10 (330) PCV7 (330)	3+1 (2,3,4 months (11 months BD))	50%	Serotypes of *S. pneumoniae* isolated through Nasopharyngeal colonization	Cohort	A questionnaire filled by nurses on possible predictors of NP carriage	PCV7: 2010-2011 PCV13: 2012-2013	A: *S. pneumoniae* carriage (all serotypes), 11 months B: *S. pneumoniae* carriage (all serotypes), 24 months"	A: 193/330 (59%) B: 211/330 (64%)	A: 173/330 (52%) B: 185/330 (56%)	A: 1.12 (0.97, 1.28) B: 1.46 (1.26, 1.68)	Pfizer, GSK, Government
Dagan 2013	Israel	2 months	PCV13 (890) PCV7 (889)	3+1 (2,4,6,12 months)	N/A	Serotypes of *S. pneumoniae* isolated through Nasopharyngeal colonization	RCT	N/A	2, 4, 6, 7, 12, 13, 18, and 24 months				1.00 (0.96, 1.04)	Pfizer

Table 15. Characteristics of included studies with serotype-specific 6A, 19A, and 3 nasopharyngeal carriage outcome
Note: All studies are RCTs. Endpoint determination is through opsonophagocytic assay

Author, Year	Country	Population	Vaccine	Dosing schedule	Follow-up	Outcome measured	Treatment Arm (95% CI)	Control Arm (95% CI)	Risk Ratio (95% CI)	Funding
PCV 10 versus no vaccine										
Saez Llorenz, 2017	Panama	2 months	**3 months after Dose 3**: PCV10 (788) HepB (784) **6 months after Dose 4**: PCV10 (696) HepB (690) **9 months after Dose 4**: PCV10 (627) Hep B (639)	3+1 (2,4,6, (15-18 months BD))	6 months after primary series, 3,9 months after booster dose	**Serotype 6A** A: 6 months after Dose 3 % Colonization B. 3 months after Dose 4 % Colonization C. 9 months after Dose 4 % Colonization	A: 5.2 (3.8, 7.0) B: 4.0 (2.7, 5.8) C. 2.4 (1.3, 3.9)	A: 5.0 (3.6, 6.7) B: 4.3 (3.0, 6.1) C. 4.1 (2.7, 5.9)	A: 1.05 (0.68, 1.60)	GSK
						Serotype 19A A: 6 months after Dose 3 % Colonization B. 3 months after Dose 4 % Colonization C. 9 months after Dose 4 % Colonization	A:2.2 (1.3, 3.4) B: 1.4 (0.7, 2.6) C. 1.4 (0.7, 2.7)	A: 1.1 (0.5, 2.2) B: 2.0(1.1, 3.4) C. 1.1 (0.4, 2.2)	A: 1.88 (0.84, 4.19)	
Dagan, 2013	Israel	2 months	**PCV13 (890) PCV7 (889)**	3+1 (2,4,6,12 months)	2, 4, 6, 7, 12, 13, 18, and 24 months	Serotype 6A New NP acquisition	63/881	106/873	0.58 (0.43, 0.78)	Pfizer
						Serotype 19A New NP acquisition	105/881	190/873	0.55 (0.44, 0.68) S	
						Serotype 3 New NP acquisition	16/881	16/873	0.99 (0.48, 2.06)	

Table 16. Characteristics of included studies which evaluated 2 dose effect of PCV vaccines.

Study, Year Country	Population	Vaccine (I/C)	Dosing Schedule	Follow up period	Outcome	Outcome measure	Treatment Arm	Control Arm	Mean Difference/ Risk Ratio (95% CI)^
Snape, 2010 UK	1.5-3.5 monhs	PCV13 PCV7	2+1	1 month after dose 2	Immunogenicity 6A	proportion of infants with ≥ 0.35 ug/mL antibody level	79.2 (70.3, 86.5)	12.0 (6.4, 20.0)	0.24 (0.16,0.34)
						Geometric mean IgG concentration	0.86 (0.68 , 1.07)	0.14 (0.11, 0.16)	0.72 (0.52, 0.92)

					Immunogenicity 19A	proportion of infants with > 0.35 ug/mL antibody level	92.7 (86.2, 96.8)	88.9 (81.0, 94.3)	0.65 (0.27, 1.56)
						Geometric mean IgG concentration	1.9 (1.54, 2.34)	0.92 (0.77, 1.11)	0.98 (0.55, 1.41)
					Immunogenicity 3	proportion of infants with > 0.35 ug/mL antibody level	86.0 (77.9, 91.9)	2 (0.2, 6.9)	0.14 (0.09, 0.23)
						Geometric mean IgG concentration	0.63 (0.56, 0.71)	0.04 (0.03, 0.05)	0.59 (0.51, 0.67)
Domingues, 2014 Brazil	>2 months (Meian age: 13.3 months)	PCV10 'no vaccination'	2+1	2 years	Vaccine type IPD	A. Cases for IPD B. Control for IPD	Cases: 34/316 (115) Control: 173/1219 (14%)	Cases: 129/1219 (41%) Control: 304/1219 (25%)	0.55 (0.39, 0.77)
Vesikari, 2016	1.5-6 months	PCV 10 Hepatitis B vaccine	2+1	18 months	Acute Otitis media	Vaccine effectiveness in reducing the number of children reporting ≥1 AOM episode	327/917	485/1291	0.89 (0.80, 1.00)

