Frequently asked questions and considerations for the introduction of hexavalent vaccine DTwP-HepB-Hib-IPV in routine immunization programmes

June 2024

This document is targeted primarily to countries currently using pentavalent and inactivated polio vaccine (IPV) schedules. This information is also applicable to countries planning to switch from acellular pertussis combination vaccines to the newly prequalified DTwP-HepB-Hib-IPV hexavalent vaccine

Frequently asked questions (FAQs)

Background

In March 2024, WHO prequalified a new hexavalent combination vaccine (DTwP-HepB-Hib-IPV). The vaccine, which contains whole-cell pertussis (wP) and inactivated polio antigen (IPV) components, has been developed to allow immunization programs that use whole-cell pertussis pentavalent, to reduce the number of injections in their schedule and to strengthen protection against poliomyelitis. DTwP-HepB-Hib-IPV vaccine is available from UNICEF Supply Division and Gavi offers grants to eligible countries to facilitate its introduction. Gavi eligible countries can now apply for support to introduce this vaccine.

Since 2020, the World Health Organization, through its Strategic Advisory Group of Experts of Immunization (SAGE), recommends that all countries administer at least two doses of IPV-containing vaccine in the routine schedule in addition to oral polio vaccine (OPV) vaccination. Eradication of polio virus depends on the cessation of OPV vaccination worldwide. In preparation for global OPV cessation, it is critical that countries boost IPV induced immunity. The WHO pre-qualification and availability of the new hexavalent vaccine is an opportunity to achieve the WHO recommended schedule for IPV, while strengthening the polio vaccination platform with the inclusion of 3 or 4 contacts with IPV but reducing, overall, the number of injections children are given.

1. What is the new hexavalent vaccine prequalified by WHO?

Hexavalent vaccine is a liquid, ready to use, combination vaccine that contains 6 antigens, providing protection against diphtheria, tetanus, pertussis, *haemophilus influenzae* type B, hepatitis B and polio. Hexavalent vaccines currently in the market can be manufactured either with the whole-cell pertussis (wP) or the acellular pertussis (aP) antigen.

The hexavalent vaccine prequalified by WHO on 21st March 2024 is a whole-cell pertussis-containing combination vaccine[1].

Combination vaccines are used extensively in routine immunization programs (i.e. pentavalent, measles and rubella) and are a very safe and effective way to provide recommended vaccines with fewer injections.

2. Main product characteristics of the prequalified DTwP-HepB-Hib-IPV vaccine (cold chain volume, presentation, route of administration…)[1]

	Route of administration	Shelf-life	Storage temperature	Cold chain volume per dose	Preservative	Multidose vial policy applicable
1-dose vial *	Intramuscular	24 months	2-8 °C	14.06 cm^3	2-phenoxyethanol	NA (single dose)
10-dose vial	Intramuscular	24 months	2-8 °C	2.11 cm^3	2-phenoxyethanol	Yes

**** 1 dose presentation is not available through Gavi support; available for Middle Income countries***

3. What is the difference between the current pentavalent vaccine (DTwP-HepB-Hib) used and the new hexavalent vaccine (DTwP-HepB-Hib-IPV)?

The difference between the current pentavalent and the new hexavalent vaccine is the addition of a sixth antigen in the hexavalent vaccine. The new antigen included is the inactivated polio (IPV), which provides protection against all three types of polio virus.

Many countries provide IPV as a stand-alone vaccine, as IPV1 and IPV2 vaccinations: these countries will now be able to continue vaccination against the five-antigens included in the pentavalent with the addition of IPV, therefore decreasing the number of injections overall, but increasing the number of injectable doses given against polio.

4. What is the difference between the new hexavalent vaccine (DTwP-HepB-Hib-IPV) and other hexavalent vaccines already on the market?

The new hexavalent vaccine contains whole-cell pertussis (wP) antigen, while the others contain the acellular pertussis (aP) antigen.

