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Hexavalent vaccines indicators

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Burden & epidemiology

Number of new cases per year (last 3-5 years)

NOT RELEVANT FOR CURRENT DECISIONS - PLEASE CONSULT THE RELEVANT WHO POSITION PAPERS. 1, 2, 3, 4, 5, 6, 7, 8 For disease burden for relevant diseases (at least D,T,P) countries can consult the WHO JRF data for their country, or subregion per WHO JRF. 9

Proportion of the population affected by the disease or infected with the antigen

NOT RELEVANT FOR CURRENT DECISIONS - PLEASE CONSULT THE RELEVANT WHO POSITION PAPERS. 1, 2, 3, 4, 5, 6 For disease burden for relevant diseases (at least D,T,P) countries can consult the WHO JRF data for their country, or subregion per WHO JRF. 10

Serogroup or serotype distribution (for serogroup- or serotype-specific vaccines)

NOT RELEVANT FOR CURRENT DECISIONS - PLEASE CONSULT THE RELEVANT WHO POSITION PAPERS 1, 2, 3, 4, 5, 6, 7, 8

Number of deaths from the disease per year

NOT RELEVANT FOR CURRENT DECISIONS - PLEASE CONSULT THE RELEVANT WHO POSITION PAPERS 1, 2, 3, 4, 5, 6

Case Fatality ratio (number of deaths / number of new cases, in %)

NOT RELEVANT FOR CURRENT DECISIONS - PLEASE CONSULT THE RELEVANT WHO POSITION PAPERS

Outbreak, epidemic or pandemic risk

Diphtheria, though largely controlled in many regions thanks to vaccination, outbreaks are still reported today, especially in populations with low immunization coverage, high mobility, or poor living conditions. 11 Diphtheria outbreaks have been reported in various settings, including refugee camps in Asia, and among asylum seekers in Europe. 12, 13

Tetanus is generally rare in areas with high vaccination coverage, and since it is acquired from environmental sources, it does pose a risk for outbreaks. 14

Pertussis has a well-documented history of causing outbreaks, even in populations with high vaccination coverage. Recent trends show that pertussis continues to have significant outbreak

potential worldwide, affecting both children and adults, and posing particular risks to infants. [15], [16]

Hepatitis B has significant potential for outbreaks, especially in settings with poor infection control or low vaccination coverage. Outbreaks of hepatitis B have been documented in both healthcare and community settings, and the virus remains a persistent public health threat in many regions. [17], [18]

Prior to widespread vaccination, small outbreaks or clusters of cases of Hib disease have been noted in day-care centres and there were reports of nosocomial transmission in hospitals. The risk of Hib disease was also higher in larger families. [19]

The risk of poliovirus outbreaks and localised epidemics remains significant in areas with low vaccination coverage, fragile health systems, or gaps in immunization campaigns, particularly in regions experiencing conflict or displacement. Wild poliovirus (WPV) is endemic to Afghanistan and Pakistan, while vaccine-derived poliovirus (cVDPV) outbreaks have been reported in 20 countries in 2024. There is a rising risk of outbreaks of cVDPV2 since the global switch to bivalent oral poliovirus vaccine (bOPV). Although the global pandemic potential is low due to widespread immunity and effective vaccines, lapses in immunization and surveillance have led to the detection of poliovirus in environmental samples in previously polio-free countries. [6], [7], [8], [20]

Contribution of the vaccine to achievement of the national, regional or global disease goals

There are no established global elimination goals for Diphtheria or Pertussis (some countries have defined control goals for Diphtheria)

The Maternal and Neonatal Tetanus Elimination (MNTE) initiative, launched by the World Health Organization (WHO) in 1989, initially aimed to eliminate neonatal tetanus by 1995. As of June 2024, 47 out of 59 priority countries have achieved MNTE status, significantly reducing neonatal tetanus cases by 89% and deaths by 84% since 2000. Vaccination is the cornerstone of the strategy. Immunizing women of reproductive age with tetanus toxoid-containing vaccines (TTCVs) has been the primary driver of this reduction. [21], [22]

There is a clear and internationally recognized goal to eliminate hepatitis B as a public health threat. The World Health Organization (WHO) has set a target to achieve hepatitis B elimination by 2030, aiming for a 90% reduction in new infections and a 65% reduction in deaths.

