Considerations for Pneumococcal Conjugate Vaccine (PCV) Product Choice

Disclaimer: WHO does not endorse the use of specific branded products over others; this publication may not be used for any commercial or promotional purposes.

Background

This document summarizes current technical and programmatic information on WHO prequalified PCV products to facilitate informed country choices for PCV introduction or product switch for childhood immunization programmes. Three PCV products are prequalified by the World Health Organization (WHO) for use in infants and children. They include the 13-valent PCV manufactured by Pfizer (PCV-13, Prev(e)nar®), a 10-valent PCV manufactured by GlaxoSmithKline (PCV-10^{GSK}, Synflorix®), and a 10-valent PCV manufactured by Serum Institute of India (PCV-10^{SII}, PNEUMOSIL®). Manufacturers are expected to seek WHO prequalification for additional higher valent PCV products in the future. This summary of considerations may be updated in the future to address new products.

This document is based on published sources except for content related to the newest prequalified product, PNEUMOSIL®, where the manufacturer provided the unpublished Clinical Study Report confidentially. The document should not be viewed as formal WHO recommendations or guidelines.

WHO Position on Pneumococcal Vaccines in Infants and Children

The 2019 WHO position paper[1] presents the current policy recommendations for pneumococcal conjugate vaccines in infants and children. The document does not express preference among prequalified PCV products but does not reference PCV-10^{SII} or data specific to this product given that it was prequalified in December 2019 after the paper's publication. Despite the most recent product not being mentioned, the 2019 policy recommendations are considered applicable to PCV-10^{SII}. The position paper states:

- "Both PCV10 and PCV13 have substantial impacts against pneumonia, vaccine type (VT) invasive pneumococcal disease (IPD), and nasopharyngeal (NP) carriage" in a variety of settings".
- "The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes and antimicrobial resistance patterns".
- "PCV13 may have an additional benefit [over PCV-10^{GSK}] in settings where disease attributable to serotype (ST) 19A or ST 6C is significant".

[1] Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly epidemiological record (Relevé épidémiologique hebdomadaire). 2019;94(8):85–104.

Vaccine Characteristics

In considering the biological characteristics of the three prequalified PCV products, a key difference is the number and selection of STs included. Additionally, differences in carrier proteins, conjugation method, and preservatives are shown in Table 1.

Table 1: Biological characteristics of available pneumococcal conjugate vaccines

			Pneumococcal Serotype (ST)													
Product	**Carrier protein(s)**	**Conjugation method & Preservative**	**1**	**3**	**4**	**5**	**6A**	**6B**	**6C**	**7F**	**9V**	**14**	**18C**	**19A**	**19F**	**23F**
PCV-10^{GSK} Synflorix®	Protein D (PD), tetanus toxoid (TT), diphtheria toxoid (DT)	*Conjugation:* CDAP* *Preservative:* 1-dose vial – none 2-dose vial – none 4-dose vial – 2-phenoxyethanol														
PCV-10^{SII} PNEUMOSIL®	CRM197	*Conjugation:* CDAP* *Preservative*: 1 dose vial – none 5 dose vial – thimerosal														
PCV-13 Prevnar®	CRM197	*Conjugation:* Reductive amination *Preservative*: 1-dose vial – none 4-dose vial – 2-phenoxyethanol														

* CDAP: 1-cyano-4-dimethylaminopyridinium tetrafluoroborate

ST included in vaccine
ST not included in vaccine
ST not included in vaccine but some evidence of cross-protection
ST3 included in PCV-13 but no conclusive evidence for protection

Safety

- The safety profiles of both PCV-10^{GSK} and PCV-13 have been reviewed as part of the WHO prequalification process and by the Global Advisory Committee on Vaccine Safety (GACVS). Both products have accrued extensive post-marketing safety surveillance data, and both are assessed as having excellent safety profiles.
- Clinical trial data for PCV-10^{SII} were reviewed during the WHO prequalification process; the product was well tolerated and has a comparable safety profile to the other prequalified PCVs[2].

[2] Public Assessment Summary Report. Pneumococcal Conjugate Vaccine, (adsorbed, 10-valent), Serum Institute of India Pvt. Ltd. 17 December 2019. https://extranet.who.int/pqweb/content/pneumosil%C2%AE-0

PCV Performance

Efficacy/effectiveness or immunogenicity

- Measurements of disease effectiveness following PCV use in routine use settings, measured at the community level, do not meaningfully distinguish PCV-10^{GSK} from PCV-13
    - Both products show high levels of immunogenicity, reduction in VT IPD, all cause pneumonia, chest x-ray (CXR) confirmed pneumonia, and VT colonization (the effector of herd effect)
- Efficacy data for PCV-10^{SII} are not available, but efficacy is expected to be equivalent to PCV-13 and PCV-10^{GSK} based on immunogenicity data showing non-inferiority[2,3,4].