The wP vaccines were introduced widely in industrialized countries in mid-20th century and included in the EPI since 1974. While most high-income countries have replaced wP with aP vaccines, most developing countries use the wP vaccines as they are the vaccines procured by UNICEF Supply Division, in line with the WHO recommendation on maintaining wP vaccination in countries currently doing so[2].

[1] https://extranet.who.int/prequal/vaccines/p/hexasiil-0
[2] https://www.who.int/publications/i/item/WHO-WER9035

5. Basic safety information

Diphtheria, tetanus and pertussis combination vaccines (DTP) have been in use since the 1940s. Most recently, this DTP combination has been used as the basis for the development of combination vaccines containing additional vaccine antigens such as hepatitis B and *Haemophilus influenzae* type b, resulting in pentavalent vaccine, or with the additional IPV, resulting in hexavalent vaccine.

None of these combination vaccines has produced any adverse events that had not been observed with the individual components and currently used combination vaccines have excellent safety records.

As for any new vaccine introduction, it is important that countries are able to adequately monitor its safety, including detecting and investigating possible reactions or adverse events following immunization (AEFI).

6. What is the current WHO recommendation for polio vaccination?

WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale vaccination programmes. They summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccines worldwide.

In the WHO Position Paper of June 2022, WHO recommends that all children worldwide should be fully vaccinated against polio, and every country should seek to achieve and maintain high levels of coverage with any of the vaccines in use in their immunization programmes in support of the global commitment to eradicate polio. Different schedules and vaccine products are recommended and used in different countries or regions.

Vaccination with bOPV and IPV

For all countries using OPV in their national immunization programme, WHO recommends 3 doses of bOPV and 2 doses of IPV as the vaccination schedule. In polio endemic countries and in countries at high risk of polio virus importation, WHO recommends a bOPV dose at birth, followed by the 3 bOPV primary doses and 2 IPV doses.

Sequential IPV-bOPV schedule

Where a sequential IPV–bOPV schedule is used, the initial administration of 2 doses of IPV should be followed by ≥2 doses of bOPV.

IPV-only schedule

For IPV-only schedules, a primary 3-dose series of IPV administered beginning at 6 or 8 weeks of age, with a minimum 4-week interval between doses, is recommended. If the primary series begins at 6 weeks of age, a booster dose should be given 6 months or more after the third dose.

Alternatively, a 2-dose or fractional dose IPV schedule, starting at 14 weeks of age or older, with a second dose 4 months or more later can be considered.

7. Schedule options with hexavalent vaccine

There are several schedule options with hexavalent vaccine. The schedule recommendation for hexavalent consists of 3 primary doses, starting as early as 6 weeks of age, with a minimum interval of 4 weeks between doses.

Many countries are following a pentavalent schedule of 3 primary doses at 6, 10 and 14 weeks. In this case, the pentavalent vaccine can be substituted by the hexavalent vaccine at the same age.

However, for this schedule in which primary doses start at 6 weeks of age, a hexavalent booster dose is recommended at least 6 months after the third dose.

Countries that are currently following other pentavalent schedule options, can continue to maintain their schedules if they switch to hexavalent vaccine. Some schedules include, but are not limited to, primary doses given at 8, 12 and 16 weeks (equal to 2, 3 and 4 months of age) or, 8, 16 and 24 weeks (equal to 2, 4 and 6 months of age). In these cases, pentavalent vaccine can be substituted by the hexavalent vaccine at the same age.

8. Why is a booster needed if the hexavalent schedule starts at 6 weeks?

Immunogenicity against polio induced after IPV vaccination in infancy, increases with age of administration. For instance, a first dose administered at 8 weeks for the primary series generates greater immunogenicity when compared to a dose administered at 6 weeks of age.

Furthermore, available data suggests significant variability in immune response to IPV administered at an "early" primary series schedule of 6, 10 and 14 weeks, despite overall high seroconversion rates.

