EVIDENCE DOSSIER

PNEUMOCOCCAL CONJUGATE VACCINE (PCV) INTERCHANGEABILITY

SUMMARIZING AVAILABLE EVIDENCE TO INFORM POLICY RECOMMENDATIONS

SUMMARY

Two pneumococcal conjugate vaccine (PCV) products are currently World Health Organization (WHO)-prequalified and available for use worldwide. A third, indigenous PCV is expected to be prequalified in the near future. As additional products become available, countries will need to consider interchangeability issues, namely the ability to use more than one PCV product without adversely affecting the safety or the effectiveness of the PCV program. To help inform policy on interchangeability of PCV, we reviewed current evidence to assess the biologic and epidemiologic impact described in settings where children received two different PCV products.

Our review found no evidence suggesting cause for concern for children who may have received a combination of products in routine use. Further, we did not see evidence of dampening of the downward trend in rates of disease due to serotypes common to both vaccines during or after a product switch. Given the number of countries (and sub-national jurisdictions) that have successfully switched products without adverse outcomes, the likelihood of undesirable consequences from a mixed product schedule are low.

Below we describe our review and note the programmatic considerations that would also play a role in policy and program decisions.

OBJECTIVES

1. Review available evidence on PCV interchangeability from an individual beneficiary level, synthesizing data on children who complete their PCV schedule with mixed products
2. Provide synthesized evidence to inform policies on PCV procurement, specifically feasibility of brand switching

BACKGROUND

PCV licensure and recommendations

The U.S. Food and Drug Administration (FDA) licensed the first PCV product, PCV7 (Wyeth, Prevenar), for use in infants in 2000. A recommendation for inclusion of PCV in the routine infant immunization schedule was made by the U.S. Advisory Committee on Immunization Practices (ACIP) in July 2000 and was implemented in the U.S. later that year [1]. Many countries then licensed and adopted its use. In 2007, WHO adopted a policy, as recommended by the Strategic Advisory Group of Experts (SAGE) on Immunization, that all countries should include PCV as part of the routine infant immunization schedule [2]; WHO prequalification (PQ) for PCV7 was issued the same year. The WHO recommendation was made with evidence from two large phase III efficacy trials (using an investigational 9-valent PCV [Wyeth]) in Africa (the Gambia [3] and South Africa [4]) confirming the generalizability of efficacy beyond that observed in trials from North America and Europe.

Since then, two additional PCV products—PCV10 (GSK, Synflorix™) and PCV13 (Pfizer, Prevenar 13®)—have received WHO PQ, both of which include more serotypes than those found in PCV7; PCV13 replaced PCV7, which is no longer on the market [5]. With the removal of PCV7 from the global market, countries using PCV7 switched to either PCV10 or PCV13. It also gave countries a choice of PCV products for the first time, and some countries opted to make both products available or switched from one product to the next. This created the possibility that some children completed their vaccine series with a different product—which differ in serotypes, carrier proteins, and conjugation chemistries, as well as in programmatic aspects. Experience using more than one PCV product, therefore, occurred on both an individual basis (with children receiving more than one product) and on a country basis (with some children receiving one product while others received a different product). Product selection decisions between PCV10 and PCV13 generally are based on a combination of factors that largely fall into five categories: disease epidemiology, product performance, programmatic considerations and feasibility, supply, and financial considerations.

Factors influencing initial product selection or product switch decisions:

- disease epidemiology
- product performance
- programmatic considerations and feasibility
- supply
- financial considerations

In February 2019, WHO issued a new pneumococcal vaccine position paper that summarized global technical consensus on various considerations, including PCV interchangeability [6].

PCV interchangeability

Co-availability of the two currently WHO-PQ PCV products (PCV10 and PCV13) in a national immunization program, along with additional PCV products in development (Table 1), has given rise to questions related to their interchangeability. Here we define "*interchangeability*" as the ability to use more than one PCV product without adversely affecting either the safety or the effectiveness of the PCV program, either in the individual or in the population as a whole. PCV products differ in many respects—both biologic, including serotype composition, carrier protein, and conjugation methods (Table 1.A), and programmatic (Table 1.B), including presence of preservative and number of doses per container. These factors can influence immunogenicity, impact on disease occurrence, nasopharyngeal colonization, and other components described in total system effectiveness, including vaccine handling, storage, and delivery; safety; cost per dose delivered; and equity.

Two PCV products are currently WHO-prequalified: a 10-valent **PCV10 (GSK, Synflorix™)** and a 13-valent **PCV13 (Pfizer, Prevenar 13®)**. A 10-valent PCV **(PNEUMOSIL, Serum Institute of India [SIIPL-PCV])** is under consideration for WHO prequalification.

Although there is substantial experience with interchangeability of the currently licensed PCVs globally, few studies have evaluated the effect of having more than one product available in a country or administration of a mixed schedule of PCV products in an individual child on outcomes listed above. Although limited, phase II safety and immunogenicity data on interchangeability between PCV13 and the investigational 10-valent PCV (PNEUMOSIL, Serum Institute of India [SIIPL-PCV]) are available in toddlers primed with PCV13 in infancy [7-9]. Therefore, the available data and similarities between products, including those under development and PCV10/13, allow inferences to be made concerning their interchangeability.