Serotype-specific coverage

Available local, regional, and global pneumococcal disease surveillance data should be considered as part of a decision to switch or introduce a new PCV product. The proportion of IPD in children under 5 years of age, caused by STs included in the available PCVs, by region, before PCV introduction is similar across the three products, as shown in the figure below.

ST 3 (contained in PCV-13 only):

- Data on PCV-13 impact on ST 3 are inconclusive, with most studies showing no impact.

ST 6A, 19A (contained in PCV-13 and PCV-10^{SII}):

- PCV13 stimulates strong immune response to ST 6A and 19A as well as demonstrated impact on ST 19A and 6A IPD in both immunized and unimmunized age groups.
- PCV-10^{SII} was also shown to stimulate strong immune responses for ST 6A and 19A in phase 3 trials but disease impact data are not yet available.
- For PCV-10^{GSK}, while reduction in disease from ST 6A has been documented in immunized populations, there is no conclusive evidence of cross-protection for ST 19A. Little to no impact on unimmunized individuals (i.e. indirect protection) has been observed for these STs following PCV-10^{GSK} implementation.

ST 6C (possible cross-protection conferred by ST 6A, contained in PCV-13 and PCV-10^{SII})

- Some studies have shown a significant impact of PCV13 on ST 6C IPD and on carriage[1].
- Given that PCV-10^{SII} contains ST 6A, it may provide impact on ST 6C disease, but impact data are not yet available.

[3] Clarke E, Bashorun A, Adigweme I et al. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Infectious Diseases. 2021. https://doi.org/10.1016/S1473-3099(20)30735-0

[4] Clinical Study Report PCV-10-003. A Phase 3, Randomized, Double-Blind Study to Evaluate the Immunogenicity, Safety and Tolerability of Serum Institute of India's 10-valent Pneumococcal Conjugate Vaccine (PNEUMOSIL®) in Healthy Indian Infants. Serum Institute of India Pvt. Ltd. 24 June 2020.

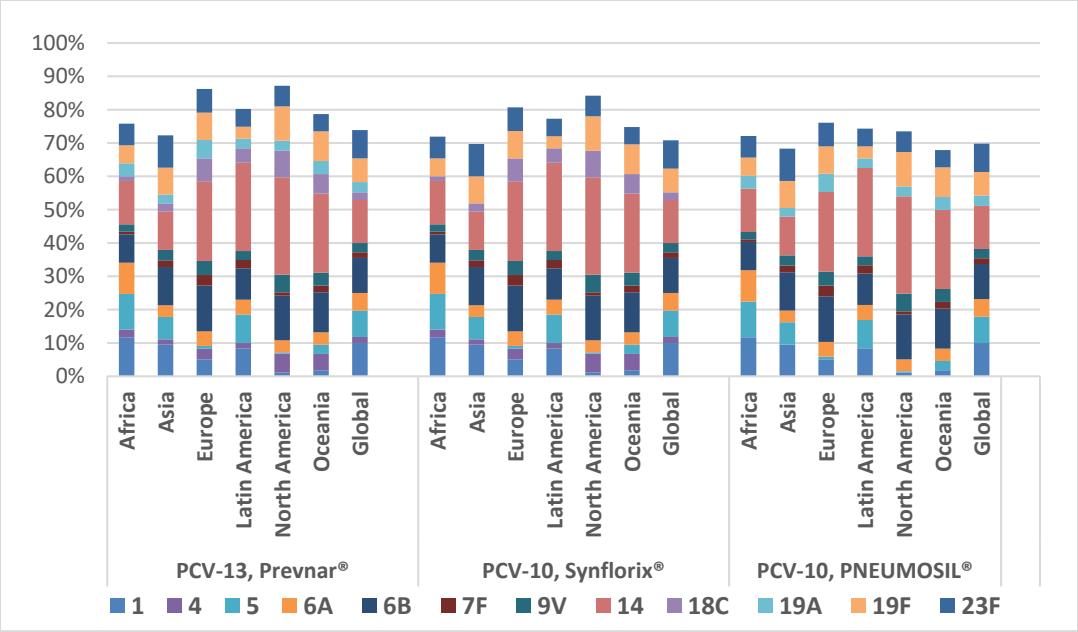

Figure: Proportion of invasive pneumococcal disease (IPD) in children under 5 years of age before PCV introduction, caused by vaccine serotypes (ST) included in available PCV products, by region. Data adapted from Johnson et al, 2010. PLoS Med 7(10): e1000348.

This figures shows that prior to PCV introduction, similar proportions of IPD were caused by the ST included in each of the three vaccine products. Please note that this pre-PCV distribution may vary from the percent reduction of ST-specific disease that might be observed after PCV introduction. ST shown include ST included in the product plus ST where evidence of cross-protection has been observed. This applies to ST 6A impact observed for Synflorix®. Evidence of ST 6C cross protection by PCV-13 has been observed but the percent IPD due to this ST are not available from the pre-PCV period and cannot be quantified.