Finally, polio is a disease that requires long term protection in order to achieve and maintain eradication. To reduce any concerns about duration of immunity against polio by administering "early" IPV schedules, administering a booster at 12-24 months is recommended.

In summary, these three aspects (i.e. lower immunogenicity against polio of "early" schedules, variability in polio seroconversion rates of "early" schedules and need to assure long term protection against polio) constitute the rationale for recommending a booster of hexavalent at 12-24 months if the primary series of hexavalent begins at 6 weeks of age.

9. Is it necessary to continue bOPV vaccination if the national immunization programme introduces hexavalent vaccine?

In the current epidemiological context, WHO recommends that regions and countries are cautious about moving to IPV-only schedules. Only countries in polio-free regions with very low risk of importation and sustained high routine coverage of DTP3 above 90%, could consider moving to IPV-only schedules.

For most countries that are currently providing bOPV in their national schedules, there is a need to continue using bOPV, regardless of the IPV schedule followed. The administration of bOPV and IPV containing vaccines in immunization programs will help close the immunity gaps for poliovirus type 2 as well as boost immunity to types 1 and 3 polioviruses.

10. What are the benefits of switching to hexavalent if the national immunization programme already uses 2 doses of IPV in the schedule?

Countries which have achieved the WHO recommendation of providing 2 IPV doses in routine immunization have the choice of maintaining that schedule option or switching to hexavalent vaccine. Both options fulfill the vaccination recommendation for polio.

However, combination vaccines such as hexavalent, might bring additional value to immunization programs. While these benefits ultimately depend on each country's program characteristics, the main benefits that are commonly expected are:

- **Reduction in the number of injections needed**, by combining IPV into the already existing pentavalent
- **Potential cost savings** due to reduced operational/administration costs, such as less syringes and safety boxes, less cold chain requirement and transportation, among others
- **Additional opportunities and contacts to administer IPV doses**, thereby increasing the chances to achieve the necessary protection against polio
- **Opportunity to build or strengthen a booster program at second year of life (2YL) or beyond**

11. If a country is planning to introduce IPV2 in the 2024-25 period, should the country prioritize IPV stand-alone introduction over hexavalent introduction?

Yes. Countries which have already decided and/or have already initiated the process for an IPV2 introduction, should continue their plans to achieve introduction of IPV2 as soon as possible, to optimize protection against poliovirus. Countries can always decide at a later stage if switching to a hexavalent vaccine is appropriate.

Countries that have not yet planned the introduction of IPV2, are encouraged to do so as soon as possible, and should consider either IPV stand alone or hexavalent.

12. Which countries are eligible for Gavi support for hexavalent introduction?

Countries that are eligible for Gavi support based on their transition status, are available for support of hexavalent introduction. Please refer to question 14 for more details about the co-financing policy[3].

13. What are the additional recurrent costs for hexavalent vs. pentavalent and IPV?

A hexavalent schedule will be more expensive than pentavalent and IPV schedule. However, the actual additional cost of switching to hexavalent vaccine from pentavalent and IPV is complex and will depend on multiple factors. This includes the country's GAVI transition status, the schedule of hexavalent to be implemented (3 or 4 doses), the pentavalent and IPV presentations currently in use and the existence of a DTP-containing booster already in the programme. The country could also benefit from saved ancillary costs (syringes, safety boxes, transportation, cold chain) by switching to hexavalent.

The table below provides an indication of the UNICEF negotiated prices of hexavalent, pentavalent and IPV in 2024 and 2025.

