



# **THE RIGHT SHOT:** **EXTENDING THE REACH OF** **AFFORDABLE AND ADAPTED** **VACCINES**

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Each year, MSF teams vaccinate over 10 million people, primarily as outbreak response to diseases such as measles, meningitis, diphtheria, pertussis, and yellow fever. MSF also supports routine immunisation activities in some projects where we provide healthcare to mothers and children.

In 1999, on the heels of MSF being awarded the Nobel Peace Prize—and largely in response to the inequalities surrounding access to HIV treatment between rich and poor countries—MSF launched the Access Campaign. Its purpose has been to push for the access to, and development of life-saving and life-prolonging medicines, diagnostics and vaccines for patients in MSF programmes and beyond.



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## VACCINE PRODUCT, PRICING AND SCHEDULE RESOURCES:

The WHO Vaccine Prequalification site provides detailed product information on all WHO prequalified vaccines. It can be searched by vaccine type, manufacturer or country of manufacture.  
[http://www.who.int/immunization\\_standards/vaccine\\_quality/PQ\\_vaccine\\_list\\_en/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html)

The PAHO Revolving Fund, a mechanism established in 1977 for the procurement of vaccines, syringes and related health supplies for PAHO Member States, maintains a site with information on the weighted average cost per dose of vaccine, and injection supplies.  
<http://www.paho.org/revolvingfund>

The UNICEF Vaccine Price Data site provides information on prices contracted with suppliers by UNICEF per vaccine for the years 2001–2011. The site also includes a related link to GAVI-specific procurement information.  
[http://www.unicef.org/supply/index\\_57476.html](http://www.unicef.org/supply/index_57476.html)

The US CDC Vaccine Price List Archives site provides information on CDC contract prices, as well as private sector vaccine prices, since 1986.  
<http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list-archives.htm>

The WHO Recommendations for Routine Immunization Summary Tables site provides detailed information on the recommended antigens, vaccination schedule, and protocol for an interrupted or delayed vaccination series. The tables also include links to the related WHO Position Papers.  
[http://www.who.int/immunization/policy/immunization\\_tables/en/](http://www.who.int/immunization/policy/immunization_tables/en/)



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# ACCESS TO VACCINES – AN OVERVIEW

Lack of information on both the price and the different product characteristics of vaccines has been limiting countries' ability to operate affordable and effective immunisation programmes. This publication seeks to remedy some of the existing knowledge gaps by raising awareness on existing price differentials, exploring what factors drive fluctuations in vaccine prices, and discussing where development of better adapted vaccines could reduce barriers to immunisation and increase coverage levels of traditional and newer vaccines. This publication serves as a resource for immunisation stakeholders, such as donors, implementing partners, and developing countries, which are ultimately responsible for their national immunisation programmes.

The positive impact of vaccines on public health is well-documented—in the past century, vaccines have helped eradicate smallpox and significantly reduced the burden of communicable childhood diseases such as diphtheria and measles. Each year, immunisation with eight standard antigens<sup>1</sup> is estimated to avert 2.5 million future deaths.<sup>1</sup>

According to the Global Alliance for Vaccines and Immunisation (GAVI Alliance), the introduction of new vaccines against pneumococcal disease and rotavirus is expected to increase that number significantly.

Additional attention is being focused on immunisation with the launch of the “Decade of Vaccines,” an initiative designed to re-energise global efforts toward ensuring access to immunisation for all. The Decade of Vaccines calls to increase public and political support for vaccination, improve delivery of vaccines, strengthen research and development for new and improved vaccines, and address supply security and affordability.<sup>2</sup> The World Health Assembly first discussed the Decade of Vaccines in 2011 and is expected to validate a new Global Vaccine Action Plan (GVAP) in May 2012.<sup>3</sup>

This report explores two key challenges that will need to be overcome if immunisation coverage is to be improved and new vaccines are to be introduced in a sustainable manner. First, we explore more than ten years of pricing data for traditional and newer vaccines to see what factors had the most influence on bringing down vaccine prices. Second, considering the weak Expanded Programme on Immunisation (EPI) in many developing countries, we examine the potential role of vaccine adaptation in increasing the reach of immunisation services to difficult-to-reach populations.



Measles vaccination at a transit camp in Ethiopia.

i. Diphtheria, tetanus, pertussis, measles, polio, BCG, hepatitis B, haemophilus influenzae type B.

The prices of vaccines became a significant issue for immunisation stakeholders in 2011, when GAVI faced a US\$3.7 billion financial shortfall for its 2011–2015 programme implementation. GAVI's procurement strategies were an important contributing factor to this deficit, in as much as they had failed to adequately lower prices for newer vaccines. At the same time as high vaccine prices are increasingly in the spotlight, 16 lower-middle income countries are slated to “graduate” from GAVI, meaning that they will no longer benefit from GAVI subsidies.

Although stakeholders in global immunisation were generally united in their support and exceeded GAVI's call for funds at a June 2011 pledging conference, the need for GAVI to be more effective in bringing prices down has been emphasised by donors and recipient countries. This was evidenced by the adoption of a new Vaccine Supply and Procurement Strategy by the GAVI Alliance Board in November 2011.

The new Global Vaccine Action Plan underlines the need to strengthen national EPI programmes in countries with low immunisation coverage.

Recently, more attention has been paid to introducing new vaccines in national EPI schedules than to identifying and addressing challenges in traditional EPI delivery.

The focus on expediting introduction of new vaccines also means that recent products purchased for GAVI-eligible countries are often the same as those used in the U.S. or Europe, and are not always appropriate for the epidemiology or operating conditions in developing countries. GAVI has yet to use its buying power or donor influence to drive a research and development agenda focused on vaccines relevant for use in developing countries.

In this report we examine one strategy that could expand the reach of EPI programmes: vaccine adaptation. By adaptation, we mean altering vaccine profiles and presentations to make the product more suitable for developing country contexts. The need for vaccine products that are formulated for local epidemiology to combat the most prevalent strains of a disease is critical. Additionally, products that do not require cold chain and that can be delivered

through alternative technologies, such as microneedles, inhalation, or oral administration, is paramount for ensuring that vaccines reach their intended recipients.

Although this agenda is being promoted by Project Optimize, and advisory groups such as the Immunization Practices Advisory Committee (IPAC, founded in 2010) and the Vaccine Presentation and Packaging Advisory Group (VPPAG, founded in 2007), there is a need to bring this work to scale. With GAVI's new Supply and Procurement Strategy there is now a strong mandate to use GAVI's buying power to stimulate development of more adapted vaccines.

Based on Médecins Sans Frontières' field experience, we believe there is a need to put more emphasis on the adaptation agenda to help improve the efficacy of vaccines considering disease burden and improve the impact of programme delivery in countries with weak health system capacity. Coupled with greater price transparency and competition, vaccines will become more affordable and accessible to the countries that stand to benefit from them most.

