Pentavalent Vaccines (DTP-HepB-Hib)
The pentavalent vaccine combines diphtheria, tetanus, whole-cell pertussis, hepatitis B and *Haemophilus influenzae* type b (DTwP-HepB-Hib) vaccines to prevent all five diseases. Annually across the world, diphtheria accounts for an average of 2,500 deaths, pertussis for 89,000 deaths and tetanus for 72,600 deaths among children aged under five years. Hepatitis B (HepB) alone accounts for between 500,000 and 700,000 deaths per year, with most cases occurring in developing countries. Most cases of liver cancer across the world (60–80%) are also attributable to infection with the HepB virus. *Haemophilus influenzae* type b (Hib) accounts for 200,000 annual deaths, with a disease incidence of two to three million cases; the most serious cases occur in children aged six to 12 months. Historically, the trivalent diphtheria-tetanus-pertussis (DTP) vaccine was considered the cornerstone of the Expanded Programme on Immunization (EPI) that was started in 1974. HepB vaccines were first WHO prequalified in 1987, followed by Hib vaccines in 1998. DTP vaccines were first used in 1948, and then integrated with HepB and Hib to form a pentavalent vaccine. The first pentavalent vaccine was introduced in the late 1990s. Vaccine efficacy for the components of the pentavalent vaccine is 85–95% for Hib, 95% for HepB, 95.5% for diphtheria, 61–89% for pertussis, and 80–100% for tetanus. Studies evaluating the combined efficacy of the diphtheria-tetanus-whole-cell-pertussis (DTwP) vaccine found efficacy ranged from 46% to 92%. More than 170 countries worldwide, including all 73 Gavi-eligible countries, have introduced the pentavalent vaccine, including India, which independently is forecast to account for 20% of the global demand for pentavalent vaccine (28,000,000 doses) in 2014.

Perinatal infections account for 21% of the overall global HepB disease burden, the highest proportion of deaths from which occur in Asia and Africa. At present only 18 out of 56 Gavi-eligible countries offer the WHO-recommended HepB birth dose, and even among them coverage is poor. However, with support, there is evidence to suggest that coverage rates can reach ≥90%. This was exemplified by the partnership between Gavi and the Chinese government, whereby provision of a HepB birth dose free of charge to the public (through co-financing between Gavi and the government of China) catalysed a dramatic scale-up in coverage rates from around 40% in poorer counties to >90% in most parts of the country, with <1% of children overall being infected with HepB.

The WHO recommends that all infants receive their first dose of monovalent HepB vaccine within 24 hours of birth; such administration is 90% effective in halting vertical disease transmission.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age at 1st dose</th>
<th>Doses in primary series (interval between doses)</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTwP-HepB-Hib</td>
<td>6 weeks</td>
<td>3 doses (4 weeks between 1st and 2nd doses; and 2nd and 3rd dose)</td>
<td>• DTP booster at 1–6 years (preferably in 2nd year of life)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hib booster only where high disease burden exists, at 15–18 months</td>
</tr>
</tbody>
</table>

Perinatal infections account for 21% of the overall global HepB disease burden, the highest proportion of deaths from which occur in Asia and Africa. At present only 18 out of 56 Gavi-eligible countries offer the WHO-recommended HepB birth dose, and even among them coverage is poor. However, with support, there is evidence to suggest that coverage rates can reach ≥90%. This was exemplified by the partnership between Gavi and the Chinese government, whereby provision of a HepB birth dose free of charge to the public (through co-financing between Gavi and the government of China) catalysed a dramatic scale-up in coverage rates from around 40% in poorer counties to >90% in most parts of the country, with <1% of children overall being infected with HepB.