Programmatic Considerations

- Several programmatic characteristics are similar or identical between the three PCV products (e.g. presentation, administration, formulation, storage temperature, vaccine vial monitor (VVM), wastage rate).
- Other important factors —such as cold chain and storage space, doses per container, and price—differ by product and may require additional planning for countries choosing to switch or incorporate multiple products (Table 2).
- Training of immunization staff is required for use of all PCV products prior to introduction and may be required for situations where a product and/or presentation switch is undertaken.

Table 2: Vaccine presentation, administration, storage and cold chain requirements

	PCV-10^{SII}	PCV-10^{SII}	PCV-13	PCV-13	PCV-10^{GSK} *
Presentation	1 dose/vial, liquid	5 doses/vial, liquid	1 dose/vial, liquid	4 doses/vial, liquid	4 doses/vial, liquid
Dose quantity	←----------0.5 ml----------→				
Dose measurement needed	No	Yes	No	Yes	Yes
Vaccine vial monitor type	←----------Type 30----------→				
Open vial handling[5]	n.a.	May be kept for use up to 28 days if stored at 2-8°C	n.a.	May be kept for use up to 28 days if stored at 2-8°C	May be kept for use up to 28 days if stored at 2-8°C
Shelf-life	←----------36 months, 2 - 8 °C----------→				
Cold chain volume per fully immunized person (cm3)	53	11	37.8	11.7	8

*This table shows product presentations supplied by Gavi. PCV-10^{GSK} 1 and 2 dose vials are also WHO prequalified[6]

Recommended vaccination schedules

- Per the 2019 position paper, WHO recommends a 3-dose schedule administered either as 2 primary doses plus a booster dose (2p+1) or as 3 primary doses without a booster (3p+0), starting as early as 6 weeks of age. For the 2p+1 schedule, an interval of ⩾8 weeks is recommended between the 2 primary doses, but the interval may be shortened if there is a compelling programmatic reason to do so. The booster dose should be given between 9–18 months of age. If the 3p+0 schedule is used, a minimum interval of 4 weeks should be maintained between doses.
- In choosing between the 2p+1 and 3p+0 schedules, countries should consider programmatic factors, including timeliness of vaccination and expected coverage.
- PCV-10 ^{SII} clinical trial data support its use in a 3p+0 schedule. Additional data from trials in India and the Gambia assessing the immunogenicity of the 2p+1 schedule are expected soon.

Co-Administration

- Based on the Gambian phase 3 trial[3], PCV-10 ^{SII} was shown not to interfere with the performance of pentavalent vaccine (diphtheria, tetanus, whole-cell pertussis, hepatitis B, and *Haemophilus influenzae* type b) when given at the same time.
- WHO recommends that despite the lack of comprehensive data on the immunogenicity, effectiveness and safety of all possible combinations of PCV and other routine vaccines, co-administration for programmatic reasons appears to be acceptable[1].

[5] WHO policy statement: multi-dose vial policy (MDVP): handling of multi-dose vaccine vials after opening, Revision 2014. https://apps.who.int/iris/handle/10665/135972

[6] https://extranet.who.int/pqvdata/PreviewVaccine.aspx?nav=0&ID=384

Interchangeability

- A 2019 review of evidence on PCV interchangeability synthesized data on children who completed PCV schedules with mixed products to inform policies on PCV procurement and product switching[7]. Available evidence suggests that countries can use PCVs interchangeably in routine programmes when continuing the entire series with the same product is not feasible.
- Given limited evidence on interchangeability, once a PCV vaccination programme has been initiated, product switching may be recommended in the event of substantial changes in the epidemiological or programmatic factors that determined the original choice of product, such as increase in the burden of disease from a serotype(s) better covered by an available alternative vaccine formulation[1].

Cost and financial considerations

- PCV pricing varies by product and procurement method. PCV public market prices per dose for PCV-10^{GSK} and PCV13 range from $3 USD for Gavi countries[8] through UNICEF (and the AMC) to $132 USD in the USA[9]. PCV-10^{SII} has the lowest Gavi price of all PCVs ($2.95 USD, 1 dose/vial; $2.00 USD, 5 doses/vial)[10] and is expected to be the lowest-price option for non-Gavi countries, though data on non-Gavi pricing are not yet available.
- The table below provides an overview of median price per dose for PCV-10^{GSK} and PCV13 by income and procurement group.[11]

	UNICEF Supply Division – Gavi eligible country purchases	UNICEF Supply Division – MIC procuring purchases	PAHO Revolving Fund purchases	Self- procured MIC purchases	Self-procured HIC purchases
PCV* Median price/dose (USD)	$3.05	$9.39	$14.50	$18.29	$45.44

*PCV13 and PCV10^{GSK}

- WHO publishes annually Vaccine Purchase Data[12] reported by countries through the WHO/UNICEF Joint Reporting Form. This database is available for countries to be able to