## VACCINE PRICES: ENSURING VACCINES ARE AFFORDABLE

In 1974, WHO founded the Expanded Programme on Immunisation (EPI) with the goal of providing all children under one year of age access to vaccines against six key diseases: diphtheria, tetanus and pertussis (DTP), tuberculosis (TB), measles, and polio. In 2001, in the early days of GAVI operations, the total cost of purchasing a full course of these EPI vaccines averaged only \$1.37 per child.<sup>ii</sup>

Adding two GAVI priority vaccines in the early 2000s—Hepatitis B (HepB) and Haemophilus influenza type B (Hib)—increased the price

of the recommended childhood immunisation schedule by over \$10.<sup>iii</sup> Prices offered to UNICEF for pentavalent vaccine—a five-in-one shot that combines DTP vaccine with HepB and Hib vaccines, providing the cornerstone of childhood immunisation in developing countries—did not decrease significantly for most of the last decade.

In the past five years, WHO has recommended products that have higher unit costs such as pneumococcal conjugate vaccine (PCV) and rotavirus vaccine for global use in infants, as well as

human papilloma virus (HPV) vaccine against cervical cancer for use in young adolescent girls (other less expensive vaccines such as rubella and meningococcal A conjugate have also been the subject of recent global and regional WHO recommendations).

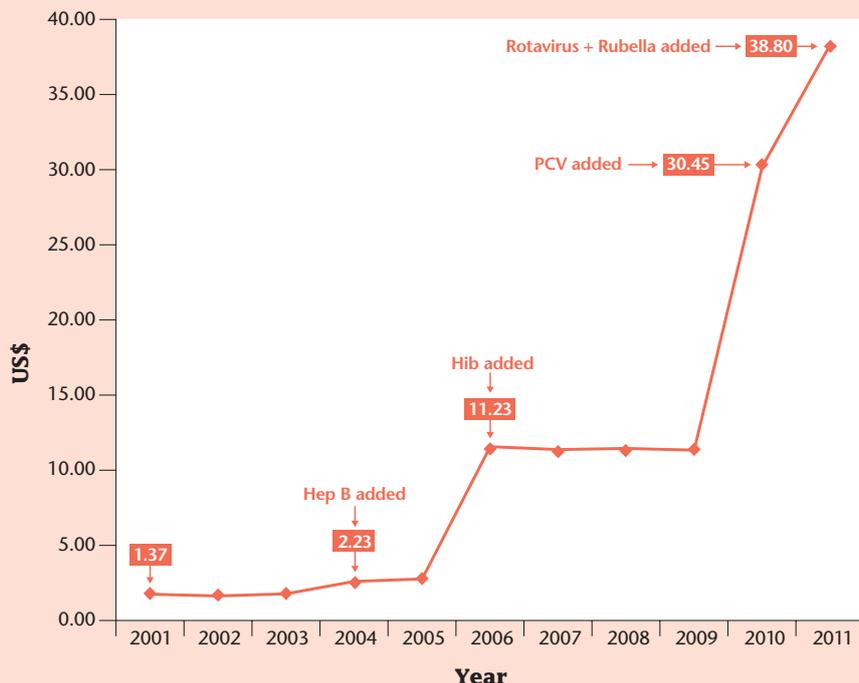
The expansion of the EPI programme has therefore raised the price of purchasing a full vaccination course for a child in a GAVI-eligible country from \$1.37 in the year 2001 to over \$38.80 in 2011 (**see Graph 1**). This price does not include other programmatic costs or cost associated with vaccine wastage.

ii. Calculated using average of supplier prices offered to UNICEF for 1 BCG (\$0.0793) + 3 OPV (\$0.2601) + 2 Measles (\$0.7952) + 3 DTP (\$0.2340).

iii. In 2001, UNICEF purchased pentavalent for \$3.50 a dose, or \$10.50 for the three recommended doses. When added together with BCG, OPV and measles vaccines, the total cost to fully vaccinate a child was \$11.63.

## GRAPH 1: THE RISING PRICE OF IMMUNISING A CHILD

### Estimated cost to purchase a full course of vaccines according to WHO Recommended Routine Immunisation Schedule



### Timeline: WHO recommendations & vaccine introduction

**2001:** Baseline vaccine package includes 1 BCG, 3 oral polio vaccine (OPV), 3 DTP and 2 measles.

**2004:** WHO reiterates 1992 recommendation for universal vaccination against Hepatitis B.

**2006:** WHO recommends universal vaccination against Haemophilus influenzae type B.

**2010:** First GAVI-eligible country receives pneumococcal conjugate vaccine under the Advance Market Commitment (WHO recommended vaccination with PCV in 2007).

**2011:** First GAVI-eligible country in Africa receives rotavirus vaccine (WHO recommended vaccination with rotavirus vaccine in 2009). WHO recommends universal immunisation with rubella vaccine and GAVI Board endorses decision to open a rubella vaccine funding window.

**Notes:** Price of an individual vaccine is defined as the average price per dose offered by contracted suppliers to UNICEF in a given year, multiplied by the WHO-recommended number of doses. Where there was a price range for an individual supplier for one product in a given year, the average price was used. For example, in 2001 the cost included 1 BCG (\$0.0793) + 3 OPV (\$0.2601) + 3 DTP (\$0.2340) + 2 measles (\$0.7952).

A vaccine is included in the calculated price once it is recommended by WHO and more generally available in GAVI-eligible countries. For example, although rotavirus vaccine was introduced in select GAVI-eligible countries in the PAHO region starting in 2006, the graph includes it from 2011. The year in which a new vaccine was added to the total price is noted on the right. Measles-rubella combination vaccine was used for the 2011 price, although GAVI had not yet financed its purchase at the time of publishing. Combination vaccine prices were used, when available, to calculate the total price. The PCV price used is \$7.00 per dose for three doses (\$21.00 total), i.e. includes the AMC subsidy. The rotavirus price is an average of the two full course products at June 2011-announced prices (\$7.75 total). This graph does not include the HPV vaccine, as the WHO recommendation is for use in adolescent girls, or the meningitis A conjugate vaccine, as its recommended use is region-specific.

Calculations do not include wastage rates factored into vaccine forecasting and purchasing.

Traditionally, vaccine prices have been set for wealthy countries based on a vaccine's value as it relates to savings in health care spending (such as days of hospital stays averted) rather than the cost of R&D and production. Prevnar (PCV-13), for example, is Pfizer's second best selling product grossing \$2.82 billion in the first nine months of 2011; the majority of revenue was earned from industrialised country sales where the vaccine costs as much as \$97 a dose.<sup>4</sup>

In the developing world, vaccine prices are substantially lower. There is, however, a significant price variance between GAVI-eligible countries and middle-income countries. Regardless, the cost of newer vaccines is often impossible for lower middle-income and least-developed countries to self-finance. On the other hand, growing private and public markets in wealthier middle-income countries

such as Argentina, Brazil and South Africa, have become a significant and fast-growing source of revenue for multinational pharmaceutical companies.<sup>5</sup>

But even these countries are facing a strain from the cost of purchasing newer vaccines and are exploring ways to bring down prices through more aggressive tendering.

Prices in least-developed countries have, for the most part, not gained much attention as GAVI-supported countries pay a minimal co-payment toward the total price of new vaccines (up to \$0.30 per dose).<sup>6</sup> GAVI donors shoulder the bulk of the financial burden for purchasing newer vaccines such as pentavalent, rotavirus, and pneumococcal vaccine.