The WHO recommends that all infants receive their first dose of monovalent HepB vaccine within 24 hours of birth; such administration is 90% effective in halting vertical disease transmission.
<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>WHO PQ date</th>
<th>Form and presentation</th>
<th>Lowest known price (UNICEF, US$)</th>
<th>Vaccine vial monitor (VVM) type and cold chain volume (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinavaxem DTwP-HepB-Hib vaccine</td>
<td>Berna Biotech (Crucell)</td>
<td>Sep 2006</td>
<td>Liquid, 1-dose vial</td>
<td>2.40–2.60</td>
<td>VVM 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ml vial = 10.28 cm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 ml vial (Green Cross)* = 12.85 cm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 ml vial (Berna) = 13.14 cm³</td>
<td></td>
</tr>
<tr>
<td>DTwP-HepB-Hib vaccine</td>
<td>Biological E</td>
<td>Aug 2011</td>
<td>Liquid (DTP-HepB) + lyophilised (Hib), 1- and 10-dose vials</td>
<td>1.80 (10-dose vial)</td>
<td>VVM 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Box, 24 vials of 1-dose DTwP-HepB and 24 vials of 1-dose Hib = 29.36 cm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Box, 15 vials of 10-dose DTwP-HepB and 15 vials of 10-dose Hib = 7.8 cm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Additional 1-dose mono carton packaging presentation with one set of 2 vials DTwP-HepB-Hib = 34.7 cm³</td>
<td></td>
</tr>
<tr>
<td>DTwP-HepB-Hib vaccine</td>
<td>Biological E</td>
<td>May 2012</td>
<td>Fully liquid, 1- and 10-dose vials</td>
<td>1.19 (10-dose vial)</td>
<td>VVM 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.35 (1-dose vial)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Box, 24 vials of 10-dose = 2.9 cm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Box, 48 vials of 1-dose = 14.6 cm³</td>
<td></td>
</tr>
<tr>
<td>Euforva/Hib Inj DTwP-HepB-Hib vaccine</td>
<td>LG Life Sciences</td>
<td>Aug 2012</td>
<td>Liquid (DTP-HepB) + lyophilised (Hib), 1- and 2-dose vials</td>
<td>1.96 (2-dose vial)</td>
<td>VVM 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Box, 1 vial Hib + 1 vial DTwP-HepB = 41.33 cm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2-dose vials)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Box, 5 vials DTwP-HepB + 5 vials Hib = 14.15 cm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2-dose vials)</td>
<td></td>
</tr>
<tr>
<td>Tritanrix HB-Hib DTwP-HepB-Hib vaccine</td>
<td>GSK</td>
<td>May 2006</td>
<td>Liquid (DTP-HepB) + lyophilised (Hib), 1- and 2-dose vials</td>
<td>2.95 (2 dose)</td>
<td>VVM 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Packaging: N/A</td>
<td></td>
</tr>
<tr>
<td>Easyfive – TT DTwP-HepB-Hib vaccine</td>
<td>Panacea Biotec</td>
<td>Oct 2013</td>
<td>Fully liquid, 1- and 10-dose vials</td>
<td>2.96 (1 dose)</td>
<td>VVM 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.94 (10 dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carton, 800 vials = 18.05 cm³ (1-dose vials)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carton, 24x25 = 600 vials = 4.30 cm³ (10-dose vials)</td>
<td></td>
</tr>
<tr>
<td>DTwP-HepB-Hib vaccine</td>
<td>Serum Institute of India</td>
<td>Sep 2010</td>
<td>Fully liquid, 2-dose vial</td>
<td>N/A</td>
<td>VVM 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carton, 24x25 = 600 vials = 4.30 cm³</td>
<td></td>
</tr>
</tbody>
</table>

*Green Cross is a contracted manufacturer of Berna Biotech, responsible for filling the WHO prequalified Quinavaxem in vials of 3 ml occupying a cold chain volume of 12.85 cm³.
**DTwP-HepB-Hib vaccine**  
Serum Institute of India  
May 2010  
Liquid, 1- and 2-dose ampoule (DTwP-HepB) + lyophilised 1- and 2-dose vials (Hib)  
2.25 (2011 price)  
VVM 14  
Carton, 4x50 = 200 vials Hib + 4x50 = 200 ampoules DTwP-HepB = 39.2 cm³ (1-dose vial)  
Carton, 4x50 = 200 vials of Hib + 4x50 = 200 ampoules of DTwP-HepB = 19.6 cm³ (2-dose vial)

**DTwP-HepB-Hib vaccine**  
Serum Institute of India  
Sep 2010  
Fully liquid, 1- and 10-dose vials  
2.70 (1 dose)  
1.95 – 2.10 (10 dose)  
VVM 14  
Carton, 50 vials = 26.1 cm³ (1-dose vials)  
Carton, 50 vials = 2.6 cm³ (10-dose vials)