Programmatic considerations of product switches and implications for government policy

In addition to biologic interchangeability of PCV products, it is critical to also consider programmatic or operational characteristics of each product and their suitability for the existing routine immunization system and infrastructure in making procurement decisions and establishing interchangeability or mixed schedule policies. These may include impact on cold chain, logistics, supply management, training, administrative functions, and other considerations which may increase the complexity of managing the immunization program when multiple formulations of a single vaccine are used. The number of doses per vial will have implications on price, wastage, missed opportunities when multi-dose vials are not opened due to wastage concerns, and in some cases safety (although this is less of a concern with all-liquid formulations with preservatives).

Before committing financial resources to vaccine supply, countries must assess the operational feasibility and costs of switching products or choosing to implement multiple products within the same country or subnational region. Concurrent use of multiple PCV products in the same region or program will have implications for cold chain, training, and other operational components (Table 1.B) and will require precise coordination. Total systems effectiveness (TSE)—a new framework that aims to incorporate "coverage, equity, programmatic implications, and fully systems cost" in the prioritization process—may inform decision making as countries consider product options and evaluate tradeoffs [10]. The TSE approach seeks to disrupt the traditional product development paradigm by placing country demand at the center of product development and creating new opportunities for accelerated licensure-to-uptake timelines for new products that meet low- and middle-income country preferences [10, 11]. This approach may be suitable for countries considering expanding upon or switching the PCV products used in the national immunization program (NIP), particularly with the anticipated WHO prequalification of a new PCV10 product manufactured by Serum Institute of India (SII).

METHODS

In this review, we aimed to describe PCV interchangeability by reviewing studies of safety and immunogenicity as well as country product switch experiences in order to summarize the biologic and epidemiologic impact documented in published literature that specifically describe scenarios where multiple products were used interchangeably or a switch from one product to another was made at the national level. Our evaluation was restricted to the question of interchangeability and does not consider whether one product is superior to another nor detail considerations for product comparisons.

PCV product interchangeability was assessed by reviewing **published studies** and **country experiences.**

Studies reviewed in this document were identified through searches of PubMed, ClinicalTrials.gov, national surveillance websites, and studies known to the Bill & Melinda Gates Foundation. We sought studies specifically looking at mixed products in individual children or documentation of a programmatic switch in PCV products that could potentially have led to individual children receiving a mixed schedule of at least two different products. These studies included clinical trials with at least one group that assessed children receiving a mixed PCV product schedule and observational studies of routine use of PCV in the NIP evaluating the effect of concurrent product use or switching from one product to another in the NIP on individual participants or in the population. We limited our assessment to effects in children under 5 years and did not evaluate indirect protection (i.e., herd protection).

Table 1: Prequalified PCVs or those submitted for prequalification

Part A: Biological characteristics

Product	Formulation specifications*	Type of carrier protein(s)	Conjugation method	Serotypes												
				1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Currently WHO Prequalified																
Synflorix™ (GSK)	10-valent *Preservative*: 1-dose vial* – none 2-dose vial – none 4-dose vial – 2-phenoxyethanol	Protein D (PD), tetanus toxoid (TT), diphtheria toxoid (DT)	CDAP**	1µg PD		3µg PD	1µg PD		1µg PD	1µg PD	1µg PD	1µg PD	3µg TT		3µg DT	1µg PD
Prevenar 13® (Pfizer)	13-valent *Preservative*: 1-dose vial* – none 4-dose vial – 2-phenoxyethanol	CRM_{197}	Reductive amination	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	4.4µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}	2.2µg CRM_{197}
Submitted for WHO Prequalification																
PNEUMOSIL® (SII)	10-valent *Preservative*: 1 dose vial* – none 5 dose vial – thimerosal	CRM_{197}	CDAP**	2µg CRM_{197}			2µg CRM_{197}	2µg CRM_{197}	4µg CRM_{197}	2µg CRM_{197}	2µg CRM_{197}	2µg CRM_{197}		2µg CRM_{197}	2µg CRM_{197}	2µg CRM_{197}
No longer available																
Prevenar 7® (Wyeth/Pfizer)	7-valent *Preservative:* 1-dose vial* – none	CRM_{197}	Reductive amination			2µg CRM_{197}			4µg CRM_{197}		2µg CRM_{197}	2µg CRM_{197}	2µg CRM_{197}		2µg CRM_{197}	2µg CRM_{197}

* Other formulations/presentations (e.g. pre-filled syringe) may be available in some countries but are not currently WHO-prequalified
** CDAP: 1-cyano-4-dimethylaminopyridinium tetrafluoroborate

Part B: Programmatic characteristics for WHO-PQ PCV and products under PQ consideration [12-14]