The full costs of a national immunisation programme, however, go well beyond just that of the vaccine. The more immediate budgetary impact for GAVI

countries is the costs for expanding national immunisation programmes to accommodate these new vaccines. Fixed costs, such as those to expand cold chain capacity and immunisation programme infrastructure, as well as running costs, such as the cost of fuel for vaccine transportation, are significant elements of the EPI budget.

Some GAVI countries have seen EPI programme costs double, triple and even quadruple as they have added new vaccines to national immunisation schedules.<sup>7</sup> Ethiopia, for example, which introduced liquid pentavalent in 2007, increased its central refrigeration volume by 106% and saw a significant increase in transportation demands. While GAVI provides one-time grants for vaccine introduction costs, increased costs for budget items such as vaccine transportation continue to be borne by the host government.<sup>8</sup>

Countries supported by GAVI have concerns over their ability to afford to pay for vaccines in the long run. A Kenyan Ministry of Health official equated adding multiple new vaccines to a national immunisation programme as “taking out multiple mortgages”.<sup>9</sup> Sustainability of introducing new life-saving vaccines requires that the full cost of national immunisation programmes, with all of their component parts, be taken into account. Increased domestic allocations will be needed as well as international support.

High vaccine prices have implications particularly for countries being weaned off donor subsidies. In 2011, the GAVI Board adjusted country eligibility criteria, resulting in 16 lower-middle-income countries losing their GAVI-eligible status, with support to be phased out by the end of 2015.<sup>10</sup> Honduras, for example, will graduate from GAVI support in 2015, though its 2009 average per capita income was only \$1,800.<sup>11</sup> With GAVI’s help, the country has introduced immunization for both rotavirus and PCV, and currently pays \$1.09 per child for the

two vaccines.<sup>12</sup> Once GAVI support ends Honduras will have to pay \$25.50 per child—assuming it pays the PAHO, non-GAVI price—for PCV and rotavirus, to which the cost of other routine immunisations must be added. In 2015, the country is projected to have a birth cohort of 202,000 children; at \$25.50 per child, vaccinating against rotavirus and PCV would cost an estimated \$5.1 million per year. Honduran authorities are hoping to get GSK’s approval to continue paying the GAVI price, even if the country will no longer be GAVI-eligible.

## PROCUREMENT AND PRICING STRATEGIES:

❖ **Pooled procurement:** Lower prices for vaccines have been consistently achieved through pooled procurement—where countries aggregate their demand and buy vaccines in bulk. As technical and capital barriers to market entry are quite high for manufacturers, most vaccines are initially offered by only one or two multinational pharmaceutical companies. Aggregating demand to guarantee large-volume purchases over one or multiple years decreases manufacturer risks, reduces transaction costs, and allows suppliers to offer prices closer to the cost of production.

Both UNICEF and PAHO use pooled procurement as a means to negotiate more affordable prices. The two agencies have different policies and operating principles for negotiating contracts, promoting competition, and ensuring supply security.

At UNICEF, the Supply Division procures for about 40% of the global demand for children’s vaccines for both low- and middle-income countries (as measured in units). Products must be prequalified by WHO. UNICEF conducts annual demand forecasting activities with countries. While contracts have ranged from one to five years, UNICEF has found through experience and consultation with industry that the longer-term stability of a three-year contract allows companies to offer better prices. At the same time, UNICEF proactively leaves quantities unallocated when new producers are reaching market.

At PAHO, a Revolving Fund was established in 1977 to purchase vaccines and related immunisation supplies. Today most low- and middle-income countries in the region of the Americas purchase some or all of their vaccines from the PAHO Revolving Fund. PAHO also advises governments on product choices. PAHO conducts procurement activities on an annual basis, establishing annual arrangements with manufacturers for the forthcoming year.

Products must be prequalified by WHO, or registered in a PAHO-recognised national regulatory authority when products are not in the WHO prequalification system. PAHO charges countries the average weighted price for each vaccine it offers.

Other WHO regions are considering a similar regional pooled vaccine procurement system inspired by the PAHO Revolving Fund model.

### THE PAHO REVOLVING FUND

For more than 30 years the PAHO Revolving Fund, through its ‘lowest price’ clause, has guaranteed access to a single and lowest worldwide price regardless of territorial size or economic development. The Fund has also created sustained predictable demand and led to less fluctuation in vaccine prices as well as contributed to national financial self-sufficiency.

But the clause is disliked by companies which practice tiered pricing. Some are unwilling to offer middle-income countries in the PAHO region—such as Brazil or Ecuador—the same prices as offered to least-developed countries through GAVI. Some have side-stepped the lowest price clause by offering different product presentations to GAVI and other developing countries.

In the case of pneumococcal conjugate vaccines, for example, GSK developed a two-dose vial for sale to UNICEF (\$7.00 per dose, which includes \$3.50 AMC subsidy), while offering PAHO a one-dose vial (\$14.85).

PAHO’s use of the lowest price clause for an entire region has been a successful tool in obtaining affordable vaccine prices for both its low- and middle-income member countries. However this mechanism is under pressure as companies move toward prices that are significantly higher for middle-income countries.

❖ **Tiered pricing:** Many multinational companies practice tiered pricing –different categories of buyers are charged different prices for the same product. The highest prices are charged in wealthy markets, intermediate prices in middle-income countries, and lower prices in the poorer countries, such as those eligible for GAVI support. Under the current system, producers are setting prices and the sharing of information on prices paid has been limited (beyond UNICEF and PAHO prices). Limitations of this system are demonstrated with the pneumococcal vaccine. Although the cost of production has been estimated to be well below \$3.50,<sup>13</sup> Pfizer is charging \$14.85 to PAHO countries, \$26.00 to South Africa, and \$7.00 per dose to GAVI.<sup>iv</sup> As concluded in an analysis on tiered pricing where the cost of GSK’s PCV vaccine supplied to PAHO, GAVI and the government of Brazil was examined, “currently, there is no straightforward, equitable way to set tiered prices to achieve affordability.”<sup>14</sup>

❖ **Price transparency:** Until recently, the only public information available on how much individual companies charge for vaccines were the postings of average weighted prices from PAHO’s Revolving Fund. But PAHO’s system does not communicate individual supplier prices, so it was

impossible to know when prices varied considerably between similar products.

The lack of pricing information made it difficult for governments and donors, as well as other vaccine procuring stakeholders, to ascertain whether or not they were receiving a fair deal. Without a good frame of reference for negotiation, countries pay too much,

particularly those outside of pooled procurement mechanisms. While some middle-income countries in the PAHO region benefit from prices obtained through pooled procurement, countries such as South Africa—despite having a lower income level—pay nearly four times as much for the same products (See Table 1).

**TABLE 1:**

**2011 price per dose of new vaccines for South Africa, compared to PAHO and GAVI/UNICEF prices**

VACCINE	PURCHASER		
	South Africa	PAHO	GAVI / UNICEF
Pentavalent	\$9.35	\$2.95	\$1.75
Rotavirus	\$7.75	\$7.50	\$2.50
PCV	\$26.00	\$14.85	\$7.00

**Notes:** Prices paid by the government of South Africa are quoted from information obtained from correspondence with the Department of Health. Prices have been converted from South African Rand using a 26 March 2012 conversion rate.