^ Risk ratio- % responders, IPD, AOM; Mean difference- GMT

Appendix B: Risk of bias assessment of included studies

Table 1. Risk of bias score for systematic reviews

	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15	16*	Quality
1. WHO, 2017	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	NO	NO	YES	YES	NO	YES	Critically Low
2. Ciapponi 2016	YES	YES	NO	PARTIAL YES	YES	YES	YES	YES	YES	YES	N/A	N/A	NO	N/A	N/A	YES	Critically Low
3. de Oleivera 2016	YES	YES	NO	YES	YES	YES	YES	PARTIAL YES	YES	YES	N/A	N/A	YES	YES	N/A	YES	Moderate
4. Alicinio 2017	YES	PARTIAL YES	YES	PARTIAL YES	YES	NO	YES	YES	YES	NO	YES	NO	NO	YES	NO	YES	Critically Low
5. Duan 2016	YES	YES	NO	PARTIAL YES	YES	YES	YES	YES	YES	NO	N/A	N/A	YES	YES	N/A	YES	Critically Low
6. Choe 2019	YES	PARTIAL YES	YES	PARTIAL YES	YES	NO	PARTIAL YES	PARTIAL YES	NO	NO	YES	NO	NO	YES	NO	YES	Critically Low
7. Berman 2020	YES	YES	NO	PARTIAL YES	YES	YES	YES	PARTIAL YES	YES	NO	N/A	N/A	NO	YES	NO	NO	Critically Low
8. Tin Tin Htar 2019	YES	NO	YES	PARTIAL YES	YES	NO	YES	PARTIAL YES	NO	NO	N/A	N/A	NO	YES	N/A	YES	Critically Low
9. Sings 2018	YES	YES	YES	PARTIAL YES	NO	YES	YES	PARTIAL YES	PARTIAL YES	YES	YES	YES	YES	YES	YES	YES	Critically Low
10. Fortanier 2019	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	N/A	N/A	YES	YES	N/A	YES	High
11. McGirr 2019	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	N/A	N/A	YES	YES	N/A	YES	High
12. Moreira 2016	YES	NO	YES	PARTIAL YES	YES	NO	YES	YES	NO	NO	N/A	N/A	NO	NO	N/A	YES	Critically Low
13. Ruiz-Aragon 2013	YES	YES	YES	PARTIAL YES	NO	NO	YES	YES	PARTIAL YES	NO	YES	YES	YES	YES	NO	NO	Critically Low
14. Sucher 2011	YES	NO	YES	PARTIAL YES	NO	NO	NO	YES	NO	NO	N/A	N/A	NO	NO	N/A	YES	Critically Low
No. of YES	14	9	10	4	11	8	12	9	8	4	4	2	7	11	1	12	
% of YES	100%	64.29%	71.43%	28.57%	78.57%	57.14%	85.71%	64.29%	57.14%	28.57%	80%	40%	50%	84.62%	16.67%	85.71%	

*Critical domains of AMSTAR 2

Table 2. Risk of bias scores for RCTs

	1. Random sequence generation	2. Allocation concealment	3. Blinding	4. Blinding of outcome assessment	5. Incomplete outcome data	6. Selective reporting	7. Other sources of bias	Quality
Palmu, 2013	Low	Low	Low	Low	Low	Low	High	High
Huang 2012	Low	Low	Low	Low	Low	Low	High	High
Kieninger 2010	Low	Low	Low	Low	Low	Low	High	High
Snape 2010	Low	Low	Low	Low	Low	Low	High	High
Wechx 2012	Low	Low	Low	Low	Low	Low	High	High
Bryant 2010	Low	Low	Unclear	Unclear	Low	Low	High	Intermediate
Yeh 2010	Low	Low	Low	Low	Low	Low	High	High
Amdekar 2013	High	High	High	High	Low	Low	High	Low
Bermal 2009	Low	High	Low	Low	Low	Low	High	Intermediate
Wysocki 2009	Low	Unclear	High	High	Low	Low	High	Low
Vesikari 2016	Low	Low	Unclear	High	High	Low	Low	Intermediate
Payton 2013	Low	Unclear	Low	Low	Low	Low	High	Intermediate
Saez Llorenz 2017	Low	High	High	Unclear	High	High	High	Low
Kilpi 2018	Low	Low	High	Low	Low	Low	High	Intermediate
Pomat 2018	Low	Unclear	Unclear	Low	Low	Low	Low	Intermediate
Temple 2013	Low	High	High	Low	Low	Low	Low	Intermediate
Esposito 2010	Low	Low	Low	Low	Low	Low	High	High
Dagan, 2013	Low	Low	Low	Unclear	Low	Low	High	Intermediate
Vesikari, 2009	Low	High	High	Low	Low	Low	High	Intermediate
No. of Low Risk	18	11	10	13	17	18	3	
% of Low Risk	94.74%	57.89%	52.63%	68.42%	89.47%	94.74%	15.79%	