		WHO-PREQUALIFIED				UNDER PQ CONSIDERATION	
Vaccine		**Synflorix (PCV10)**		**Prevenar 13 (PCV13)**		**PNEUMOSIL (SIIPL-PCV)[a]**	
Manufacturer		GlaxoSmithKline (GSK)		Pfizer		Serum Institute of India (SII)	
Number of serotypes		10		13		10	
Doses per container[b]		1	4	1	4	1	5
Pharmaceutical form		Liquid		Liquid		Liquid	
Administration		Intramuscular		Intramuscular		Intramuscular	
WHO prequalified		2009	2017	2010	2016	Under consideration (2019)[c]	
Schedule		3 doses		3 doses		3 doses	
Available secondary cartons		1, 10, 100 vials	100 vials	25 vials, 50 vials			300 vials
Storage temperature		2-8°C		2-8°C		2-8°C	
Shelf life at 2-8°C		48 months	36 months	36 months		36 months	
Cold chain volume per dose		58 cm^3, 11.5 cm^3, 10 cm^3	2.4 cm^3	12.0 cm^3	3.6 cm^3		3.5 cm^3
Vaccine vial monitor		VVM 30		VVM 30		VVM 30	
Open vial handling guidelines[d]		N/A	Up to 28 days	N/A	Up to 28 days	N/A	Up to 28 days
Indicative wastage rate			8%	5%	8%	5%	8%
UNICEF price per dose for Gavi countries, 2020 (USD)		N/A	$3.05	$3.30	$2.90	$3.50 (expected)[e]	$2.00 (expected)[e]
Price range per dose by income group, 2018 (USD)[f] [15]	**LIC**	*No data*	$3.05	$2.67-12.20	$2.95-7.00	TBD	
	LMIC	$3.61-13.85	$3.05	$2.64-22.04	$2.90-3.30		
	UMIC	$12.85-38.04	*No data*	$3.07-29.22	$3.05		
	HIC	$28.42-58.03		$13.72-57.42	$55.05		

[a] Subject to change upon release/confirmation of product details by manufacturer (upon PQ and/or licensure); sourced from Gavi product profiles [12, 13]
[b] Other formulations/presentations (e.g. pre-filled syringe) may be available in some countries but are not currently WHO-prequalified
[c] PNEUMOSIL has received its export license and is under consideration for WHO PQ
[d] Requires specific open vial training [16]
[e] Final price to be confirmed after signature of Long Term Agreement between UNICEF SD and the manufacturers. Price is volume-dependent and may be higher in launch period.
[f] MI4A/V3P database does not include all countries; 4-dose vial pricing only available for Gavi countries; price ranges shown here exclude other presentations available in some LMIC, UMIC, and HIC (e.g. pre-filled syringe)

RESULTS

Safety and Immunogenicity trials

In this section, we summarized the safety and immunologic evidence for mixed PCV10 (Synflorix)-PCV13 (Prevenar 13) and mixed PCV10 (PNEUMOSIL)-PCV13 (Prevenar) schedules only. We have not included the immunologic studies assessing interchangeability between PCV7 and either PCV10 or PCV13; mixed schedules involving PCV7 are described only in the Effectiveness Studies section below.

Because antibody response is correlated with individual-level protection against pneumococcal disease and licensure of new PCV products is based on demonstrating non-inferiority of immunogenicity, immunogenicity can be used to evaluate interchangeability of PCV products. There are several ways to assess immunogenicity. Licensure is based on an ELISA test which measures the amount of IgG antibody produced, assessed as geometric mean antibody concentration [GMC] and the percent achieving ≥0.35 ug/ML. Functional activity of the antibodies elicited by vaccination are assessed by a functional antibody test, the o-Phthalaldehyde Fluorescent Protein Assay [OPA] test, which evaluates the ability of the antibodies produced to kill targeted cells. OPA responses are assessed as a geometric mean titer (GMT) and as the percent achieving titer ≥8.

Four trials in five different countries have evaluated safety and immunogenicity of a mixed PCV10 (Synflorix) - PCV13 (Prevenar 13) schedule (Table 2): three (Urbancikova, et al. [17]; Truck, et al. [18]; Clinicaltrials.gov NCT #01641133 [19]) evaluated 2+1 schedules and one (Urbancikova, et al. [17]) evaluated a 3+1 schedule; one (Leach, et al. [20]) evaluated a novel 4+0 schedule that included a birth dose and no results are as yet available (as of May 2019). One trial (Clarke, et al. [8]) evaluated safety and immunogenicity of a mixed PCV10 (PNEUMOSIL)-PCV13 (Prevenar) schedule, which shares the same carrier protein. Details of each trial are presented below, but to summarize, antibody production was greater for some serotypes with the single-product schedules than for mixed schedules, but when functional antibody was assessed, 100% of children receiving a mixed schedule had a functional antibody response.

Antibody production was greater for some serotypes with the single-product schedules than for mixed schedules, but **when functional antibody was assessed, 100% of children receiving a mixed schedule had a functional antibody response**.