Price quoted for the South Africa, PAHO and GAVI/UNICEF rotavirus vaccine is the GSK product.

The GAVI/UNICEF rotavirus vaccine price is that announced in June 2011.

Price quoted for the GAVI/UNICEF PCV vaccine includes the AMC subsidy.

In January 2011, UNICEF published an historical online database with vaccine prices, listing prices paid by product and supplier.<sup>15</sup> The UNICEF database revealed some striking disparities in price. For example, pentavalent vaccine,

the five-in-one shot that is the mainstay of GAVI purchases, is being offered by Indian manufacturers such as the Serum Institute at prices almost 40% less than Crucell, a European company, the most expensive competitor (See Table 2).

**TABLE 2:**

**2011 UNICEF price per dose of DTP-HepB-Hib (pentavalent) vaccines, by supplier**

	SUPPLIER				
	Crucell Switzerland AG	GlaxoSmithKline Biologicals S.A.	Serum Institute of India Ltd.		
Presentation	single-dose liquid	two-dose lyophilised	single-dose liquid	two-dose lyophilised	ten-dose liquid
Country of Manufacture	Republic of Korea	Belgium	India	India	India
2011 Price per dose	\$2.80–3.20	\$2.95	\$2.25–2.50	\$2.25	\$1.75–2.11

**Notes:** Prices sourced from: [http://www.unicef.org/supply/files/11\\_05\\_23\\_DTP-HepB-Hib.pdf](http://www.unicef.org/supply/files/11_05_23_DTP-HepB-Hib.pdf)

Country of manufacture information obtained from: [http://www.who.int/immunization\\_standards/vaccine\\_quality/PQ\\_vaccine\\_list\\_en/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html)

Continuing to improve price transparency is critical both for donors supporting GAVI and for countries that must negotiate with companies

outside of pooled procurement mechanisms. One of the initiatives that is exploring the creation of a pricing and product database is the Vaccine

Product, Price and Procurement Project (V3P) which began in September 2011.

iv. This price is inclusive of the Advance Market Commitment per-dose subsidy of \$3.50 per dose. After selling a pre-determined number of doses, the GAVI price for PCV will drop to \$3.50 per dose.

**Competition from lower-cost manufacturers:** The vaccines market is evolving quickly, and a growing number of quality-assured suppliers in emerging markets are able to undercut the prices of traditional multinationals.

The UNICEF database demonstrates that vaccine prices are highly dependent on where a product is produced. Labour and other production inputs can be obtained at lower prices in emerging markets, but lower fixed costs for constructing facilities are also important, particularly as these typically account for 60% of vaccine production costs.<sup>16</sup> Developed country manufacturers spend \$200 to \$400 million per vaccine on production facilities, while emerging company manufacturers, such as in India, typically spend less than \$100 million.<sup>17</sup>

The UNICEF database illustrates how, as with the price evolution of HIV medicines,<sup>18</sup> the entry of low-cost suppliers into a vaccine market puts downward pressure on the prices charged by industrialised country manufacturers. Following competition

from several Indian producers in the pentavalent market, for example, GSK and Crucell lowered their UNICEF prices by approximately 15% between 2009 and 2010 (see product card page 17).

Examples such as the development of the Meningitis A vaccine specifically for use in Africa's Meningitis Belt, show that lower-cost manufacturers can produce affordable and appropriate products that meet developing countries' priorities, if adequate support and incentives are in place. Of particular note, the Meningitis Vaccine Project facilitated technology transfer and utilised the lower costs of emerging market producers to develop the vaccine now WHO-prequalified and sold at \$0.525 per dose (2012).<sup>19</sup>

In vaccine markets, however, competition is generally slower to emerge when compared to drug markets, as "generic" vaccines do not exist. Vaccine manufacturers must not only develop or obtain the technological know-how but must also conduct clinical trials on their products to prove safety and efficacy.

Access to licensing technology for production of new vaccines has often proved difficult for emerging market manufacturers. Working around process patents, or having delayed access to technology, lengthens the amount of time it takes emerging market producers to get their lower-cost vaccines to market.

Competition from emerging market manufacturers is likely to increase since March 2011, when China's regulatory authority, the State Food and Drug Administration, was recognised to meet international standards for vaccine regulation by WHO. Chinese manufacturers are now eligible to submit their products for WHO prequalification. When Chinese products are prequalified, their producers will be eligible to sell to UNICEF and PAHO.<sup>20</sup>

Chinese manufacturers are already supplying vaccines, such as Japanese encephalitis, to their domestic markets and have other products against pneumococcal disease and rotavirus under development.<sup>21</sup>

## VACCINE ADAPTATION: ESSENTIAL TO INCREASING IMMUNISATION COVERAGE IN AREAS WITH WEAK HEALTH CARE SYSTEMS

The past decade has seen rising global immunisation coverage but data are not always reliable. According to WHO, global coverage with three doses of DTP vaccine (DTP3) has risen from 66% since GAVI's inception in 2000 to 82% in 2011.<sup>8</sup> But household survey results call official figures into question—while WHO estimated DTP3 coverage in Ethiopia at 86% in 2011,<sup>22</sup> the 2011 Ethiopia Demographic and Health Surveys estimated DTP3 coverage at only 37%.<sup>23</sup>

Additionally, reported progress in global immunisation often hides significant inequities, both across and within countries. Many countries are still failing to raise coverage levels; Chad's coverage level, for example, has fluctuated between 19–59% for DTP3 coverage over the last five years, one of the lowest levels of coverage of any country in the world.<sup>24</sup> States such as Bihar in India have coverage levels

of 40%, lagging at least 30 percentage points behind others such as Tamil Nadu and Kerala.<sup>25</sup>

Even though many countries have improved EPI coverage, vast numbers of infants are still not being reached. Approximately 20% of babies born every year—over 19 million infants—do not receive the cornerstone of basic immunisation, three doses of DTP vaccine.<sup>26</sup> For this "fifth child", a vaccine's price is not necessarily the most prohibitive barrier to receiving immunisations—a measles vaccine, costing under \$0.30, may be equally unlikely to reach a child in an African village as a \$3.50 dose of pneumococcal vaccine. This failure is primarily due to weak health systems and vaccine products which are not appropriately tailored to the country context.

Adaptation of vaccines and revising immunisation strategies could have

significant impact on improving coverage. Many vaccine presentations are not practical for use in resource-poor settings where electricity is non-existent or erratic. Additionally, unlike the oral polio vaccine (OPV) which can be administered by lay volunteers, most other traditional and newer vaccines require trained health workers which are often in short supply in the neediest areas.

As with drugs, novel vaccines have predominantly been brought to market to answer developed country needs. The products are therefore tailored to wealthy market disease epidemiology, as well as to be used in wealthy market health systems. The research and development (R&D) that goes into producing a vaccine does not necessarily take into account the resources and conditions of developing countries.

