PCV and rotavirus vaccine introduction options

Introducing PCV & Rotavirus Vaccine Workshop, N’Djamena, Chad

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PCV Policy recommendations 1/2

- **Most recent WHO Position Paper on PCV use in children**, February 2019

- **Recommended schedules:**
  - 3-dose schedule (either 2p+1 or 3p+0) for infants starting as early as 6 weeks of age with a minimum interval of 4 weeks between doses
  - For the 2p+1 schedule, the booster should be given between 9–18 months of age, and an interval of ≥8 weeks is recommended between primary doses

- **Catch up vaccination** in children aged 1–5 years, at time of introduction of PCV, should be used to accelerate vaccine impact on disease

- Three prequalified PCV products: two 10-valent (PCV-10) and one 13-valent (PCV-13)
WHO considerations for vaccination in adults (2021)

- Bimodal distribution of pneumococcal disease (children under 5 and adults >50 yrs)
- Prioritize introduction of PCV into national childhood immunization programmes and measures to sustain high coverage over initiating a pneumococcal vaccination programme for older adults
- In countries with mature childhood PCV programmes, decisions on initiating an adult programme (using PPV23 or PCV13), should take into account:
  - Local disease burden
  - Cost-effectiveness
  - Population structure and demographics
  - Enhanced surveillance to monitor serotypes in older adults
  - Operational factors
Global PCV introduction status to the national immunization programme

- Introduced (154 countries)
- Partially introduced (1 countries)
- Not introduced or data not available (39 countries)
- Not applicable
Coverage estimates, pneumococcal conjugate vaccine 3rd dose, 2021
Global PCV dosing schedules in use
PCV introduction decision-making considerations

Six key aspects of the immunization programme should be assessed to weigh the potential benefits and trade-offs of each introduction or switch option.

<table>
<thead>
<tr>
<th>Efficacy, effectiveness, safety</th>
<th>Ease of use</th>
<th>Expected coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disease burden and local/regional epidemiology (incl. serotype prevalence &amp; AMR patterns)</td>
<td>• Doses per schedule</td>
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</tr>
<tr>
<td>• Clinical trial data</td>
<td>• Doses per vial</td>
<td>• Impact on HW hesitancy to open a vial (missed opportunities)</td>
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<td>• Country-specific data</td>
<td>• Volume to administer</td>
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<tr>
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<td>• Wastage rates (doses/vial, sessions sizes, discard period)</td>
<td>• Size of supplier’s capacity</td>
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<td>• Freeze-thaw flexibility</td>
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<td>• Lead time for supplier to manufacture</td>
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Adapted from: WHO’s Principles and considerations for adding a vaccine to a national immunization programme (2014)
Key questions for PCV introduction or switch decision-making

Considerations for NITAG/ICC recommendation:

1. Which vaccine product and presentation to use?
2. Which PCV routine schedule to use (3+0 or 2+1)?
3. Will a PCV catch-up campaign be done at the time of launch (if yes: when)?
4. Are there opportunities for integration with other antigens, both for a catch-up campaign and for introduction in routine immunization?
   - In routine, whether to launch PCV in routine together with vaccination against rotavirus (dose schedule identical in most cases, high potential for impact)
   - If introducing PCV and rotavirus vaccine together, which rotavirus vaccine presentations are preferred
### WHO prequalified PCV products*:
**Serotypes included and possible cross-protection**

<table>
<thead>
<tr>
<th>Product</th>
<th>Carrier protein(s)</th>
<th>Conjugation method &amp; preservative</th>
<th>Pneumococcal serotypes</th>
</tr>
</thead>
</table>
| PCV13 Prevenar 13®, Pfizer | CRM197 | Conjugation: Reductive amination  
Preservative:  
1-dose vial: none  
4-dose vial: 2-phenoxethyl | 1 | 3 | 4 | 5 | 6A | 6B | 6C | 7F | 9V | 14 | 18C | 19A | 19F | 23F |
| PCV10 PNEUMOSIL®, Serum Institute of India | CRM197 | Conjugation: CDAP*  
Preservative:  
1-dose vial: none  
5-dose vial: thimerosal | 1 | 3 | 4 | 5 | 6A | 6B | 6C | 7F | 9V | 14 | 18C | 19A | 19F | 23F |
| PCV10 Synflorix®, GSK | Protein D (PD), tetanus toxoid (TT), diphtheria toxoid (DT) | Conjugation: CDAP*  
Preservative:  
1-dose vial: none  
2-dose vial: none  
4-dose vial: 2-phenoxethyl | 1 | 3 | 4 | 5 | 6A | 6B | 6C | 7F | 9V | 14 | 18C | 19A | 19F | 23F |

* CDAP: 1-cyano-4-dimethylaminopyridinium tetrafluoroborate

- Serotype included in vaccine
- Serotype not included in vaccine
- Serotype not included in vaccine but some evidence of cross-protection
- Serotype 3 included in vaccine but no conclusive evidence for cross-protection

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

PCV immunogenicity, efficacy, effectiveness

**2019 WHO position paper**

“PCV10 and PCV13 have comparable immunogenicity and impact on IPD, pneumonia and NP carriage due to shared vaccine serotypes. While differences were found in their immunogenicity and impact on the 3 serotypes included in PCV13 and not PCV10 and on serotype 6C, there is currently insufficient evidence that the 2 vaccines differ in their impact on overall pneumococcal disease burden.”