Table 2: Summary of safety and immunogenicity trial characteristics

Study	PCV products mixed	Schedule	Countries	Immunogenicity assessment method
Urbancikova, et al. [17]	PCV10 (Synflorix) with PCV13 (Prevenar 13)	2+1, 3+1	Slovakia, Czech Republic	ELISA and OPA
Truck, et al. [18]		2+1	United Kingdom	ELISA and OPA
Clinicaltrials.gov NCT #01641133 [19]		2+1	Mexico	ELISA
Leach, et al. [20]		4+0	Australia	ELISA*
Clarke, et al. [8]	PCV10 (PNEUMOSIL) with PCV13 (Prevenar 13)	3+1	The Gambia	ELISA and OPA

*Results are not yet available; unknown if OPA testing will also be performed.

Interchangeability of PCV10 (Synflorix) and PCV13 (Prevenar 13)

Urbancikova et al. (Slovakia and Czech Republic) [17]

Schedules evaluated: This trial evaluated interchangeability of the booster dose by comparing children primed with PCV10 (Synflorix) and boosted with PCV13 (Prevenar 13) with children primed and boosted with PCV13 only in 2+1 and 3+1 schedules.

Primary objective: The primary objective of the study was to assess non-inferiority of functional antibody responses by measuring geometric mean titers (GMTs) specifically for serotype 19A, but immunogenicity (OPA GMTs as well as percent achieving ≥1:8 titers and ELISA geometric mean antibody concentrations [GMCs] and percent achieving ≥0.35 ug/ML) was tested for all serotypes, allowing comparisons of interchangeability at the booster dose.

Results:

- *Immunogenicity:*
    - **2+1 schedule:** Results demonstrated that post-booster 19A OPA GMTs were comparable in PCV10-primed/PCV13 boosted and PCV13-primed/PCV13-boosted groups, thus meeting the prespecified noninferiority primary endpoint. For the remaining serotypes, OPA GMTs were similar between groups for serotypes 1, 3, 5, 6B, 18C, 19F, and 23F. OPA GMTs were similar in PCV10-primed subjects for seven serotypes (1, 3, 5, 6A, 6B, 9V, and 19F) and inferior for six (4, 6C, 7F, 14, 18C, and 23F). All subjects had OPA titers ≥ 8 in the two groups for all serotypes, except for serotypes 3 and 6A (≥97.4%). Importantly, the PCV10-PCV13 mixed product schedule was highly immunogenic, with 100% of children having an OPA titer >1:8 one month after the booster dose for all PCV10 serotypes, as was observed for the PCV13-only recipients.

      When evaluated one year after the booster dose to assess presence of longer-term functional antibody, the PCV13-only schedule had a greater proportion of children with a functional antibody response for serotypes 4 (82% vs 47%) and 14 (94% vs 76%). Responses for all other serotypes were similar by vaccine group. Statistical testing for this outcome was not presented in the paper, but sample size was small (range n=38 to 51 per group), so smaller differences are likely not statistically significant.

    - **3+1 schedule:** Results demonstrated that post-booster 19A OPA GMTs were comparable in PCV10-primed/PCV13 boosted and PCV13-primed/PCV13-boosted groups, thus meeting the prespecified noninferiority primary endpoint. For the remaining serotypes, OPA GMTs were similar between groups for serotypes 1, 3, 5, 6B, 18C, 19F, and 23F but, with the 3+1 schedule, they were higher in the PCV13 group for serotypes 4, 6A, 6C, 7F, 9V, and 14. All subjects had OPA titers ≥ 8 in the two groups for all serotypes, except for serotypes 3 and 6A (≥97.4%). Importantly, the PCV10-PCV13 mixed product schedule was highly immunogenic, with 100% of children having a an OPA titer >1:8 one month after the booster dose for all PCV10 serotypes, as was observed for the PCV13-only recipients.

      When evaluated one year after the booster dose to assess presence of longer-term functional antibody, the PCV13-only schedule had a greater proportion of children with a functional antibody response one year after the booster dose for serotypes 4 (71% vs 61%), 7F (100% vs 92%), and 9V (98% vs 86%). The mixed product schedule had a greater proportion of children with a functional antibody response for serotypes 1 (43% vs 13%), 5 (84% vs 67%) and 19F (94% vs 80%). Statistical testing for this outcome was not presented in the paper, but sample size was small (range n=38 to 51 per group), so smaller differences are likely not statistically significant. Responses for all other serotypes were similar by vaccine group.

- *Safety:*
    - **2+1 schedule:** Serious reactions (defined as Grade 3 reactogenicity or severe unanticipated adverse events) were rare and there was no indication of higher reactogenicity in the mixed product group. Three serious reactions were observed: two in the children receiving the mixed products (respiratory tract inflammation and gastroenteritis) and one in the PCV13-only group (dyspepsia); none were considered related to PCV. One child in each vaccine group had a vaccination-related unsolicited adverse event: acute gastroenteritis and dehydration in a PCV10-primed child and sideropenic anemia in a PCV13-primed child.
    - **3+1 schedule**: Serious reactions were rare and there was no indication of higher reactogenicity with the mixed product schedule. There were four serious reactions: one in a child who was primed with PCV10 (falling on head) and three in children primed with PCV13 (acute laryngitis, head and neck burn, and herniotomy). No child receiving the mixed products experienced a vaccination-related unsolicited adverse event compared to two in the PCV13-only group.