Table3. Risk of bias scores for cohorts

	Selection				Comparability	Outcome			
	1. Representativeness of the Exposed Cohort	2. Selection of the Non-Exposed Cohort	3. Ascertainment of Exposure	4. Demonstration that Outcome of Interest Was Not Present at Start of Study	5. Comparability of Cohorts on the Basis of the Design or Analysis	6. Assessment of outcome	7. Was Follow-up Long Enough for Outcomes to Occur?	8. Adequacy of Follow-up of Cohorts	Quality
Heinsbroek 2018	1	0	1	1	0	1	1	1	Poor
Jokinen 2015	1	1	1	0	1	1	1	1	Good
Naucler 2017	1	0	1	0	0	1	1	1	Poor
Becker-Dreps 2014	1	0	1	0	0	1	1	1	Poor
Bosch 2015	1	0	1	0	0	1	1	1	Poor
Kaur 2016	1	0	1	1	0	1	1	1	Poor
Varon 2015	1	0	1	1	0	1	1	0	Poor
Jayasinghe 2017	1	0	1	0	0	1	1	1	Poor
Waight 2015	1	0	1	0	0	1	1	0	Poor
Brandileone 2018	1	1	1	1	1	1	1	1	Good
Rinta-Kokko 2018	1	1	1	1	1	1	1	1	Good
Pichichero 2018	1	1	1	1	0	1	1	1	Poor
Kawai 2018	1	1	1	1	0	1	1	1	Poor
Picazo 2019	1	1	1	1	1	1	1	1	Good
Total	14	5	14	8	4	14	14	12	
	100%	42.86%	100%	50.00%	25.00%	100%	100%	75.00%	

Table 20. Risk of bias scores for case controls

	Selection				Comparability	Exposure			
	1.Is the case definition adequate?	2.Representativeness of the cases	3.Selection of controls	4.Definition of controls	5.Comparability of cases and controls on the basis of the design	6.Assessment of exposure	7.Same method of ascertainment for cases and controls	8.Non-response rate	Quality
Domingues 2014	1	1	1	1	0	1	1	1	Poor
Van der Linden 2016	1	1	1	1	0	1	1	1	Poor
Moore 2016	1	1	1	1	0	1	1	0	Poor
Total	3	3	3	3	0	3	3	2	
	100%	100%	100%	100%	0%	100%	100%	66.67%	

Appendix C: Reason for exclusion of studies submitted by proponents and studies used as the basis of the Philippine FDA on the approval of PCV10 indication for serotype 19A.

Author, Year Country	Stakeholder	Reason for exclusion
Deceuninck, 2015 Canada	PCV manufacturer	Did not evaluate the effect of 3 doses
Andrews, 2014 UK	PCV manufacturer	Single-arm study only
Diawara 2015 Morocco	PCV manufacturer	No ascertainment of the vaccination status of subjects
Andrade, 2017 Brazil	PCV manufacturer	Did not establish vaccination coverage
Moore, 2014 USA	PCV manufacturer	No full text found
Verani, 2015 Brazil	PCV manufacturer	Overlap with Dominguez et al
Harboe, Dalby, 2014 Denmark	PCV manufacturer	Did not establish vaccination coverage
Le Poutre, 2015 France	PCV manufacturer	Overlap with Varon, 2015 (already included in the review)
Miller, 2011 UK	PCV manufacturer	Evaluated only effect of at least 1 dose
Izurieta, 2018 (SR)	PCV manufacturer	Did not match PICO
Kamdasamy, 2019 UK	PCV manufacturer	Insufficient follow-up period
Gisselson-Solen, 2017 Sweden	PCV manufacturer	Cannot extract data on treatment effect
Ben-Shimol, 2014 Israel	PCV manufacturer	Evaluated effect of at least 2 doses only
Steens, 2013 Norway	PCV manufacturer	Cannot delineate the effect of comparator from intervention
Ben-Shimol, 2014 Israel	PCV manufacturer	Evaluated effect of at least 2 doses only

Danino, 2019 Israel	PCV manufacturer	Cannot extract data on treatment effect
Ladhani, 2018 UK	PCV manufacturer	Did not establish vaccination coverage
Lopez, 2018 Argentina	PCV manufacturer	Insufficient follow-up period
Cassiolato, 2018 Brazil	PCV manufacturer	Did not establish vaccination coverage
Setchanova, 2018 Bulgaria	PCV manufacturer	Did not match PICO
Omenaca, 2011 Green, Spain	Philippine FDA	Single-arm study only
Silfverdal, 2009 Denmark, Norway, Slovakia, and Sweden	Philippine FDA	Did not match PICO
Silfverdal, 2011 Slovenia, Sweden	Philippine FDA	Did not match PICO
Vesikari, 2011 Finland	Philippine FDA	Did not match PICO
Van der Westen, 2015	PCV manufacturer	No full text found
Azzari, 2019	PCV manufacturer	Did not match PICO
Lu, 2019	PCV manufacturer	Cannot delineate the effect of comparator from intervention
Prichter, 2019	PCV manufacturer	No ascertainment of the vaccination status of subjects
Potin, 2016	PCV manufacturer	No full text found
Moreno, 2020`	PCV manufacturer	Cannot delineate the effect of comparator from intervention
Negash, 2019	PCV manufacturer	Did not match PICO
Lau, 2015	PCV manufacturer	No full text found