GAVI has not thus far created incentives for adapting vaccines for developing countries. Instead its principal focus has been to aggregate demand and reduce the time lag that developing countries have to wait before they can access new products.

The Bill and Melinda Gates Foundation, through its Grand Challenges programme, is addressing the need for adaptation by funding early stage research into technologies such as needle-free vaccines or vaccines that do not require refrigeration. The Gates Foundation is also funding several emerging country supplier products to help diversify the vaccine market. Until now, this work has not been coordinated with GAVI's procurement strategy.

Political will and access to resources is key for expanding the reach of vaccines, but the availability of adapted products also plays as essential role as resources.

❖ **How ill-adapted vaccines complicate delivery:** There are a number of challenges that complicate the delivery of vaccines.

Many current products have attributes that make their use difficult in countries or regions with weak health systems. Most vaccines must be kept in a cold chain, at temperatures between two to eight degrees Celsius. Heat-instable vaccines can only be out of the cold chain for one week at temperatures up to 37°C. In areas where electricity is unreliable and transportation difficult, these vaccines are not suitable. Conversely, due to challenges in maintaining a proper cold chain, vaccines are often accidentally frozen, which can result in damaged and unusable vaccine, such as in the case of the tetanus toxoid vaccine. More research is needed to determine the extent of vaccine wastage due to cold chain failures, or accidental freezing, but it is clear that these conditions require a more appropriate vaccine adaptation.

Vaccines that are administered by injection make it difficult to extend their reach to locations where health care workers visit infrequently. The Global Polio Eradication Initiative has relied on lay community health workers to vaccinate children in

**TABLE 3:**  
**Vaccine Vial Monitor ratings for select products**

Vaccine	Vaccine Vial Monitor (VVM) 37°C
Pentavalent (Serum Institute of India)	14 days
Measles-containing vaccine	14 days
Pneumococcal vaccine	30 days
Rotavirus (GSK Rotarix)	14 days
Rotavirus (Merck Rotateq)	No VVM approved for this product. Cold chain storage conditions must be maintained from delivery to administration.

**Notes:** See annex 1 for information on VVM. A vaccine vial monitor (VVM) is a label containing a heat sensitive material which is placed on a vaccine vial to register cumulative heat exposure over time. There are four different types of VVMs designed for different types of vaccines depending on their heat stability. The VVMs above refer to the number of days a vaccine can last in temperatures to endpoint at 37°C.

Information is included as part of the WHO Prequalification information at [http://www.who.int/immunization\\_standards/vaccine\\_quality/PQ\\_vaccine\\_list\\_en/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html)

the most remote villages, which has been possible in part due to oral administration of the vaccine.<sup>27</sup> Most vaccines however, remain injectables, which require health workers who have been trained in proper injection techniques. Proper disposal of injection waste is also a challenge in developing countries where incinerators are expensive and not readily available in most communities. Vaccine administration technologies, such as products that can be inhaled, administered orally or through microneedle are important for the adaptation agenda.

In countries with limited healthcare workers and health facilities, more children may be vaccinated if there is a mix of vaccine presentations. Despite WHO's recommendation to open a vaccine vial when any eligible child is present, healthcare workers are often reticent to open multi-dose vials if they do not have a quorum of children present for fear of wasting vaccine. Although multi-dose vials significantly reduce the price per dose of vaccine, in areas where healthcare workers resist opening vials when there are fewer children than doses, having both single and multi-dose vials available may be advantageous.

❖ **How dosing schedules hinder a completed vaccination series:**

There is room for improving the vaccine schedule to reduce the number of children not completing their vaccination series.

Dosing schedules should be explored to maximise the number of children completing their full vaccination series. In countries with ongoing measles transmission, the first dose of measles vaccine is recommended at nine months of age, while children should have already received their three-dose DTP series at six, ten, and 14 weeks. Many children do not receive vaccination against measles due to the timing of the primary shot, which is not bundled with other antigens, in most of the developing world. In some instances, the low coverage of measles vaccine has manifested as mass measles outbreaks, most acutely in Africa where 28 countries faced outbreaks in 2010; in the Democratic Republic of the Congo (DRC), over 100,000 measles cases were reported from January to October 2011.<sup>28</sup>

Further research is needed on the immunologic response to vaccines if children are vaccinated at ages outside of the current recommendations.

Changing the dosing schedule to improve EPI effectiveness will need to be balanced with the immunologic issue of ensuring that vaccine protective efficacy is as high as possible.

According to the currently recommended immunisation schedule, even if all vaccines are bundled to achieve the minimum number of health facility visits, caretakers must still bring their child to a facility five times for vaccinations in its first year. Research into adapting products so as to make the dosing schedule as convenient for caretakers as possible, while also maintaining vaccine efficacy, must be prioritised.

❖ **Some vaccines are not specifically designed for developing country epidemiology:** The epidemiology of diseases in developing countries is not fully incorporated into vaccines produced for developed country markets.

The epidemiology of diseases differs between regions. For example, meningococcal meningitis has five

serotypes that cause the most disease worldwide: A, B, C, W135 and Y. In the United States, the most circulating serotypes are B, C, and Y, whereas in the African Meningitis Belt, meningitis type A is the most prevalent strain, followed by W135. Rotavirus, which causes diarrhoeal disease, has a number of different genotypes. Despite the availability of two WHO-prequalified vaccines against rotavirus—Rotarix and Rotateq, which are made of one and five rotavirus genotypes, respectively—there is a need for further research to determine the most prevalent genotypes of rotavirus circulating in high-burden countries. Although each vaccine may protect against multiple rotavirus genotypes, it has not been concluded if the efficacy against other genotypes is the same. As the body of research on disease epidemiology in developing countries grows, it will be important that vaccines be modified to be most efficacious for those contexts and not only for that of the developed world.

In some cases, adapted products may

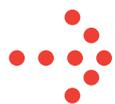
cost more per dose to manufacture than traditional products. However, if the vaccine is more efficacious against the disease, if vaccine wastage can be minimised by ensuring that all doses reach their intended children, or if programme costs can be reduced by decentralising delivery to lay community health workers through non-injectable products, overall EPI costs may actually come down.

Investment and additional clinical trials are needed to further the vaccine adaptation agenda. As the Decade of Vaccines moves forward, it will be critical to look at synergies between Gates Foundation-funded product development and GAVI's procurement strategy and seek additional investments by governments and companies. There will need to be a concerted effort to define desirable products and product profiles, and to support development of these adapted products so as to meet country needs.



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In the DRC, MSF measles vaccination teams make their way through the forest to reach isolated villages totally inaccessible by vehicle.



# CONCLUSIONS AND RECOMMENDATIONS

In recent decades, improved vaccine access has averted deaths and serious illness in developing countries. But there is still a need for increasing the impact of vaccination by increasing the reach of immunisation programmes. In order to fully realise the benefits of immunisation, two key challenges will need to be overcome.

**First, newer vaccines need to be made affordable.** Although GAVI-eligible countries are so far spared the burden of financing most of the cost of newer vaccines, some are being weaned off GAVI support and others will be in the future. High prices are prohibitive for donors and unsustainable for the vast majority of developing countries.