Truck et al. (United Kingdom) [18]

Schedules evaluated: This trial evaluated a 2+1 schedule in which children received PCV13 (Prevenar 13) for the primary doses at 2 and 4 months of age and either PCV13 or PCV10 (Synflorix) for the booster dose at 12 months of age.

Primary objective: The primary objective was to evaluate whether PCV10 was noninferior to PCV13 as assessed by proportion with IgG ≥0.35 µg/mL for PCV10 serotypes 1 month following booster vaccination.

Results:

- *Immunogenicity*: One month after the booster dose, the IgG response in PCV13-primed, PCV10-boosted recipients as assessed by proportion ≥0.35 ug/mL was inferior to that of PCV13-primed and boosted recipients for serotypes 5 and 9V. For all other serotypes in common (i.e., PCV10-types), at least 97% of children reached that threshold. GMCs were significantly higher in the PCV13-only group compared to the mixed product group for seven of the 10 of the serotypes in common (1, 5, 6B, 7F, 9V, 14 and 23F); serotypes 4, 18C and 19F were significantly higher in the mixed product schedule compared to the PCV13-only schedule.

  The proportion with a functional antibody response (i.e., OPA titer ≥ 8) was similar between the two groups for all PCV10-types except serotypes 1 and 9V for which the PCV13-only schedule had significantly more responders. When the proportion with a functional response was assessed again one year later, the mixed product schedule performed as well (serotypes 1, 4, 5, 14 and 18C) or statistically better (serotype 19F) for six of the PCV10-type serotypes, but statistically more PCV13- only recipients responded for the remaining serotypes (6B, 7F, 9V and 23F). The OPA GMTs, however, were generally higher in the PCV13-only recipients one month after the booster dose; the mixed product was the same (serotypes 4 and 18C) or significantly better (serotype 19F) for only three serotypes while the PCV13-only schedule had statistically higher OPA GMTs for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F. One year after the booster dose, OPA GMTs were similar between vaccine groups (1, 4, 5, 14, and 18C) or significantly higher in the mixed product group (19F) for six of the 10 PCV10 serotypes, but remained statistically higher in PCV13-only recipients for serotypes 6B, 7F, 9V and 23F.

- *Safety*: Only reactogenicity data following immunization were reported by the study authors, which were similar between the two vaccine groups (PCV10 group: n=87; PCV13 group: n=90). Severe irritability was observed in three PCV13-only children compared to five mixed product children. Severe drowsiness was observed in two PCV13-only children and no children that received mixed products. No fevers >40ºC were observed in any child.

Clinicaltrials.gov NCT #01641133 (Mexico) [19]

Schedules evaluated: This trial evaluated interchangeability of primary doses of PCV10 (Synflorix) and PCV13 (Prevenar 13) with boosting by PCV10 with the following 2+1 schedules:

2 mo	4 mo	12-15 mo
PCV13	PCV10	PCV10
PCV13	PCV13	PCV10
PCV10	PCV10	PCV10

Primary objective: The primary objective of this trial was to describe the adverse events for the mixed- and single-product schedules.

Results:

- *Immunogenicity*:

  1-month post-dose 2: The mixed PCV13-PCV10 schedule had similar IgG GMCs to at least one of the single product schedules (PCV10-PCV10 or PCV13-PCV13) for PCV10-type serotypes 1, 4, 6B, 7F, and 18C, and significantly better than single-product schedules for 19F, but had significantly lower GMCs for serotypes 5, 9V and 23F (statistical testing was inferred from confidence intervals as this was not provided).

  8-months (long-term) post-dose 2 (pre-booster): The mixed PCV13-PCV10 schedule performed similarly (serotypes 1, 4, 6B, 9V, 14 and 18C) or significantly better (19F) than the single-product schedules for seven of the ten PCV10-types, but had significantly lower average antibody for serotypes 5 and 23F and possibly 7F (statistical testing not shown).

  1-month post-booster dose: In general, children who received PCV10-only had higher average antibody levels

than either mixed product schedule: for PCV13-PCV13-PCV10, only serotypes 1 and 19F had similar antibody levels to the PCV10-only schedule, and for PCV13-PCV10-PCV10, only serotypes 1, 4, 6B and 19F had similar antibody levels.

- *Safety*: Although no statistical comparisons were provided, serious adverse events (defined as medical occurrences that result in death, are life-threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity) were uncommon in all schedules: n=3 (3.1%) in the PCV10-only group, n=4 (4.0%) in the PCV13-PCV10-PCV10 group, and n=1 (1.0%) in the PCV13-PCV13-PCV10 group). Grade 3 general symptoms assessed following dose 2 of the mixed product (PCV13-PCV10) were similar to or fewer than the single-product schedules, except Grade 3 pain which was 10% (9/90) in the mixed product vs. 4% (4/90) for PCV13-only and 7% (6/87) for PCV10-only. Post-booster Grade 3 symptoms were more slightly more common in the mixed products than for PCV10-only recipients but differences may not be statistically significant (statistical testing was not provided): having any Grade 3 symptom was 16% (14/85) for PCV13-PCV13-PCV10 recipients, 14% (12/87) for PCV13-PCV10-PCV10 recipients, and 12% (10/86) for PCV10-only recipients.