Vaccination is the single most important tool in the global effort to eliminate Hepatitis B. Widespread and timely hepatitis B vaccination, especially starting at birth, dramatically reduces new infections, chronic disease, and deaths from liver complications. The prevalence of hepatitis B surface antigen (HBsAg) in children under 5 dropped from 4.7% before vaccination to 1.3% by 2015, thanks to universal vaccination programs in 189 countries. 23, 24, 25

While no formal global Hib elimination goal is set by WHO, elimination of invasive Hib disease is considered biologically and programmatically possible, and has been achieved in some countries through high vaccination coverage. After the introduction of Hib conjugate vaccines, countries like the US, UK, and Canada saw a reduction in Hib disease incidence by over 95%, with some regions achieving near elimination of invasive Hib disease in children under five years old. More than 90% of countries have included Hib vaccines in their national immunization programs, resulting in significant global decreases in Hib disease, though complete eradication has not yet been achieved. 26, 27

Polio vaccination has reduced poliomyelitis cases by over 99.9% globally since the launch of the Global Polio Eradication Initiative in 1988. Coordinated immunization campaigns have led to the certification of polio-free status in the Americas (1994), the Western Pacific (2000), Europe (2002), and Africa (2020). Globally, the vaccines (Polio mono and multivalent and IPV-containing combination vaccines) have brought the world closer to eradicating wild poliovirus, which is now confined to Afghanistan and Pakistan. In addition, they play a critical role in controlling outbreaks of vaccine-derived poliovirus (cVDPV). 28, 29, 30, 31, 32

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Benefits of the intervention

Serogroup or serotype coverage by vaccines considered (for serogroup- or serotype-specific vaccines)

Serogrouping is not a relevant concept for diphtheria, tetanus, pertussis, or hepatitis B in the context of vaccine coverage

There are 6 serotypes of Haemophilus influenzae (a to f) of which type b was the commonest

cause of severe disease in children. Disease due to other serotypes and non-typeable Haemophilus influenzae can cause disease. 33, 34, 35, 36, 5

Poliovirus exists in three distinct serotypes: types 1, 2, and 3. Immunity to one serotype does not confer protection against the others, necessitating vaccines that target all three (trivalent vaccine). All the available Hexavalent vaccines contains all the three Polio serotypes. 6, 37

Efficacy and effectiveness estimates (e.g. against infection, disease, hospitalization, death), including in different populations

Clinical studies consistently show that hexavalent vaccines are highly effective in generating protective immune responses against all six targeted diseases35, 38, 39, 40, 41, 42, 43, 44, 45 :

- Diphtheria - Nearly all children achieve seroprotective antibody levels after vaccination and booster doses with non-inferior protection compared to monovalent or pentavalent vaccines. 39
- Tetanus - 100% seroprotection rates reported post-booster; strong and persistent antibody responses with no evidence of reduced efficacy compared to monovalent or other combination vaccines. 39
- Pertussis - High seroconversion rates (94–95% for Bordetella pertussis, 77–87% for pertussis toxin). Head-to-head studies and clinical trials confirm that the immune response to pertussis antigens in hexavalent vaccines is non-inferior to that of other licensed combination vaccines, including pentavalent and monovalent formulations. Some differences in antibody levels (e.g., anti-pertussis toxin, anti-pertactin) exist, but these have not shown clear clinical relevance. Hexavalent vaccines may contain either whole cell pertussis (wP) or acellular pertussis (aP) antigens, which influence immunogenicity and reactogenicity profiles, with aP generally associated with lower reactogenicity. 45
- Hepatitis B - >99% seroprotection post-booster with no significant reduction compared to the monovalent vaccine. 42
- Hib - 96–100% achieve protective antibody levels post-primary and booster doses. There is some evidence that Hib conjugate vaccine in combination with acellular pertussis (DTaP-Hib) induces a lower antibody response than Hib conjugate in combination with whole cell pertussis (DTwP-Hib) or separately administered DTaP and Hib conjugate vaccines. 44
- Poliomyelitis - 98–100% seroprotection for all three poliovirus types post-booster. Non inferiority (as measures by antibody titers) has been demonstrated for wP containing Hexavalent and IPV/OPV. 40, 41, 43

Duration of protection and waning of immunity in general and risk groups

The duration of protection varies by disease component, but evidence shows that these vaccines provide strong initial immunity and long-lasting immune memory, especially when booster doses are included . 1, 2, 3, 4, 5, 6, 46, 47, 48, 49, 50, 51, 52, 53 .