There is at present insufficient evidence of a difference in the net impact of the 2 products on overall disease burden. PCV13 may have an additional benefit in settings where disease attributable to serotype 19A or serotype 6C is significant. 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 pattern.”

- All three PCV products show **high levels of immunogenicity and are recommended** based on WHO prequalification
- Efficacy and effectiveness data are not available for PCV10SII

**Serotype-specific coverage differences**

- There is **cross-protection** for some serotypes, making PCV10SII expected protection similar to PCV13
- **Serotype 19A** is only present in PCV13 and PCV10SII
- The three PCV products are considered **interchangeable**
PCV safety and co-administration

- The safety profiles of both PCV-10\textsuperscript{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 extensive post-marketing data and have excellent safety profiles.

- Clinical trial data for PCV-10\textsuperscript{SII} were reviewed during the WHO prequalification process; the product was well tolerated and has a comparable safety profile to the other prequalified PCVs\textsuperscript{2}.

- Despite 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 is acceptable.

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\textsuperscript{®}-0
Role of catch-up campaigns

- **Timing:** just before introducing PCV into routine programme (new introductions)
- **Value:** accelerate direct & indirect protection and hasten impact of PCV
- **Target:** children from 12–59 months
- **Doses:** one single dose or 2 PCV doses separated with at least 8 weeks
- **Considerations:**
  - Implementation synergies and budget efficiencies if timed right
  - Use operational support for long-term strengthening of routine programme
  - Resources used for catch-up diverted away from routine immunization or delay PCV introduction
  - Only moderate vaccine serotype carriage/disease in catch-up age cohort

https://cdn.who.int/media/docs/default-source/immunization/training/vaccine-specific/pneumo/pcv_catch-up_faq_final.pdf
Catch-up vaccination (after introduction)

- WHO recommends a catch-up schedule for delayed or interrupted vaccination (for all antigens in the schedule)

- Interrupted schedules should be resumed without repeating the previous dose.

- Catch-up vaccination can be done with a single dose of PCV for children ≥24 months

- Unvaccinated children aged 1–5 years who are at high risk for pneumococcal infection because of underlying medical conditions, such as HIV infection or sickle-cell disease, should receive at least 2 doses separated by at least 8 weeks.

- WHO does not currently have recommendations on the use of PCV in individuals over 5 years of age
WHO has published recommendations and operational guidance for catch-up vaccination.
Future updates to PCV recommendations

- The SAGE pneumococcal vaccines working group will be convened in 2023–24 to review evidence in the following areas:
  - **Schedule optimization in childhood** (2+1 versus 3+0, 1+1, 0+1)
  - **Multi-age cohort PCV campaigns** in response to outbreaks, in humanitarian settings or in areas where uptake is very low
  - Review of available data and timelines to licensure/prequalification for **newer PCV products (including higher valent)** with pediatric indication
  - Recommendations expected late 2024 or 2025
Rotavirus Policy recommendations (2021)

- WHO recommends rotavirus vaccines be **included in all national immunization programmes**
- All prequalified products are **oral rotavirus vaccines**
- **RotaTeq, Rotavac and ROTASIL** should be administered in a **3-dose schedule**, while a **2-dose schedule** should be used for **Rotarix**
- 1st dose: Administered as soon as possible after 6 weeks of age with a minimum of 4 weeks between doses
- Rotavirus vaccinations may be administered simultaneously with other vaccines of the childhood immunization programme
WHO position – catch-up vaccination

- If a child <24 months of age misses a rotavirus dose or series for any reason, WHO recommends rotavirus vaccination for that child.

- Interrupted schedules should be resumed without repeating the previous dose. Because of the typical age distribution of RVGE, rotavirus vaccination of children >24 months of age is not recommended.

- This WHO-recommended upper age limit for rotavirus vaccination is higher than the age restrictions indicated by manufacturers and thus constitutes an off-label recommendation for these products.

- The need for rotavirus vaccination for children with missed, delayed or interrupted routine immunization is particularly important after significant disruptions to immunization programmes and in high-mortality or crisis contexts.