Leach et al. (Australia) [20]

Schedule evaluated: This trial evaluated children who received a novel 4+0 mixed product schedule of PCV10 (Synflorix) at 1, 2, and 4 months and PCV13 (Prevenar 13) at 6 months of age compared to children receiving 3+0 regimens of PCV10 or PCV13 at 2, 4, and 6 months of age.

Primary objective: The primary outcome of this trial was immunogenicity; secondary outcomes evaluated include nasopharyngeal carriage of vaccine-type pneumococci, nasopharyngeal carriage of nontypable *Haemophilus influenzae* (NTHi), and otitis media.

Results: The trial is complete (March 2018) but no results are published/available as of May 2019.

Interchangeability of an investigational 10 valent vaccine (PNEUMOSIL, Serum Institute of India [SIIPL-PCV]) and PCV13 (Prevenar 13)

***Clarke et al. (The Gambia)* [7-9]**

Schedule evaluated: This trial evaluated children primed with 3 doses (at 6-10-14 weeks) of PCV13 (Prevenar 13) and boosted with either the investigational 10-valent PCV (PNEUMOSIL, SIIPL-PCV) or PCV13 at 12-15 months of age.

Primary objective: The primary endpoint of this study was safety and tolerability of the toddler dose; secondary and exploratory endpoints were immunogenicity measured by IgG levels and functional activity by OPA, respectively. As this was a phase I/II de-escalation study, the number of subjects was limited (112 children in the safety cohort, 34 of whom had immunogenicity evaluated).

Results:

- *Immunogenicity:* Results for the secondary endpoint of immunogenicity demonstrated serotype-specific IgG GMCs following the booster dose with SIIPL-PCV ranged from 2.30 µg/mL (95% CI: 1.57–3.72) for serotype 5 to 15.77 µg/mL (95% CI: 11.51–23.96) for serotype 6B and from 3.35 µg/mL (95% CI: 2.46–5.35) to 19.16 µg/mL (95% CI: 14.98–30.46) for the same serotypes, respectively, following the booster dose with PCV13. Although SIIPL-PCV GMCs were generally lower than those following PCV13, there were only 17 children in each group and differences were not statistically significant. Functional antibody activity was an exploratory endpoint and results demonstrated that OPA GMTs following the booster vaccination in toddlers were broadly comparable, with overlapping ranges for the point estimates for all serotypes except serotype 14 for which the response was greater in the SIIPL-PCV group.

- *Safety:* Results of the primary endpoint demonstrated comparable safety in these PCV13 primed toddlers between the two groups. Generally, reactogenicity was mild or moderate in both groups and of limited duration. Systemic reactions were also comparable between groups.

Effectiveness studies evaluating NIPs using PCV10 (Synflorix) and PCV13 (Prevenar 13) concurrently or switching products

Nine countries have used both products concurrently in their national immunization programs (Table 3). Five of these countries have published data on the incidence of vaccine-type IPD, NP carriage, and otitis media. Although these studies do not describe the conditions of the co-available products, including the percent of children who receive mixed doses or whether both products are available at the same clinic vs. in different geo-political sectors such as states or provinces, they demonstrate decreases over time in vaccine-type IPD and have reported no concerns with impact on disease by having more than one product available in the country.

Studies demonstrate **decreases over time in IPD** due to serotypes common to both vaccines and have reported **no concerns with impact on disease** by having more than one product available in the country.

Table 3: Countries that use both PCV10 and PCV13 products concurrently in the NIP

Country	Dosing schedule	Years used concurrently°	References on incidence of vaccine-type IPD, NP carriage, or otitis media during period where both products were being used (if available)
Austria	2+1	7	
Canada*	2+1, 3+1	9	Deceuninck (2015) [21]
Estonia	3+1	5	
Germany	2+1	9	VanDerLinden (2016) [22], Weinberger (2016) [23], Weinberger (2018) [24]
Korea, Republic of	3+1	5	Ahn (2015) [25], Cho (2016) [26], Kim (2016) [27]
Philippines	3+1	6	
Slovakia	2+1	8	Macaj (2016) [28], Macaj (2016) [29], Madarova (2016) [30]
Slovenia	2+1	5	
Sweden	2+1	9	Galanis (2016) [31]

° As of June 2019

* Quebec is the only Canadian province to use PCV10, all the other provinces use PCV13. Quebec used PCV10 starting in 2009, then switched to PCV13 starting in 2011, and switched back to PCV10 in 2018; it is unclear how long both products were in use simultaneously.

Of the seven studies that evaluated IPD, only one (Deceuninck, et al., 2015) compared vaccine effectiveness against IPD between children receiving mixed-product schedules to children receiving single-product schedules (i.e. PCV10 alone or PCV13 alone). The study (Quebec, Canada) followed children for a median of 3.7 years for the mixed group, 4.4 years for the PCV10-only group, and 17 months for the PCV13-only group. It found no significant difference in vaccine efficacy against PCV13-type IPD between a PCV10-only schedule, a PCV13-only schedule, or a mixed PCV10+PCV13 schedule [21]. These results suggest children receiving mixed products are just as protected from IPD as those who receive full courses of a single product.