Appendix D: Local serotype prevalence by age group

Table 1. Serotype prevalence in children ≤5 years old

Serotype	ARSP			AMES			Microbiology Lab Surveillance			CUMULATIVE SEROTYPES		
		N=	140		N=	18		N=	54		N=	212
	2012-2019			2015-2018			2012-2019			2012-2019		
	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13
1		9	9		1	1		4	4		14	14
4	4	4	4				1	1	1	5	5	5
5		7	7					3	3		10	10
6B	8	8	8				6	6	6	14	14	14
7								1	1		1	1
9V/A	6	6	6				1	1	1	7	7	7
14	12	12	12	3	3	3	2	2	2	17	17	17
18C	12	12	12				2	2	2	14	14	14
19F				1	1	1	3	3	3	4	4	4
23F	9	9	9				3	3	3	12	12	12
3			5						3			8
19A			6			1			2		9*	9
6A			4						5			9
ISOLATES (n)	**51**	**67**	**82**	**4**	**5**	**6**	**18**	**26**	**36**	**73**	**107**	**124**
Percentage	**36%**	**48%**	**59%**	**22%**	**28%**	**44%**	**33%**	**48%**	**69%**	**34.43%**	**50.47%**	**58.49%**

*Note: *Serotypes 19A was included in the cumulative serotype coverage of PCV10 since FDA-approved PCV10 indication for 19A was considered in this assessment.; **ARSP**-Antimicrobial Resistance Surveillance Program; **AMES**- Acute Meningitis Encephalitis Surveillance*

Table 2: Serotype prevalence in children 6-18 years old

Serotype	ARSP			AMES			Microbiology Lab Surveillance			CUMULATIVE SEROTYPES		
		N=	38		N=	9		N=	25		N=	72
	2012-2019			2015-2018			2012-2019			2012-2019		
	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13
1		8	8		3	3		4	4	0	15	15
4	3	3	3				1	1	1	4	4	4
5		2	2		1	1		1	1	0	4	4
6B	1	1	1				1	1	1	2	2	2
7					1	1				0	1	1
9V/A	1	1	1				1	1	1	2	2	2
14	2	2	2				2	2	2	4	4	4
18C	4	4	4							4	4	4
19F										0	0	0
23F				1	1	1	1	1	1	2	2	2
3			2			2						4
19A			2						1		3*	3
6A			1						2			3
ISOLATES (n)	**11**	**21**	**26**	**1**	**6**	**8**	**6**	**11**	**14**	**18**	**41**	**48**
Percentage	**29%**	**55%**	**68%**	**11%**	**67%**	**89%**	**24%**	**44%**	**56%**	**25.00%**	**56.94%**	**66.67%**

*Note: *Serotypes 19A was included in the cumulative serotype coverage of PCV10 since FDA-approved PCV10 indication for 19A was considered in this assessment.; **ARSP**-Antimicrobial Resistance Surveillance Program; **AMES**- Acute Meningitis Encephalitis Surveillance*

Table 3. Serotype prevalence in individuals 19-49 years old

Serotype	ARSP			AMES			Microbiology Lab Surveillance			CUMULATIVE SEROTYPES		
		N=	80		N=	1		N=	15		N=	96
	2012-2019			2015-2018			2012-2019			2012-2019		
	PCV 7	**PCV 10**	**PCV 13**	**PCV 7**	**PCV 10**	**PCV 13**	**PCV 7**	**PCV 10**	**PCV 13**	**PCV 7**	**PCV 10**	**PCV 13**
1		15	15					3	3		18	18
4	9	9	9				3	3	3	12	12	12
5		7	7		1	1		5	5		13	13
6B										0	0	0
7								1	1		1	1
9V/A	2	2	2							2	2	2
14										0	0	0
18C	2	2	2							2	2	2
19F										0	0	0
23F	7	7	7							7	7	7
3			4									4
19A			1								1*	1
6A			2									2
ISOLATES (n)	**20**	**42**	**49**	**0**	**1**	**1**	**3**	**12**	**12**	**23**	**56**	**62**
Percentage	**25%**	**53%**	**61%**	**0%**	**100%**	**100%**	**20%**	**80%**	**80%**	**23.96%**	**58.33%**	**64.58%**

*Note: *Serotypes 19A was included in the cumulative serotype coverage of PCV10 since FDA-approved PCV10 indication for 19A was considered in this assessment.; **ARSP**-Antimicrobial Resistance Surveillance Program; **AMES**- Acute Meningitis Encephalitis Surveillance*

Table 4. Serotype prevalence in individuals >50 years old.