[Link to WHO website for more information](www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization/implementation/catch-up-vaccination)
Global rotavirus vaccine introduction status to the national immunization programme

- **Introduced (116 countries)**
- **Partially introduced (2 countries)**
- **Not introduced or data not available (76 countries)**
- **Not applicable**
Coverage estimates, rotavirus vaccine last dose, 2021

The map shows the coverage estimates for the last dose of the rotavirus vaccine in 2021, with different colors representing various coverage ranges. The map is sourced from WHO/UNICEF estimates as of July 2022.
Global rotavirus vaccine introduction status & product choice

- ROTARIX (71 countries)
- RotaTeq (15 countries)
- ROTARIX & RotaTeq (9 countries)
- ROTAVAC (10 countries)
- ROTASIL (5 countries)
- ROTAVAC & ROTASIL (1 countries)
- Not available (83 countries)
- Not applicable
### Rotavirus vaccine introduction/switch decision-making

Six key aspects of the immunization programme should be assessed to weigh the potential benefits and trade-offs of each introduction or switch option.

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<td>• Country-specific evidence (where available)</td>
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Adapted from: WHO’s Principles and considerations for adding a vaccine to a national immunization programme (2014)
Key questions for rotavirus introduction or switch decision-making

Considerations for NITAG/ICC recommendation:

1. Which vaccine presentation to use (many options available)?

2. Are there opportunities for integration with other antigens for introduction in routine immunization, as well as with other health programmes (child health, WASH)?
   - In routine, whether to launch rotavirus vaccine in routine together with vaccination against PCV (dose schedule identical in most cases, high potential for impact)
   - If introducing PCV and rotavirus vaccine together, which rotavirus vaccine presentations are preferred
WHO prequalified oral rotavirus vaccine products*

<table>
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<tr>
<th>Characteristics</th>
<th>Rotarix™ (GlaxoSmithKline)</th>
<th>Rotateq™ (Merck)</th>
<th>Rotavac™ (Bharat Biotech International)</th>
<th>Rotasiil™ (Serum Institute of India Pvt Ltd)</th>
</tr>
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<tr>
<td><strong>Efficacy for severe rotavirus gastroenteritis by child mortality rate stratum of country of study site (at 2 years follow-up</strong>)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Mortality</td>
<td>90% (95% CI, 86-93%)</td>
<td>94% (95% CI, 61-99%)</td>
<td>No data available</td>
<td>No data available</td>
</tr>
<tr>
<td>Medium Mortality</td>
<td>78% (95% CI, 70-83%)</td>
<td>81% (95% CI, 66-89%)</td>
<td>No data available</td>
<td>No data available</td>
</tr>
<tr>
<td>High Mortality</td>
<td>54% (95% CI, 9-77%)</td>
<td>44% (95% CI, 23-59%)</td>
<td>54% (95% CI, 40-65%)</td>
<td>44% (95% CI, 26-58%)</td>
</tr>
<tr>
<td>Study sites</td>
<td>Multiple countries at different income and mortality levels.</td>
<td>3 sites in India</td>
<td>6 sites in India; 1 center, multiple sites in Niger</td>
<td></td>
</tr>
<tr>
<td><strong>Date of WHO prequalification</strong></td>
<td>March 2009</td>
<td>October 2008</td>
<td>January 2018</td>
<td>September 2018</td>
</tr>
<tr>
<td><strong>Recommended number of doses</strong></td>
<td>2 doses</td>
<td>3 doses</td>
<td>3 doses</td>
<td>3 doses</td>
</tr>
</tbody>
</table>

Current evidence indicates local data on circulating rotavirus strains should NOT drive product choice as all WHO prequalified rotavirus vaccines provide protection against heterologous strains.

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** One year follow-up efficacy estimates for severe rotavirus gastroenteritis diarrhoea were reported in the 2020 Cochrane review and are similar to those for 2 year follow-up.
1. Systematic review and meta-analysis of the safety, effectiveness and efficacy of childhood schedules using Rotavirus Vaccines – Cochrane Response. October 2020 SAGE Meeting, Rotavirus Vaccines – Session 6. Background documents. [https://www.who.int/publications/m/item/review-meta-analysis-rotavirus-vaccines](https://www.who.int/publications/m/item/review-meta-analysis-rotavirus-vaccines)
Safety considerations

- All WHO prequalified rotavirus vaccines are **safe** and **effective**
- In the past, the first rotavirus vaccine (Rotashield™) caused intussusception (IS), a serious but very rare bowel obstruction
- With the new rotavirus vaccines, there seems to be a very small increased risk of IS in infants following rotavirus vaccination, mainly in the first 1–7 days following the first dose of rotavirus vaccine
- The risk of IS after rotavirus vaccination is much lower than the risk of severe rotavirus disease in unvaccinated children
- Data continue to be monitored globally. **Lack of IS surveillance in a country should not be an impediment to rotavirus vaccine introduction.**