Fifteen countries have had a documented switch between PCV10 and PCV13 products, four countries that switched from PCV13 to PCV10 and 13 that switched from PCV10 to PCV13, including two countries that have had multiple switches (Table 4). Two additional countries (Anguilla and Piedmonte, Italy) have been noted to have switched [7] but there is currently no documentation that describes the switch. Four countries (Belgium, Canada, New Zealand and Peru) have published data on the impact of the product change on the incidence of vaccine-type IPD or carriage. All of these studies have shown continued decreases in shared vaccine-type disease and do not report on any concerns after the switch in products.

Table 4: Countries that switched between PCV10 and PCV13 products

Country	Dosing schedule	Product switch	Years since switch*	References on post-switch incidence of vaccine-type IPD or NP carriage (if available)
Albania	3+0	PCV10 to PCV13	1	
Armenia	3+0	PCV10 to PCV13	3	
Azerbaijan	3+0	PCV10 to PCV13	2	
Barbados	3+0	PCV10 to PCV13	8	
Belgium	2+1	PCV13 to PCV10	3	Wouters (2018) [32], Wouters (2018) [33]
Quebec, Canada	2+1	PCV10 to PCV13	7	Demczuk (2013) [34], De Wals(2014) [35], De Wals (2018) [36]
		PCV13 to PCV10	1	
Ontario, Canada	2+1	PCV10 to PCV13	9	Desai (2016) [37], Eton (2017) [38], Lim (2013) [39], Rudnick (2013) [40], Shigayeva (2016) [41]
Chile	2+1	PCV10 to PCV13	2	
El Salvador	2+1	PCV13 to PCV10	1	
Mozambique	3+0	PCV10 to PCV13	2	
Myanmar	3+0	PCV10 to PCV13	1	
New Zealand	3+1	PCV10 to PCV13	3	ESR (2019) [42]
		PCV13 to PCV10	1	ESR (2019) [42]
Paraguay	2+1	PCV10 to PCV13	2	
Peru	2+1	PCV10 to PCV13	4	Luna-Muschi (2018) [43]
Slovenia	2+1	PCV10/13 to PCV13	4	
Trinidad and Tobago	3+1	PCV10 to PCV13	4	

* As of June 2019

De Wals et al. (Canada) [36] and Eton et al. (Canada) [38]

Following the switch in Quebec, Canada, from PCV7 to PCV10 in 2009, and then from PCV10 to PCV13 in 2011 continued declines in all IPD as well as and persistent reductions in the serotypes in common between products after each switch were observed. In Ontario, IPD was evaluated following switches from PCV7 to PCV10 in 2009, and from PCV10 to PCV13 in 2010; they observed no PCV13-type IPD pediatric cases in 2015.

Wouters et al. (Belgium) [32]

Evaluation of carriage in both asymptomatic children and acute otitis media (AOM) cases following a switch in Belgium from PCV13 to PCV10 found that carriage of PCV13-type serotypes was rarely detected after the switch.

Institute of Environmental Science and Research (ESR) (New Zealand) [42]

In New Zealand, IPD has been monitored following two product switches (from three years of PCV10 use to three years of PCV13 use and back to PCV10 in 2017) through national IPD surveillance [42, 44]. New Zealand made the decision to switch back to PCV10 based on higher hospitalization numbers in children for otitis media than for pneumonia and the potential for PCV10 to have additional effect on otitis media due to its carrier protein. During each period following the switch, PCV10-type IPD continued to decline.

Luna-Muschi et al. (Peru) [43]

Peru switched from PCV7 to PCV10 in 2011, and then from PCV10 to PCV13 in 2015. IPD was evaluated from the pre-PCV period through 2018. IPD due to PCV7-type serotypes continued to decline after switches to the higher valency products and PCV10 types continued to decline after the switch from PCV10 to PCV13.

NIPs switching from PCV7 (Prevenar 7) to PCV10 (Synflorix)

In addition, 12 countries (Table 5) have switched from PCV7 (which has the same carrier protein as PCV13) to PCV10 (which has different carrier proteins). Available literature from seven countries shows a continued decrease in PCV7-

type IPD and decreases in PCV10-type IPD, pneumonia, carriage, and otitis media after the product switch (Table 5). It should also be noted that many countries switched from PCV7 to PCV13 and also demonstrate a continued decrease in PCV7 IPD and decreases in PCV13-type IPD, pneumonia carriage and otitis media following the product switch but, because these vaccines have the same carrier protein and are manufactured by the same company using the same processes, they are not further described in this dossier.