Serotype	ARSP			AMES			Microbiology Lab Surveillance			CUMULATIVE SEROTYPES		
	N= 127			N= 1			N= 28			N= 156		
	2012-2019			2015-2018			2012-2019			2012-2019		
	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13	PCV 7	PCV 10	PCV 13	PCV 9	PCV 10	PCV 13
1		14	14					2	2		16	16
4	1	1	1							1	1	1
5		11	11					1	1		12	12
6B	6	6	6				1	1	1	7	7	7
7		9	9					4	4		13	13
9V/A	1	1	1							1	1	1
14	2	2	2							2	2	2
18C	4	4	4							4	4	4
19F										0	0	0
23F	6	6	6				1	1	1	7	7	7
3			24						3			27
19A			5								5*	5
6A			1									1
ISOLATES (n)	**20**	**54**	**84**	**0**	**0**	**0**	**2**	**9**	**12**	**22**	**68**	**96**
Percentage	**16%**	**43%**	**66%**	**0%**	**0%**	**0%**	**7%**	**32%**	**43%**	**14.10%**	**43.59%**	**61.54%**

*Note: *Serotypes 19A was included in the cumulative serotype coverage of PCV10 since FDA-approved PCV10 indication for 19A was considered in this assessment.; **ARSP**-Antimicrobial Resistance Surveillance Program; **AMES**- Acute Meningitis Encephalitis Surveillance*

Appendix E: Vaccine efficacy computation for 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%**

Appendix F: Questionnaire for leaders of marginalized groups for ethical and social implication assessment

Mga Katanungan sa Pagsusuri ng Etikal at Panlipunang Epekto ng Paggamit ng Bakuna sa mga Bagong Silang na Sanggol sa Pilipinas

Ang Pneumococcal Conjugate Vaccine o PCV ay isang uri ng bakuna na ibinibigay sa mga sanggol upang maiwasan ang iba't ibang sakit tulad ng *pneumonia* (pulmonya), *meningitis* (pamamaga ng bahagi ng utak na bumabalot at prumoprotekta dito), *bacteremia* (impeksyon sa dugo), at *acute otitis media o AOM* (pamamaga ng gitnang bahagi ng tainga). Sa kasalukuyan, mayroong dalawang klase ng PCV sa bansa - ang PCV10 at PCV13.

Sa kasalukuyan, and PCV ay naibibigay ng Kagawaran ng Kalusugan (*Department of Health o DOH*) sa mga bagong silang na sanggol sa mga piling rehiyon lamang ng ating bansa.

Layunin ng DOH na mapalawak ang pagbabakuna sa mga bagong silang na sanggol sa buong bansa gamit ang angkop na uri ng PCV. Sa taong 2020, may nakalaan na 7.2 bilyong piso para sa pambansang programa sa pagbabakuna. Mula dito, may nakalaan na 4.4 bilyong piso para sa PCV. Dahil dito, naatasan ang *Health Technology Assessment Unit (HTAU)* ng DOH na magsagawa ng pag-aaral kung alin sa PCV10 o PCV13 ang magiging mas epektibo at sulit na bakuna para sa ating gobyerno.

Layunin namin na malaman ang inyong opinyon tungkol sa pagbabakuna upang magabayan ang pagpili ng angkop na uri ng PCV para sa ating bansa. Maari lamang na sagutan ang mga sumusunod na tanong sa abot ng inyong makakaya.

1. Pagsunod-sunurin ang mga sumusunod base sa kung ano mas mahalaga para sa inyo:

   A. Mas maraming bata na mababakunahan
   B. Mas maraming sakit ang maiiwasan
   C. Mas mababang presyo ng bakuna

2. Kung papipiliin sa dalawang bakuna, ano ang mas gusto ninyong maibigay ng gobyerno sa inyo? Ipaliwanag kung bakit ito ang iyong sagot.

   A. Bakuna na kayang protektahan ang mas maraming mga bata pero limitado lang sa 10 sakit.

B. Bakuna na kayang promotekta laban sa 13 sakit pero mahal kaya limitadong bata lang ang mabibigyan.

3. Pagsunod-sunurin ang mga sumusunod base sa kung alin ang pinaka malaking problema na kinakaharap ninyo sa pagpapabakuna ng inyong mga anak:
   a. presyo ng bakuna
   b. malayo ang inyong bahay sa health center
   c. kulang ang impormasyon na inyong nalalaman tungkol sa bakuna
   d. kulang ang suporta na binibigay ng gobyerno para mapadali ang pagpapabakuna ng inyong mga anak
   e. hindi ayon sa inyong relihiyon o paniniwala ang pagbabakuna
   f. kasarian o *sex* ng inyong anak

Maraming salamat po!