Diphtheria - Data on the duration of seroprotection from 2 large representative population studies from the Netherlands, using a complete 3-dose primary series plus 3-dose booster series prior to adolescence, indicate that this schedule results in very high seroprevalence above the threshold for basic protection (≥0.01 IU/mL) up to 39 years of age and potentially longer. 1, 48, 51

Tetanus - Data from serological studies suggest that a primary series of 3 TTCV doses in infancy plus a booster during the second year of life will provide 3–5 years of protection. A further booster dose (e.g. in early childhood) provides protection into adolescence, and another booster during adolescence induces immunity that lasts through much of adulthood, providing protection to women of reproductive age. 2, 47, 51

Pertussis - Whereas little is known about the duration of protection following pertussis vaccination in LMICs countries, several studies in HICs show that protection wanes after 4-12 years. 3, 46

Hepatitis B - In a study in Alaska, USA, a 3-dose vaccination schedule prevented all clinically appparent and chronic HepB infection for at least 30 years. 4, 49, 50, 52

Hib - Although there is some evidence of a decrease over time in the proportion of Hib vaccine recipients with antibody levels higher than the set thresholds, there is only limited evidence to suggest that this decline is associated with an increase in clinical disease. 5, 51

Poliomyelitis - The exact duration of immunity following a complete IPV series is not fully determined; however, it is believed to confer protection for many years. 6

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Safety of the intervention

Type, including severity, consequences and frequency of short- and long-term adverse events following vaccination

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.

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. 6, 28, 54

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Values and preferences

Perception of the target population on the risk of disease

Perception of the risk of diptheria, tetatnus, pertussis, hepatitis B, Hib and poliomyelitis among target populations varies significantly depending on local disease prevalence, cultural beliefs and awareness levels. 55, 56, 57, 58, 59, 60, 61, 62

For diphtheria, studies report that factual knowledge of the disease is generally low, yet the risk is often perceived as high during outbreaks or in regions with recent cases. In many high-income countries, diphtheria is considered a rare threat, leading to decreased awareness and sometimes

lower perceived urgency to vaccinate. [56]

Perception of the risk of tetanus tends to be higher than diphtheria due to its high case-fatality and association with wounds and childbirth, especially neonatal tetanus in low-resource settings. [56, 57]

Parents of young infants and healthcare workers usually recognize pertussis as a serious illness, given its potential severity in infants. For instance, in Georgia 81% of women believed pertussis, would be serious during pregnancy while 92% believed pertussis would be serious to their infants. [58]

For hepatitis B, awareness and perceived risk vary greatly by region. In a study among pregnant women in Uganda, perceived risk was low. [59]

Haemophilus influenzae type b (Hib) disease is often under-recognized by the public, particularly in regions where widespread vaccination has nearly eliminated severe cases like meningitis and pneumonia. [57]

In regions where polio remains endemic, such as Afghanistan and Pakistan, the public is often more aware of the disease's dangers due to its ongoing presence. However, challenges like misinformation, cultural resistance, and distrust in vaccination programs can undermine risk perception, even in high-risk areas. Conversely, in polio-free regions, the perceived risk of polio is generally low, as the disease is no longer part of the collective memory. This complacency can lead to gaps in vaccination coverage, as seen in recent outbreaks of vaccine-derived poliovirus (cVDPV) in previously polio-free countries such as the United Kingdom and Israel. [55, 60, 61]

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Acceptability to stakeholders

Acceptability of the vaccine and of vaccination against the disease

The acceptability of child combination vaccination including DTP, HepB, Hib and polio vaccination varies globally, influenced by factors such as cultural beliefs, misinformation, relationships between parents and healthcare professionals, and perceived disease risk.

In South Africa and Timor-Leste, general acceptance of immunization was observed, but with limited disease-specific knowledge. DTP vaccine acceptance was high among parents in France (85%) and India (98%).
Pertussis vaccine acceptance in countries such as the United Kingdom, Italy, Ireland, Australia, West Germany and Russia has been influenced by adverse events and to lesser extent the low effectiveness of selected wP vaccines.