This information is available on the UNICEF product menu for Gavi-supported vaccines (https://www.unicef.org/supply/documents/gavi-product-menu) and in Gavi's Detailed Product Profiles (English version: https://www.gavi.org/news/document-library/detailed-product-profiles; French version: https://www.gavi.org/fr/actualites/librarie-de-documents/profils-produit-detailles)

[3] https://www.gavi.org/types-support/sustainability/eligibility

	Weighted average price per dose	
	2024	2025
IPV 1-dose/vial, liquid	$2.80	$2.80
IPV 5-dose/vial, liquid	$1.42	$1.41
IPV 10-dose/vial, liquid*	$2.51	$2.13
Penta 1-dose/vial, liquid	$1.24	$1.21
Penta 10-dose/vial, liquid	$0.83	$0.83
Hexa 1-dose/vial, liquid**	$4.90	$4.50
Hexa 10-dose/vial, liquid**	$3.00	$3.00
Hexa 10-dose/vial, liquid***	$2.85	$2.85

(*): Middle Income Countries should reach out directly to UNICEF Supply Division to confirm prices applicable based on suppliers' offers.
(**): Prices applicable for Middle Income Countries and Gavi Countries not Eligible for hexavalent Support. Special terms apply.
(***): Prices applicable for Gavi Eligible Countries for hexavalent Support only. Special terms apply.
Source: Product-Menu-All-Vaccines-May-2024.pdf (unicef.org)

If one of the Gavi 74 countries is interested in hexavalent, the country is encouraged to reach out to Gavi Alliance partners to support with a hexavalent introduction assessment.

14. Which co-financing policy will apply to hexavalent for Gavi countries?

First doses of hexavalent vaccine will be available starting in Q4 2024, at a price of $2.85 per dose for Gavi eligible countries, and $3.00 per dose for fully self-financing countries. Note that this hexavalent vaccine cost is for a 10-dose presentation. Countries will need to co-finance hexavalent vaccine as shown in the table below but will continue to benefit from the IPV co-financing exemptions.

	Initial Self-Financing (ISF)	Preparatory Transition (PT)	Accelerated Transition (AT)	Fully Self-Financing (FSF)
3 x Penta	3 doses x $0.20/dose	Co-financed percentage of [3 doses x Penta]		100% [3 doses x Penta]
2 x IPV	$0.00	$0.00 → $0.60/child [a]		
1 x DTP Booster	Vaccine Funding Guidelines forthcoming			
4 x Hexa	4 doses x $0.20/dose	Co-financed percentage of [4 doses x Hexa at $2.85/dose minus the value of IPV funded by Gavi]		100% [4 doses x Hexa at $3.00/dose minus the value of IPV funded by Gavi]

[a]: Based on the IPV co-financing policy approved by the Board in June 2019 and December 2022, PT, AT, and FSF countries will have to co-finance a share of IPV equivalent to US$ 0.60/child post-bOPV cessation, which is not expected before 2027

15. What support is available for countries in planning and programme implementation?

Countries eligible for Gavi support can apply to switch to a hexavalent vaccine, or they can choose to continue using pentavalent and IPV. If Gavi eligible countries decide to switch to hexavalent, they can apply for operational support to introduce the hexavalent vaccine. Countries can also request technical assistance to assess feasibility and capacity – and for navigating the planning, application, and implementation processes.

Middle Income Countries (MICs) can request technical assistance from Alliance Partners to assess feasibility and capacity – and for navigating the planning, application, and implementation processes.

16. What are the next steps if a country decides to move ahead with hexavalent introduction?

With the guidance of in-country Alliance Partners and appropriate programmatic feasibility analysis, MICs can request information and procure directly through UNICEF SD whereas countries eligible for Gavi support can follow the normal Gavi application process. For the year 2024, the following deadlines for application submission have been set:

Deadline for submission	IRC meeting (indicative dates)
18 April	3-14 June
15 July	16-20 September
23 September	4-15 November

17. When are the first hexavalent doses expected to be available?

Hexavalent vaccine has received the WHO PQ at the end of March 2024. Supplier delivery lead time is 60 days following receipt of purchase order from UNICEF.

However, countries should note that the first purchase order placed by UNICEF, regardless of the country of destination, will require 120 days lead time.