Appendix G: Questionnaire for civil societies and patient groups for ethical and social implication assessment

Mga Katanungan sa Pagsusuri ng Etikal at Panlipunang Epekto ng Paggamit ng Pneumococcal Conjugate Vaccines (PCV)

<u>Konteksto at Layunin:</u>

Ang Pneumococcal Conjugate Vaccine o PCV ay isang uri ng bakuna na ibinibigay sa mga sanggol upang maiwasan ang iba't ibang sakit tulad ng:

- *pneumonia* (pulmonya)
- *meningitis* (pamamaga ng *membrane* na nagsisilbing proteksyon sa utak at *spinal cord*)
- *bacteremia* (impeksyon sa dugo)
- *acute otitis media o AOM* (pamamaga ng gitnang bahagi ng tainga)

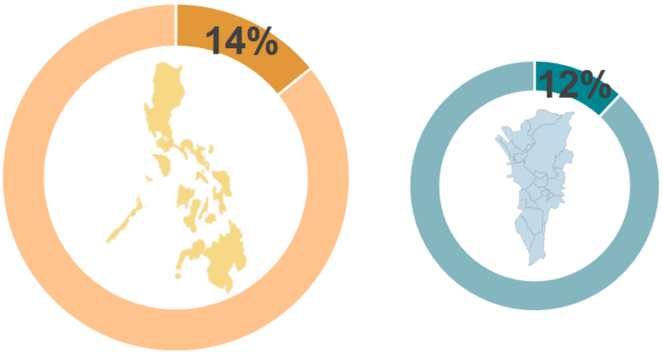
Sa kasalukuyan, mayroong dalawang klase ng PCV sa bansa - ang PCV10 at PCV13. Ang dalawang bakunang ito ay parehong nakapagbibigay ng proteksyon laban sa sampung (10) serotype o uri ng *S. pneumoniae*. Ang PCV13 ay naglalaman ng proteksyon laban sa tatlong karagdagang serotype (3, 6A at 19A).

	1	5	6B	7F	9V	14	19F	23F	6A	19A	4	18C	3
PCV10													
PCV13													

Kung inyong mapapansin, naka-shade din ng bahagya ang serotype 6A at 19A sa PCV10. Ito ay dahil ayon sa pag-aaral na sinagawa ng HTA unit, *ang PCV10 ay maaari ring makapagbigay ng proteksyon sa serotype 6A at 19A*. Ngunit itinataya na mas mataas pa rin ang antas ng proteksyon na maibibigay ng PCV13 laban sa mga serotype na ito.

Batay sa datos ng Research Institute for Tropical Medicine (RITM), may natiyak na 536 na kaso ng meningitis at bacteremia sanhi ng *S. pneumoniae* mula 2012 hanggang 2019. Pitong-put anim (76) o 14% dito ay idinulot ng 3 karagdagang serotype na laman ng PCV13. Sa 100 kaso ng meningitis at bacteremia na naiulat sa NCR mula 2012 hanggang 2019, maitataya na 12 dito ay dulot ng tatlong karagdanang serotype na nabanggit.

Porsyento ng kaso ng meningitis at bacteremia na sanhi ng 3 karagdagang *S. pneumoniae* serotype (3, 6A, 19A) na mayroon sa PCV13

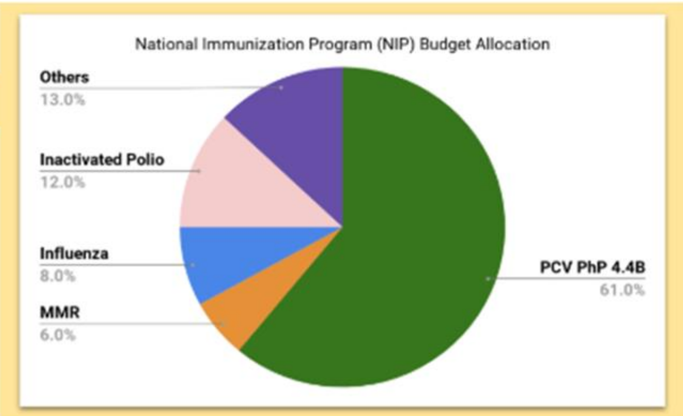


Maari lamang isaalang alang na ang datos na ito ay limitado sapagkat hindi lahat ng kaso ng meningitis at bacteremia ay naisasama sa ulat ng RITM. Ang mga datos na ito ay nagmula sa nalikom na datos ng RITM mula sa mga piling ospital lamang sa ating bansa.

Sa kasalukuyan, PCV13 ang ginagamit ng ating *National Immunization Program* (NIP) ng Kagawaran ng Kalusugan (*Department of Health*) sa pagbabakuna ng mga bagong silang na sanggol sa mga piling rehiyon ng ating bansa. Layunin ng programa na mapalawak ang pagbabakuna sa mga bagong silang na sanggol sa buong bansa gamit ang angkop na uri ng PCV batay sa klinikal na benepisyo at tamang presyo nito.

Sa taong 2020, may nakalaan na 7.2 bilyong piso para sa NIP. Mula dito, may nakalaan na 4.4 bilyong piso para sa PCV o 61% ng budget ng NIP. Samantalaga ang natitirang 39% ng budget ng NIP ay paghahatian ng 8 walo bakuna na pinopondohan ng programa.

Disease Program	National Budget Allocation (PhP)
NIP	7.2B (4.1%)
Infectious disease control	1B
TB control	949M
Rabies control	500M
NCDs	509M
Total DOH Budget	**176B**



Dahil dito, naatasan ang *Health Technology Assessment Unit (HTAU)* ng DOH na magsagawa ng pag-aaral kung alin sa PCV10 o PCV13 ang magiging mas epektibo at sulit na bakuna para sa ating pamahalaan gamit ang mga bagong siyentipikong ebidensya at presyo ng mga bakuna mula sa mga kumpanya.