Non-GAVI eligible developing countries, like South Africa, are already facing daunting vaccination bills. Ensuring that vaccine prices are reduced is therefore essential, particularly in a context of dwindling financial resources for global health.

❖ **Vaccine prices:** how to ensure vaccines are affordable

- **Harnessing the power of greater price transparency:** Additional mechanisms to share pricing data are needed to ensure that purchasers know what is being paid to each manufacturer for each vaccine. Increased public information will inform price negotiations so that purchasers can avoid paying unnecessary premiums.
- **Utilising the power of pooled procurement:** Additional pooled procurement mechanisms and/or negotiated reference prices must be developed so that developing countries outside of PAHO not eligible for GAVI support do not pay inflated prices. Other WHO regions and countries should explore opportunities to collectively negotiate reduced prices.
- **Supporting the development of lower-cost manufacturers:** Companies with production facilities in emerging countries have proven their capacity to produce quality-assured products at substantially lower prices. Technical barriers however remain considerable and will need to be overcome. Major purchasers, such as GAVI, and agencies subsidising development must better coordinate so as to speed up development of new products. Concurrently, emerging country producers must have access to licences and key technology know-how.

**Second, adapted products must be designed for local disease burden, and contexts with few healthcare workers and weak health systems.** The majority of currently available vaccine products have been developed for industrialised countries and their disease epidemiology. Increased attention and investment to developing vaccines that are more practical to use in resource-limited settings—such as products that are more heat-stable, can be administered by community health workers and with few doses or more flexible dosing schedules—and more tailored to the specific medical needs of developing countries is needed.

❖ **Vaccine adaptation:** how to increase immunisation coverage in areas with weak health systems and ensure that products match disease burden

- **Developing the vaccine adaptation agenda:** A vaccine adaptation and innovation agenda that defines products that will extend the reach of immunisation needs to be developed. As part of this agenda, WHO should take a more proactive and directed approach to determine technical product profiles that would improve the reach of immunisation programmes. This work needs to be done in conjunction with the input of countries.
- **Putting governments in the lead:** Ministries of Health in countries struggling to raise immunisation coverage must be more involved in setting priorities and feeding product development information to vaccine developers.
- **Innovating delivery strategies:** WHO, UNICEF and partners must develop additional EPI delivery strategies for countries with weak health systems. There is a need for increased investment in operations research to test delivery methods for reaching the “last 20 percent”.
- **Making vaccines more appropriate for local epidemiology:** The knowledge base on disease epidemiology in developing countries is poor, while most vaccines are tailored to markets in wealthy countries. Further research into specific disease burden in developing countries is needed to inform the development of the most efficacious vaccines.
- **Expediting implementation of new products:** As new WHO-prequalified products come to market (inhalation devices, microneedles, etc), strategies must be developed to expedite their use in developing countries.
- **Investing in products and strategies that work:** Donors and Ministries of Health should be willing to pay slightly more for vaccine presentations that are easier to administer and have the potential to reach more children, especially since some products might bring down overall programme costs.



# VIEW FROM THE FIELD: WHY WE NEED TO SIMPLIFY VACCINATION

**Why is it so difficult to achieve and sustain high levels of immunisation coverage in remote areas, or where health systems are severely limited? Dr. Michel Quéré, MSF medical advisor for programmes in Niger, Chad and the DRC, explains why the vaccines at our disposal today make reaching remote populations considerably more difficult.**

“Our catch-up vaccination programmes are quite successful—the idea is to give children the vaccines they have missed, for example against measles or the pentavalent vaccine. We get good results because we put a lot of effort into raising awareness in the community, explaining which age group will get vaccinated when and why that’s important, and our locally recruited nurses play a vital role.

But it’s definitely the case that we get good results also because we have considerable logistical support at our disposal. We’ve got the large storage facilities, the fridges and icepacks to keep the vaccines under cold chain, the transportation to get them out to the villages and the logisticians to make sure that it all runs as smoothly as possible.

With some vaccines, children need to receive several doses, several months apart to receive full protection. That means, for instance, to make sure a child is fully protected with the pentavalent vaccine, you have to trace the child on three separate occasions so that they can receive three doses of the vaccine. And if you’re also giving additional vaccines, then the ages at which you need to vaccinate don’t necessarily coincide, so for every child under the age of one, five separate visits may be needed.

Reaching children scattered across the absolutely vast and remote areas where they live is a real challenge—the roads are usually very bad, and some of the health posts—for instance in the Democratic Republic of Congo—are so isolated, or present such security concerns, they can only be reached by plane.

Keeping the cold chain when it’s 45°C outside is a major challenge. For the national health authorities, in some rural areas, just maintaining the fridges in working order is hard



Social mobilisation before a blanket measles vaccination campaign aimed at 800,000 children in Eastern DRC.

to guarantee, and then there’s the need to produce enough ice packs so that the vaccines are still cold by the time we get to the children. You can imagine how many icepacks are needed, so even getting the vaccines out to the villages is a huge logistical effort in itself.

The governments or local authorities rarely have the means at their disposal to get all this done—there might be only one nurse available, expected to provide services for 10,000 people and that number can go up to 50,000 people in some parts of Niger and he or she will often have no means of transportation.

So it’s very clear that we need things to be made simpler. A vaccine that can be taken orally is ideal. It can thus be administered more simply—even by community health workers—and so can be made available much more widely, overcoming the shortage of health staff. We also need to get around the problem of needing a cold chain as it’s a huge burden in terms of resources.

Unless vaccines are simplified so that they’re better adapted to real-life conditions, we will never get on top of these killer diseases and will always need to respond to outbreaks that we haven’t managed to prevent through effective immunisation programmes.

Sadly, there’s been little progress in this regard over the last 20 or 30 years. And unless we see some changes, we’re not likely ever to achieve the goal of good EPI coverage. Adding new vaccines to the mix isn’t going to bring us closer to achieving that goal either.

It might cost more to develop and provide better-adapted tools, of course. But responding to epidemics and disease outbreaks is hugely costly, and children who are ill become vulnerable to other conditions like malnutrition, so the extra expense should quickly be offset with other gains. That’s putting to one side the fundamental question of whether you can put a price on saving a child’s life.”



# STRENGTHENING THE EXPANDED PROGRAMME ON IMMUNISATION: LESSONS FROM CHAD

MSF has been treating patients for malaria in the Moissala district of Chad for two years, but the team has also responded to outbreaks of contagious diseases such as measles and meningitis. These outbreaks continue to occur because in recent years, the national Expanded Programme on Immunisation (EPI) has suffered from neglect. Florence Fermon, Head of MSF's Vaccine Working Group, sets out her concerns about the lack of support for EPI within the country, which has led to continued outbreaks of disease and unnecessary loss of young lives.

“What we are seeing in the country as a whole, and in Moissala in particular, is that the EPI has not been getting the support it needs from the Ministry of Health and its partners. There is competition for resources from a growing number of specific vaccination initiatives—including polio eradication, maternal and neonatal tetanus elimination, measles elimination, and the introduction of the new meningitis A vaccine.

Each of these individual vaccine initiatives conducts its own self-contained staff training programmes, funds its own vaccines and mobilises people to take part in the vaccination campaigns.