Table 5: Countries that switched from PCV7 to PCV10 products

Country	Dosing schedule	Years since switch°	References on post-switch incidence of vaccine-type IPD, Pneumonia, NP carriage, or Otitis media (if avail.)
Austria*	2+1	7	
Canada*	2+1, 3+1	9	
Cyprus	2+1	10	Hadjipanayis (2016) [45]
Ecuador	3+0	9	
El Salvador^	2+1	8	
Germany*	2+1	10	Perniciaro (2018) [46], van der Linden (2015) [47], van der Linden (2015) [48]
Iceland	2+1	8	
Korea, Republic of*	3+1	5	Ahn (2015) [25]
Netherlands	2+1	8	Bosch (2016) [49], Dias (2016) [50], Knol (2015) [51], Knol (2016) [52], Knol (2016) [53], Vestjens (2017) [54], Vissers (2016) [55], Vissers (2018) [56]
New Zealand^	3+1	3	Best (2016) [57], ESR (2019) [42]
Peru^	2+1	2	
Slovakia*	2+1	8	Hupkova (2014) [58], Macaj (2016) [28], Macaj (2016) [29], Madarova (2016) [30]
Slovenia*^	2+1	5	
Sweden*	2+1	10	Littorin (2016) [59], Galanis (2016) [31]

°As of June 2019
*Use both PCV10 and PCV13
^Later switched to PCV13 (See table 3)

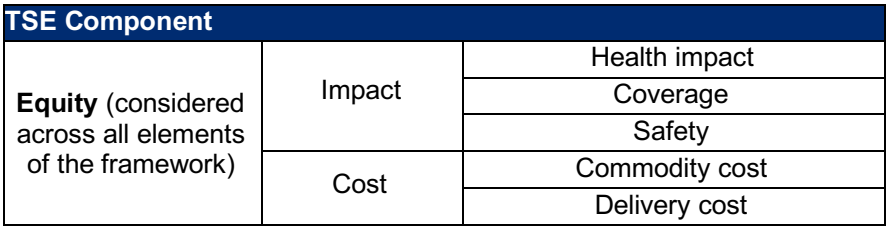
Operational/programmatic considerations

Among the currently WHO prequalified PCV options (Synflorix, Prevenar 13) and PNEUMOSIL, currently under consideration for WHO PQ, several programmatic characteristics are similar or identical, alleviating some of the potential challenges that face product switches (e.g. administration, liquid formulation, schedule, storage temperature, VVM). Other critical components—such as cold chain space, doses per container, price, and shelf life—differ by product and may require additional planning for countries choosing to switch or incorporate multiple products. Additionally, the program will need to determine which states or districts receive each vaccine, whether they will run down existing vaccine stocks, if and how to retrain health care workers, and if previously produced information, education, and communication (IEC) and training materials are still valid or need to be revised.

The TSE approach is one mechanism to weigh product profiles in a broader equity lens to help countries make informed decisions on product choice; this methodology requires consideration of an array of factors under the framework (Figure 2) that, taken together as a package, facilitate country consideration of various products, rather than considering only a select product characteristic or subset of characteristics [10, 11].

The TSE Framework is an important tool in evaluating product selection/switch and interchangeability decisions.

Figure 2: TSE vaccine product framework [10]



For example, the product characteristics of each of the PCV multi-dose vial options are very similar on many levels, but differ in terms of cold chain space requirements, number of doses per vial, and anticipated price, in addition to any health impact differences that could be considered. Other considerations include the complexity of handling multiple presentations from an inventory management standpoint, decisions about whether to run down stock completely before starting new program, and additional printing, training, monitoring, or other functions required due to a change in product. This emerging, multi-criteria approach is currently being rolled out, and may help countries weigh their options between the three products and their various presentations.

GLOBAL RECOMMENDATIONS

In 2019, the WHO issued a new pneumococcal vaccine position paper [6], stating:

> *"Once a PCV vaccination programme has been initiated, product switching is not recommended unless there are substantial changes in the epidemiological or programmatic factors that determined the original choice of product, e.g. an increasing burden of serotype 19A."*

This position statement does note that:

> *"If a series cannot be completed with the same type of vaccine, the available PCV product should be used. Restarting a series is not recommended, even for the primary series."*

Countries that have issued interchangeability recommendations generally agree/align with the WHO position paper.

CONCLUSION AND RECOMMENDATIONS

Our review demonstrates data on the immunologic, epidemiologic and especially programmatic aspects of switching between PCVs are limited. Despite differences in serotypes, carrier proteins and conjugation chemistry, the available evidence suggests that mixed or switched products perform similarly to use of a single product alone in both immunological and observational studies, did not result in concerning findings, and countries, including LMICs, have successfully switched between different PCV products. Based on the Safety and Immunogenicity and Country Switch sections, despite some differences in immunogenicity described previously, the effectiveness experience is reassuring and puts to rest questions of the clinical significance of the immunologic differences, especially following the booster dose in which immune responses are generally quite high.

The currently available evidence is sufficient to suggest that countries can treat PCVs interchangeably in routine program settings when continuing the entire series with the same product adds additional complexity or is not feasible.

Currently the available evidence is sufficient to suggest that countries can treat PCVs interchangeably in routine program settings when continuing the entire series with the same product adds additional complexity or is not feasible Therefore, we believe that there is no need for countries to conduct interchangeability studies prior to switching between PCV products. We acknowledge that the available interchangeability data, especially for PNEUMOSIL, are limited and believe continued evaluation of safety and impact post switch is critical.

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