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Ayon sa World Health Organization (WHO), hindi nila hinihikayat na magpalit ng bakuna kung nakapagsimula na ang pagbabakuna sa programang pangkalusugan ng bansa maliban na lamang kung may pagbabago sa paglaganap ng mga sakit na sanhi ng *S. pneumoniae* o sa mga salik na nakakaapekto sa programang pangkalusugan. *Ngunit*, sakaling hindi matapos ang pagbabakuna gamit ang iisang uri ng PCV, maaring gumamit ng ibang uri ng PCV upang kumpletuhin ang bakuna ng mga sanggol.

Batay sa resulta sa pagsusuring klinikal at ekonomikal, kung ikukumpara ang PCV10 at PCV13, itinataya na ang paggamit ng PCV13 ay maaring magdulot na maiwasan ang karagdagang 1,507 kaso ng meningitis at bacteremia, 15,320 na kaso ng pneumonia at 21, 937 kaso ng acute otitis media (AOM). Bukod dito, itinataya rin na ang paggamit ng PCV13 ay magdudulot na maiwasan ang karagdagang 1, 970 na pagkamatay sanhi ng meningitis at bacteremia. Ang mga datos na ito ay sakop ang mgq sakit na maiiawasan mula bata hanggang matatanda.

Tinatayang bilang ng kaso ng mga sakit na maiiwasan sa paggamit ng PCV10 o PCV13

	PCV10 vs walang bakuna	PCV13 vs walang bakuna	PCV13 vs PCV10
Meningitis at Bacteremia	2,438	3,945	1,507
Pneumonia	17,912	33,232	15,320
Acute Otitis Media	83,059	104,995	21,937

Tinatayang bilang ng pagkamatay na maiiwasan sa paggamit ng PCV10 o PCV13

	PCV10 vs walang bakuna	PCV13 vs walang bakuna	PCV13 vs PCV10
Meningitis at Bacteremia	4,935	6,905	1,970

Sa kabilang dako, kung PCV10 ang gagamitin, mabakunahan ang lahat ng sanggol sa ating bansa sa halagang 3.4 bilyong piso. Ibig sabihin ay makaktipid ang NIP ng 1 bilyon sa kanilang budget kung gagamitin ang PCV10. Samantala, kung gagamitin ang PCV13, kailangang maglaan ng 5.2 bilyong piso para dito. Masasabi na hindi sapat ang budget ng NIP upang mabakunahan ang lahat ng sanggol sa ating bansa kung ang gagamitin ay ang PCV13. Sa 4.4 bilyong piso na budget, 85% lamang ng mga sanggol ang kayang mabakunahan gamit ang PCV13.

Kailangang pondo (Bilyong piso) sa pagbabakuna ng LAHAT ng sanggol sa Pilipinas gamit ang multi-dose* vial ng PCV10 o PCV13

	PCV10	PCV13
2020	3.83	5.26
2021	3.83	5.26
2022	3.83	5.26
2023	3.83	5.26
2024	3.83	5.26
2020-2024	19.15	26.30

Bukod sa pagsusuri ng aspetong klinikal at ekonomikal ng mga bakuna, isinasaalang-alang rin ng *Health Technology Assessment (HTA)* ang mga usaping etikal, ligal, aspetong panlipunan, at maging ang epekto nito sa ating kabuuang *health system*. Mahalaga na ang resulta ng pag-aaral ay batay sa konteksto ng ating bansa.

Ang *survey* na ito ay naglalayon na masagot ang sumusunod na katanungan:
Sa inyong palagay, anu-ano ang mga usaping etikal at aspetong panlipunan ang mahalagang mapag-usapan sakaling:

A.Patuloy na PCV13 ang gamitin ng NIP na pangunahing bakuna bilang proteksyon laban sa *pneumonia*, *meningitis, bacteremia,* at *acute otitis media (AOM)* sa mga batang nasa edad 5 pababa sa bansa?

B. ipagpapalit ng NIP mula PCV13 patungong PCV10 ang pangunahing bakuna bilang proteksyon laban sa *pneumonia*, *meningitis, bacteremia,* at *acute otitis media (AOM)* sa mga batang nasa edad 5 pababa sa bansa?

Sagutin ang sumusunod na mga katanungan sa abot ng inyong makakaya:

1. Batay sa inyong pananaw, pagsunod-sunurin ang mga kadahilanang nabanggit mula sa pinaka-mainam hanggang sa pinaka-mahinang batayan ng pagpili ng bakunang gagamitin para sa mga bagong silang na sanggol sa ating bansa.

A. Bilang ng sanggol na mababakunahan
B. Bilang ng sakit na maiiwasan
C. Presyo ng bakuna
D. Matitipid na pera para sa iba pang programang pangkalusugan

Maaring ilagay dito ang inyong kasagutan:

2. Habang isinasaalang alang ang mga sumusunod, sa inyong pananaw, ano ang mas katanggap tanggap, paggamit ng NIP ng PCV13 o PCV10?