Report of the WHO Global Advisory Committee on Vaccine Safety, 6–7 December 2017
http://apps.who.int/iris/bitstream/handle/10665/259874/WER9303.pdf?sequence=1
Comprehensive package of interventions for preventing and treating pneumonia and diarrhoea

Vitamin A supplementation

Vaccination: rotavirus

Safe water & improved sanitation

Los-osmolarity ORS, zinc & continued feeding

Protect
Breastfeeding promotion & support

Adequate complementary feeding

Prevent
Measles Vaccination

Handwashing with soap

Prevention of HIV

Treat
Improved care seeking behaviour and referral

Improved case management at community and health facility levels

Continued feeding

Pneumonia

Vaccination (PCV, Hib, pertussis)

Reduced household air pollution

Antibiotics for pneumonia

Oxygen therapy (where indicated)

Source: End preventable deaths: Global Action Plan for Prevention and Control of Pneumonia and Diarrhoea
Consider simultaneous introductions

Countries are encouraged to assess opportunities that may leverage implementation synergies and budget efficiencies (see examples)

Sufficient time is required to analyse the different introduction/switch implications, including:

- NITAG recommendation
- Financial analysis
- Cold-chain analysis
- Programmatic analysis
- Time, capacity and resources to combine training of health workers
Cost considerations for new vaccine introductions

Incremental costs:
Used for fiscal impact analysis and for cost effectiveness analysis to compare different vaccines

- New vaccine and AD syringes
- Expansion of cold chain
- Social mobilization and training for new vaccine
- Revision of EPI forms, vaccination cards & other forms

Shared costs:
- Added time spent by multi-purpose health personnel
- Additional vehicles, transport costs

Full (total) cost of programme with new vaccine:
Used for cost-effectiveness analyses to compare with full costs of another (non-vaccine) intervention

Existing immunization programme costs:

Immunization programme-specific costs:
- Vaccines and injection supplies
- Time spent by immunization-only personnel
- Cold chain equipment
- Vehicles used 100% for immunization
- Social mobilization and training
- Surveillance for vaccine-preventable diseases

Shared costs:
- Health facilities (buildings, utilities)
- Equipment
- Vehicles
- Transportation costs
- Time of multi-purpose health personnel spent on immunization

Source: Principles and considerations for adding a vaccine to a national immunization program: from decision to implementation and monitoring
https://apps.who.int/iris/bitstream/handle/10665/111548/9789241506892_eng.pdf
For additional PCV and rotavirus vaccine questions, please contact:

Laura Nic Lochlainn, niclochlainnl@who.int
Jenny Walldorf, walldorfj@who.int
Alejandro Ramirez Gonzalez, ramirezgonzaleza@who.int
**PCV resources**

- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. [https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf?ua=1](https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf?ua=1)

- WHO Considerations for pneumococcal conjugate vaccine (PCV) product choice: [https://apps.who.int/iris/handle/10665/344915](https://apps.who.int/iris/handle/10665/344915)


Rotavirus vaccine resources

- Rotavirus vaccines: WHO position paper – July 2021
  https://www.who.int/publications/i/item/WHO-WER9628

- Summary of key characteristics of WHO prequalified rotavirus vaccines (under revision):
  https://apps.who.int/iris/rest/bitstreams/1366824/retrieve

- WHO rotavirus training materials: https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/rotavirus

- PATH rotavirus vaccine cost calculator: https://www.path.org/resources/rotavirus-vaccine-cost-calculator/


**General vaccine decision-making resources**

- WHO Principles and considerations for adding a vaccine to a national immunization programme: [https://www.who.int/iris/bitstream/10665/111548/1/9789241506892_eng.pdf?ua=1](https://www.who.int/iris/bitstream/10665/111548/1/9789241506892_eng.pdf?ua=1)

- WHO prequalified vaccines list: [https://extranet.who.int/pqweb/vaccines/list-prequalified-vaccines?nav=2&AspxAutoDetectCookieSupport=1](https://extranet.who.int/pqweb/vaccines/list-prequalified-vaccines?nav=2&AspxAutoDetectCookieSupport=1)

- Table 3: WHO recommendations for routine immunization [https://www.who.int/publications/m/item/table-3-who-recommendations-for-routine-immunization](https://www.who.int/publications/m/item/table-3-who-recommendations-for-routine-immunization)

- WHO: Leave no one behind: guidance for planning and implementing catch-up vaccination [https://www.who.int/publications/i/item/9789240016514](https://www.who.int/publications/i/item/9789240016514)


- WHO immunization training materials: [https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization/training/general](https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization/training/general)