In polio endemic regions, vaccine resistance has been linked to misconceptions about vaccine safety and cultural opposition, despite awareness of the disease's severity. Conversely, in polio-free countries, vaccine acceptability is generally high, though complacency has led to gaps in coverage, as evidenced by recent vaccine-derived poliovirus (cVDPV) outbreaks in the United Kingdom and Israel. Addressing these challenges, global initiatives led by WHO, UNICEF, and the Global Polio Eradication Initiative (GPEI) have prioritized public education and community engagement to sustain vaccination acceptance and achieve eradication goals. 60, 63, 64, 65, 66

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Financing & funding

Estimated financial cost of materials per vaccine dose (syringes, needles, safety box) (in USD)

Cost of syringes: UNICEF procurement 0.028$ to 0.065$ depending on supplier and product / PAHO RF procurement 0.028$ to 0.048$ depending on supplier and product. [67]

Cost of safety boxes: UNICEF procurement, a box of 25 safety boxes (each with a 5-liter capacity) is about $20.26, resulting in approximately $0.81 per safety box. Each 5-liter safety box can hold around 100 syringes, leading to a disposal cost of approximately $0.008 per syringe. [68, 69]

Estimated vaccine financial cost per dose (in USD)

In Gavi-supported countries, Serum Institute of India (SII) has offered a price of $2.85 per dose in the 10 dose presentation for hexavalent vaccines (wP). [70]
For fully self-financing countries and those eligible under Gavi's Middle-Income Countries (MICs) Approach, the cost of SII's hexavalent vaccine is $3.00 per dose. [71]
For fully self-financing MICS, the cost of hexavalent vaccines (aP containing) is on average $28.8 per dose. [72]

The UNICEF price for the pentavalent vaccine is $0.85-$1.26 per dose for Gavi supported-countries depending on supplier and presentation . [73]
The PAHO price is $1.18 per dose (wP) and ranges between $18.33 and $21.54 for vaccines with aP depending on supplier and presentation. [74]
For fully self-financing MICS, the cost is $1.25-$2.29 per dose (DTwP-HepB-Hib). [72]

UNICEF prices for the IPV vaccine for countries assessing Gavi prices range between $1.25 and $2.8 depending on supplier and presentation. [75]
UNICEF price for self-procuring MICs is €3.1 per dose. [75]
The PAHO price ranges between $1.25 and $5.5 per dose. [74]
For fully self-financing MICS, the cost ranges from $2.23 to $10.66 per dose. [72]

Estimated financial cost per person vaccinated (in USD)

In European countries with vaccine procurement through public tenders the price per child vaccinated with standard vaccines ranged from €59 to €117 when using pentavalent and from €98 to €220 when using hexavalent vaccines, both with aP. [76]
A 2022 a study focused on Peru estimated the total cost of fully vaccinating a child with the hexavalent vaccine (DTaP-HB-Hib-IPV) at $126.42, compared to $116.27 under the existing schedule using the current scheme (DTwP-HB-Hib + IPV + OPV). [77]

Cost-effectiveness ratio

While hexavalent vaccines may have higher upfront costs, they can help reduce adverse events, logistical challenges, and overall societal burdens, offering potential economic and practical benefits for immunization programs, as demonstrated by studies from countries including Peru (wP pentavalent compared to aP hexavalent), Argentina (wP pentavalent compared to aP hexavalent), Colombia (aP compared to wP hexavalent vaccines), and South Korea (DTaP-IPV-Hib-HepB compared to DTaP-IPV/Hib). [78], [79], [80], [81], [82], [83], [84]

Is there a Gavi programme to support the introduction of this vaccine? If a Gavi programme is available, what support is available to countries?

In December 2023, Gavi opened a funding window for eligible countries to switch from pentavalent to hexavalent vaccine, including assistance in assessing financial, logistical, and programmatic implications to determine suitability for their specific contexts. Operational support is also available to facilitate the introduction of the hexavalent vaccine into national immunization programs. [85], [70]

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Market (feasibility)

Available vaccines, licensing status, prequalification status, presentation, formulation, dosage and route of administration

4 Hexavalent vaccines are available, 3 of which contains acellular pertussis and one whole-cell pertussis. Three of those vaccines come in a fully liquid ready for use formulation, one has the Hib component lyophilised and requires reconstitution. Vial and prefilled syringe presentations are available. Only 2 of those vaccines are WHO prequalified (one of the aP-containing and the wP-containing). 86

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Service delivery (feasibility)

Number of doses and timing of administrations

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.
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. 87, 88 . For hexavalent vaccines, a 3-dose schedule is adequate when initiated at ≥6 weeks of age and with a minimum of 4 weeks interval between doses. 88

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Logistics (feasibility)

Cold chain volume required per vaccine dose (in cm3)

For those vaccines that have vial presentation (3 out of 4) the cold-chain space requirements varies between 2.11 and 11.32 cm3/vial 86

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