There is limited support in the country to reinforce EPI as a whole. A basic strategy to provide routine vaccination is not in place, by making sure for example that any eligible child receives their due vaccines at each contact with a health post. Another example in Moissala district is the absence of systematic vaccination at birth, when deliveries occur in a maternity ward. There are globally recommended policies to support this, but in Chad they have not been implemented. In fact, the last national EPI training in Chad took place as far back as 2004.

Moissala district provides clear illustration of this: the cold chain storage facilities are insufficient, and there isn't even a cold chain officer in place. Should the cold chain break down, there is no technical support available in the district. And only minimal social mobilisation support is at hand to inform and encourage people to bring their children to be vaccinated.

As a result, we see many vulnerable pockets where people in this area



An MSF meningitis vaccination campaign in collaboration with the Ministry of Health in Chad.

are simply not being reached and immunised—either at all or fully. That is why, despite large scale vaccination campaigns in the country, we are still encountering persistent outbreaks of diseases such as measles and pertussis.

In January 2011, a nationwide measles vaccination campaign was launched. But although the incidence of measles has decreased in most districts, there are still around 300–400 new suspected cases of measles declared each week in some places. Clearly the campaign has failed to reach some of those who were targeted. Additionally, there hasn't been an investigation to determine why these outbreaks continue so that we can implement an adequate response.

MSF is working with partners on a strategy to respond to this situation, and reverse this neglect specifically in

Moissala district. The proposed strategy includes catch-up vaccination activities in the district for all children up to two years of age for all the basic antigens, and vaccination for all children up to five years of age for measles and yellow fever. Altogether, we hope to reach the target population in this area of more than 10,000 children.

Depending on support from our partners, we are also interested in introducing the pneumococcal conjugate vaccine, at present not included in the national programme, despite a high number of pneumococcal disease cases in the district. In addition, we propose to provide technical assistance to improve planning for the EPI system, support the improved functioning of the cold chain, as well as offering local training and suggestions for improved methods of managing waste. ”



# METHODOLOGY

The idea to create this report was stimulated by the May 2011 web publication of ten years of vaccine prices paid by UNICEF for country procurement. Until these prices became public there was little knowledge about actual prices paid by donors and governments for vaccines that have been used in developing countries.

We have looked at several categories of vaccine products over the period for which data is available and have analysed movements in prices to pinpoint trends and better understand factors that impact price changes over time. In some cases, UNICEF prices have been presented alongside other reference prices including the PAHO Revolving Fund prices for Latin American countries, and other selected country public procurement prices.

For each category of products we outlined:

- 1) general information –WHO recommendations, products and manufacturers, dosing schedules and presentations;
- 2) prices for each product in the category; and
- 3) adaptation challenges.

Vaccine categories were selected because they are either cornerstones of the WHO-recommended Expanded Programme on Immunisation (EPI) or because they are newer vaccines that have recently been introduced in at least some developing countries. The breadth of these products allows for analysis of vaccines in different stages of the product life-cycle and illustrates multiple adaptation challenges, as well as different models of development. This analysis, however, does not include all antigens recommended in the WHO vaccination schedule.

All products appearing in this publication are WHO-prequalified.

The following vaccine products are included:

- Diphtheria-Tetanus-Pertussis (DTP), monovalent Hepatitis B (HepB), monovalent Haemophilus influenzae type B (Hib) and pentavalent (DTP-HepB-Hib) vaccines
- Measles containing vaccines, including monovalent measles, measles-rubella (MR), and measles-mumps-rubella (MMR) vaccines
- Meningococcal meningitis conjugates vaccines
- Pneumococcal conjugate vaccines (PCV)
- Rotavirus vaccines

## PRICE DATA

A retrospective analysis of prices charged for vaccines purchased from the years 1998 to 2011 was performed using the following sources of information:

- **UNICEF Vaccine Price Data.**<sup>v</sup>  
In 2011, UNICEF published retrospective prices paid for specific products during the period 2001–2010. The database was last updated in February 2012. Prices are either Incoterm Free Carrier (named place of delivery) (FCA) to UNICEF designated freight forwarder or Incoterm Carriage Paid To (named place of destination) (CPT) to the supplied countries. In cases where a range of prices was provided by UNICEF for the same product for the same year, the highest price was taken for the purposes of the retrospective analysis, unless otherwise noted.

- **PAHO’s Expanded Program of Immunisation Vaccine Prices.**<sup>vi</sup>  
This document provides weighted average FCA prices for each vaccine presentation that is offered by PAHO’s Revolving Fund. The weighted average price is calculated by summing up the total expected purchase value of each assigned supplier for the same type of vaccine then dividing the amount by the total of doses expected to be purchased of the given type of vaccine. PAHO does not disclose individual prices of vaccines and charges countries that participate in its Revolving Fund this average price—a ‘solidarity’ system of paying averages, not actual prices. Participating countries also contribute a percent of costs to capital for the Revolving Fund.<sup>vii</sup>

- **US CDC Vaccine Price List Archives.**<sup>viii</sup>  
The CDC Vaccine Price Lists provide vaccine contract prices for CDC contracts that are established for the purchase of vaccines by immunisation programmes that receive CDC immunisation grant funds (i.e., state health departments, certain large city immunisation projects, and certain current and former U.S. territories). Prices quoted include tax and transportation fees. This would correspond to the Delivery Duty Paid (named place of destination) (DDP) Incoterm.

For the Hepatitis B and measles graphs, where multiple suppliers with multiple price points were to be included, we took the average price across all presentations for each year for a given organisation (e.g. UNICEF or PAHO).

v. [http://www.unicef.org/supply/index\\_57476.html](http://www.unicef.org/supply/index_57476.html)

vi. <http://www.paho.org/revolvingfund>

vii. Countries participating in the PAHO Revolving Fund contribute a percentage of costs for the fund’s capital (formerly 3%). Starting in 2011, the contribution will be 3.5% (3% is the capitalization fee of the common capital fund and 0.5% is for strengthening of the procurement mechanism).

viii. <http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list-archives.htm>



**DIPHTHERIA-TETANUS-PERTUSSIS  
HEPATITIS B  
HAEMOPHILUS INFLUENZAE TYPE B  
AND COMBINATION VACCINES**



# General information

Diphtheria-Tetanus-Pertussis, Hepatitis B, Haemophilus influenzae type B and combination vaccines

## WHO RECOMMENDATIONS

- Diphtheria-Tetanus-Pertussis (DTP) vaccines have constituted the cornerstone of routine immunisation since the founding of the Expanded Programme on Immunisation (EPI) in 1974.
- Hepatitis B (HepB) vaccines were first prequalified by WHO in 1987, and first recommended for use in all national immunisation programmes in 1992.<sup>29</sup> These recommendations were further strengthened in 2004<sup>30</sup> and again in 2009.
- Haemophilus influenzae type B (Hib) vaccines were first prequalified and recommended by WHO in 1998.<sup>31</sup> The most recent recommendations from November 2006 state that all countries should introduce Hib into their routine immunisation programmes, starting the three-dose schedule for infants in line with DTP vaccination at six weeks of age.<sup>32</sup>
- Scarce data on HepB and Hib disease burdens in developing countries contributed to slow uptake of these relatively expensive vaccines into national immunisation schedules, even after WHO recommended their introduction.<sup>33, 34</sup> After its creation in 1999, one of GAVI's first priorities was to help make HepB and Hib-containing vaccines available to lower-income countries.<sup>35</sup>