---

**Notes:**

- Shantha Biotechnics, a subsidiary of Sanofi Pasteur, previously had a WHO prequalified fully liquid, pentavalent vaccine – Shan5. Absent from the prequalified list for the past four years, having been withdrawn because of quality concerns, it is in the process of regaining WHO prequalification.244,245
- Except for Serum Institute of India’s DTwP-HepB-Hib 10-dose vial, which can be kept for up to 28 days for future immunisation sessions, all multidose reconstituted vials must be discarded no more than six hours after opening (WHO’s multidose open-vial policy).172

---

**Pipeline Products**

- Gavi anticipates the entry of one to four new manufacturers within the next three years.246 One of these is the Indonesian manufacturer Bio Farma; the prequalification process for their PentaBio vaccine is ongoing, with WHO evaluation expected to take place in late 2014.247
- Several companies are developing hexavalent vaccines; building on the success of pentavalent products, these new vaccines will additionally include the inactivated polio vaccine (IPV). Merck and Sanofi Pasteur have a collaborative product in Phase III134,164,248 clinical trials and Sanofi Pasteur have a product nearing the end of Phase III.164,249 In 2013, Biological E and GSK also announced that they were jointly developing a whole-cell pertussis fully liquid hexavalent vaccine.250

**Challenges**

- Some countries continue to use vaccines containing acellular pertussis (aP). However, recent guidelines from WHO’s Strategic Advisory Group of Experts (SAGE) underline the need for countries using whole-cell pertussis (wP) to continue doing so; wP provides a higher initial efficacy and slower waning of immunity, and has a greater impact on disease transmission compared to aP vaccines.251
- Adapting existing vaccines to more thermostable variants, which could be used in a controlled temperature chain, could result in major cost savings. Modeling studies have shown that changing pentavalent vaccines to a thermostable variant could result in improved availability of other EPI vaccines by up to 93% and improved availability of pentavalent vaccines by up to 97%.222
- As countries have moved to pentavalent vaccine, demand for standalone DTP has declined significantly. In 2012, demand for DTP through UNICEF represented 17% of DTP-containing vaccine orders. In 2013, there was only one supplier (Bio Farma) for DTP vaccines through UNICEF.238
- More than 70% of Gavi and UNICEF’s pentavalent vaccine supply is from Indian manufacturers who are subject to Indian national regulatory authorities. The WHO lists six critical control functions that all national regulatory authorities must exercise in a competent and independent manner in order to guarantee vaccine quality. Dependence on a single national authority is therefore considered potentially risky in the event of any adverse changes to even one of the control functions.252
- Any decrease in the number of manufacturers producing pentavalent vaccines could adversely constrain vaccine supply. Gavi forecasts that, to meet demand, at least four critical suppliers must remain in the market for the next ten years.246
The pentavalent vaccine market is the best example of a competitive market in which entry by emerging manufacturers has greatly contributed to lowering prices [see Graph 2, page 1]. The price of pentavalent vaccines started to decline in 2008 [Graph 15] with the entrance of Shantha Biotech, offering its US$2.90 single-dose vaccine to UNICEF at a 17% reduced priced compared to the previous lowest existing price of US$3.50 per dose (GSK, two-dose presentation).

The introduction of vaccines in 10-dose vials in 2011 and 2012 and the decision of emerging manufacturers to decrease their prices further lowered the price: the lowest price available decreased by 56%, from US$2.70 per dose in 2010 (Shantha Biotech, single-dose presentation) to US$1.19 per dose in 2013 (Biological E, 10-dose presentation).

Prices of all presentations have decreased, an indication of strong competition in this market and a sustained demand over time for significant volumes. However, UNICEF prices seem to have stabilised, which means that the price for this vaccine might have reached its floor.

**Notes:**
- All single-dose and 10-dose vaccines are liquid; all two-dose vaccines are lyophilised.
- Biological E also offered a 10-dose lyophilised vaccine in 2012, not represented on this graph.