Maaring ilagay dito ang inyong kasagutan:

3: Sa inyong pananaw, mayroon bang positibong implikasyon o inaasahang benepisyo para sa mga sanggol na makakatanggap ng bakuna, kanilang mga pamilya at ng mga pasyente ang matutugunan kung:

3.1: patuloy na PCV13 ang gagamitin ng NIP

Maaring ilagay dito ang inyong kasagutan:

3.2: papalitan ng PCV10 ang PCV13 sa ating NIP

Maaring ilagay dito ang inyong kasagutan:

4: Sa inyong pananaw, mayroon bang negatibong implikasyon o epekto ang maaring kaharapin ng mga sanggol na makakatanggap ng bakuna, kanilang pamilya at mga pasyente kung:

4.1: patuloy na PCV13 ang gagamitin ng NIP

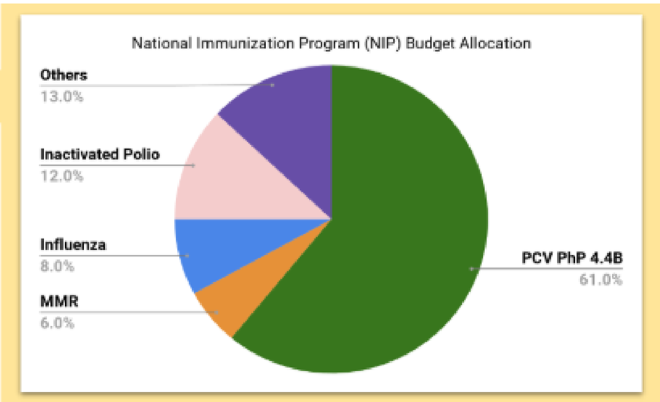
Maaring ilagay dito ang inyong kasagutan:

4.2: papalitan ng PCV10 ang PCV13 sa ating NIP

Maaring ilagay dito ang inyong kasagutan:

5. Ayon sa datos na nakalap, may nakalaan anggobyerno na 176 bilyong para sa DOH. 4% nito o 7.2 bilyong piso ang nakalaan para sa NIP. Sa kabuuan ng 7.2 bilyong piso, 61% nito o 4.4 bilyon ang nakalaan para sa PCV lamang. Samantalaga ang natitirang 39% ng budget ng NIP ay paghahatian ng 8 walo bakuna na pinopondohan ng programa.

Disease Program	National Budget Allocation (PhP)
NIP	7.2B (4.1%)
Infectious disease control	1B
TB control	949M
Rabies control	500M
NCDs	509M
Total DOH Budget	**176B**



Batay dito, ano ang masasabi mo ukol sa nakalaan na budget para sa PCV? Magbigay ng maikling paliwanag sa iyong napiling sagot.

a. masyadong malaki ang nakalaan sa PCV
b. Kulang ang nakalaan para sa PCV
c. Nararapat lamang ang nakalaan para sa PCV

Maaring ilagay dito ang inyong kasagutan:

6: Sa iyong pananaw, pagsunod-sunurin ang mga sumusunod na maaring hadlang o limitasyon upang mabakunahan ng PCV ang isang sanggol. Maaari lamang na magbigay ng maikling paliwanag sa inyong sagot:

Hadlang/ Limitasyon	Ranking (1^{st}-9^{th})	Kaunting Paliwanag
Kondisyon ng pamumuhay ng pamilya		
Kaalaman ng magulang o tagapag-alaga		
Relihiyon ng pamilyang kinabibilangan		
Kasarian ng sanggol		
Paninirahan sa urban o rural na lugar		
Paglipat ng lugar na tinitirhan (migration)		
Kadahilanang pinansyal		
Tiwala sa pamahalaan at sa *health system*		
Kadalian sa pagkamit ng mga programang pangkalusugan ng gobyerno		

7: Sa inyong pananaw, paano maapektuhan ng patuloy na paggamit ng PCV13 ang pagbabakuna sa mga sanggol na kabilang sa mga pamilya na:

(1) naninirahan sa rural na lugar o geographically isolated and disadvantaged areas

Maaring ilagay dito ang inyong kasagutan:

(2) nabibilang sa itinuturing na mahirap na sektor ng lipunan

Maaring ilagay dito ang inyong kasagutan:

(3) nabibilang sa pangkat etniko?

Maaring ilagay dito ang inyong kasagutan:

8: Sa inyong pananaw, paano maapektuhan ng posibleng pagpapalit mula PCV13 patungong PCV10 ang pagbabakuna sa mga sanggol na kabilang sa mga pamilya na: (1) naninirahan sa rural na lugar o geographically isolated and disadvantaged areas

Maaring ilagay dito ang inyong kasagutan:

(2) nabibilang sa itinuturing na mahirap na sektor ng lipunan

Maaring ilagay dito ang inyong kasagutan:

(3) nabibilang sa pangkat etniko?

Maaring ilagay dito ang inyong kasagutan:

Appendix H: Survey questions for the health systems implications assessment

Survey used for the health systems impact assessment can be accessed through the following link and QR Code:

http://tinyurl.com/HTA-HSI-PCV