**Sources:** PAHO Revolving Fund, UNICEF Supply Division

* Forecasted data
** Special terms apply that are not publicly available
For certain countries, the pentavalent vaccine remains unaffordable. For example, Egypt only introduced pentavalent vaccine to its EPI in 2014, after entering into a ten-year agreement to procure 80 million doses of Biological E’s product through the UNICEF Supply Division for US$200 million.253,254

Among the countries we analysed, few had pentavalent vaccines in their drug lists, as several other presentations are available, such as the hexavalent (DTaP-HepB-Hib-IPV) vaccine or the DTaP-Hib-IPV vaccine (e.g. South Africa). The price of these presentations is usually much higher than prices for DTwP-HepB-Hib pentavalent vaccines, and there are no WHO prequalified products yet.113 For example, in the Indian private sector, a pentavalent vaccine (Serum Institute of India) costs US$8.60 and IPV (Sanofi Pasteur) costs US$6.90 [see IPV Product Card, page 46], while a DTaP-Hib-IPV (by Sanofi Pasteur) costs US$35.54, which is more than twice the price of the two other vaccines combined. Countries introducing different combination vaccines might also scatter the demand across products, negatively impacting prices.

Looking at current prices [Graph 16], DTaP-Hib-IPV vaccines are available at similar prices across all the countries we analysed (with the exception of the US, where the vaccine retails at more than twice the price available in any other country), which may show that manufacturers are not targeting developing countries and have not developed strategies to expand affordability and access.

The hexavalent vaccine is considered a good combination vaccine to increase coverage of Hib and HepB in developing countries while integrating IPV in EPI. But the higher cost of hexavalent vaccines is likely to result in slow uptake in low- and middle-income countries, particularly until there is a broader manufacturer base to help lower costs. Currently, the cost of a hexavalent vaccine remains higher than IPV and pentavalent together.164,255

Hexavalent vaccines are also not perfectly suited to respond to needs of developing countries. Acellular pertussis is much more expensive to manufacture than whole cell, while manufacturers will have to overcome several technical difficulties before a whole-cell pertussis hexavalent vaccine is available on the global market [see page 68].164,255

Graph 16: Prices for DTaP-Hib-IPV and Hexavalent (DTaP-HepB-Hib-IPV) vaccines in several countries, by price type and manufacturers, 2013/2014*

Sources: PAHO Revolving Fund, UNICEF Supply Division, country price analysis.
* Annex A, Section C

Notes:
• All prices are for 2014, except for the DTaP-Hib-IPV in India that is from 2008.
HEPATITIS B

Early recombinant vaccines against HepB by GSK and Merck were first sold in high-income markets for US$40 a dose. Progress toward lower-cost vaccines was hindered by originator company patents. In the case of recombinant HepB vaccines, originators held dozens of process patents on development technology, delaying the efforts of lower-cost producers to create similar, lower-cost vaccines.256

Now the HepB market has matured, and the entry of several emerging manufacturers has enabled a drop in price that allows international organisations and governments to access the vaccine at a rather low price (US$0.16–0.37 per dose for WHO prequalified vaccines in our analysis – see Graph 17).

In the retail market, the vaccine is much more expensive. The lowest retail price included in our analysis ($6.20 per dose, Lebanon) is more than 15 times higher than the middle-income country government price included in our analysis (US$0.37 per dose, South Africa) for a WHO prequalified vaccine.

Outside of government purchases, affordable prices are only available from emerging manufacturers. The HepB vaccine in hospitals in Tunisia, for instance, is a LG Life Sciences Ltd product, and is available at a price almost comparable to government prices in other countries (US$0.63 per dose).

Graph 17: Prices for pediatric Hepatitis B vaccines in several countries, by income group and price type, 2013/2014*

Notes:
- Manufacturer names given in parentheses (Crucell, GSK, Merck, LG=LG Life Science; Sanofi=Sanofi Pasteur); where none is specified, the manufacturer is unknown/undisclosed.
- Paediatric presentation of the HepB vaccine only.
- Only the lowest price available to PAHO and UNICEF is presented in the graph.
- The Philippines procures through UNICEF.
- Prices for UNICEF, MSF and the Philippines are for multidose vials; two-dose vial for Thailand; single-dose vials for the other countries.
- MSF price is with Incoterm CPT (see Annex C).
- For the USA, this is the price as reported by manufacturers.

Sources: PAHO Revolving Fund, UNICEF Supply Division, MSF Supply, country price analysis
*Annex A, Section C