## PRODUCTS AND MANUFACTURERS

- The first Diphtheria-Tetanus-Pertussis (DTP) trivalent combination vaccine was developed in the United States in 1942.<sup>36, 37</sup> DTP vaccines combine three of the six antigens that constituted the original Expanded Programme on Immunisation.<sup>38</sup> They are available in liquid form in one-dose, ten-dose, and 20-dose vials.
- While the U.S. and many European countries use an acellular pertussis vaccine (DTaP), UNICEF and PAHO almost exclusively procure whole cell pertussis vaccines (DTP). Acellular pertussis vaccines are associated with fewer adverse events, such as localised pain and fever.<sup>39</sup> Whole cell pertussis vaccines, however, have been shown through clinical trials to confer higher levels of efficacy against pertussis than their acellular counterparts with a three-shot schedule, particularly when combined with other antigens.<sup>40, 41</sup>
- Current WHO-prequalified DTP manufacturers include Bio Farma, Sanofi Pasteur, and Serum Institute of India. DTP production has been reduced as countries have increasingly switched to pentavalent (DTP-HepB-Hib).
- Monovalent recombinant HepB and Hib conjugate vaccines came on the market in industrialised countries in 1986<sup>42</sup> and 1991<sup>43</sup> respectively and were quickly integrated into immunisation schedules. There are 11 manufacturers that have been prequalified for monovalent HepB and/or Hib production.
- Vaccines against HepB and Hib were combined with DTP or DTaP vaccines in the late 1990s, with the goal of expanding the protection offered through traditional routine immunisation, either as tetravalent (DTP-HepB or DTP-Hib) or as pentavalent (DTP-HepB-Hib) vaccines.
- GSK was the first to license a DTP-HepB combination vaccine in 1996, which was WHO prequalified in 1998.
- This vaccine was subsequently shown to be effective when administered with GSK's Hib vaccine<sup>44</sup> (which was also WHO prequalified in 1998), resulting in the first pentavalent vaccine to provide protection against all five antigens. GSK held a monopoly over pentavalent sales to UNICEF until 2006.
- Current WHO-prequalified pentavalent manufacturers are Bernal Biotech Korea Corporation of Crucell (one-dose liquid vial), Biological E Limited (one-dose and ten-dose liquid/lyophilised), GlaxoSmithKline (one-dose and two-dose liquid/lyophilised, one-dose liquid), and Serum Institute of India (one-dose, two-dose, and ten-dose liquid/lyophilised, and one-dose, two-dose and ten-dose liquid).

## DOSING SCHEDULES AND PRESENTATIONS

- The World Health Organization recommends that all infants receive three primary doses of DTP at six, ten, and 14 weeks of age. Hib dosage is recommended according to the same schedule as traditional DTP.
- The first dose of Hepatitis B should be given within 24 hours of birth, but no real programmatic intervention has been developed to bring this to scale due to the lack of information on prevalence of HepB in pregnant women. Additionally, in many countries where mothers rarely give birth in a health facility the HepB birth dose is difficult to implement. After HepB birth dose, two to three further infant doses are recommended, integrated into the DTP schedule, or administered through pentavalent.<sup>45</sup>
- Monovalent HepB, monovalent Hib and tetravalent vaccines are available in vials containing from one to 20 doses. Pentavalent vaccines are available in one- and two-dose vials, as well as recently prequalified ten-dose vials.
- Hib-containing vaccines are available in liquid or lyophilised formulations, while DTP-HepB or monovalent HepB are only liquid formulations. Pentavalent vaccines are available in both liquid and liquid/lyophilised combination formulations. Fully liquid vaccines do not require reconstitution by a health care worker, and are often lower-volume.



# Prices

Diphtheria-Tetanus-Pertussis, Hepatitis B, Haemophilus influenzae type B and combination vaccines

## DTP VACCINES

The cost of DTP is relatively low, with UNICEF paying between \$0.14 and \$0.42 per dose in 2011.<sup>46</sup> Vaccines containing whole-cell

pertussis antigens are also much less costly – between 1991 and 1997, while the U.S. was transitioning to DTaP, the CDC paid approximately

twice as much per dose, for vaccines with acellular rather than whole cell pertussis components.<sup>47</sup>

## HEPATITIS B VACCINES

Early recombinant vaccines against HepB by GSK and Merck were first sold in wealthy markets for \$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.<sup>48</sup>

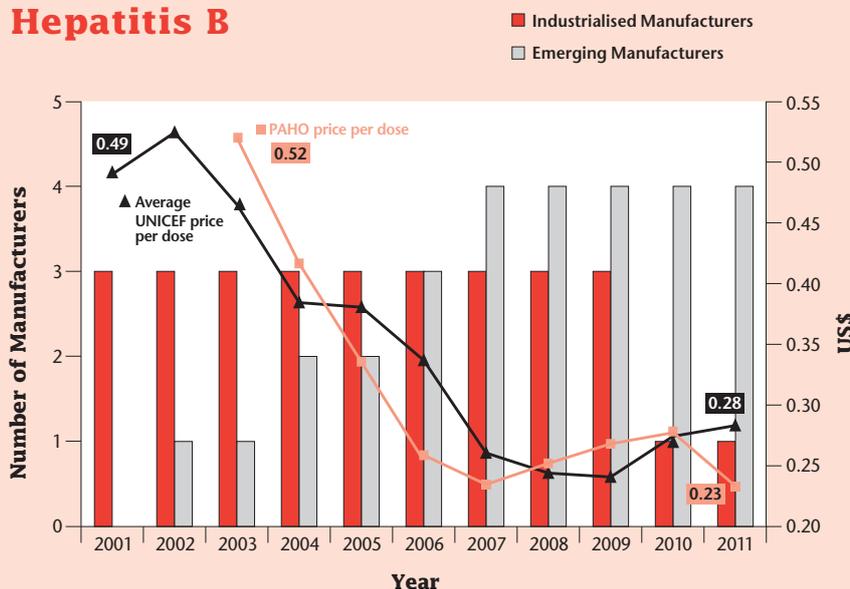
Even when lower-cost producers came on the market at prices as low as \$1.00 a dose, developing countries still considered them expensive compared to the standard EPI package.<sup>48</sup> However, when GAVI started to purchase HepB

vaccines, the price was already low by industrialised country standards, and the market was at a stage when more suppliers were primed to begin production and bring prices down through increased competition.

Once GAVI started supporting the purchase of new and under-utilised vaccines, the developing country market for Hepatitis B vaccines grew – and at a much faster rate than the market for Hib. In the early 2000s, most GAVI countries opted to first introduce only monovalent Hepatitis B, or a DTP-HepB combination, and later switched to a pentavalent vaccine to include Hib.<sup>49</sup>

UNICEF was able to obtain price reductions for monovalent HepB early on in GAVI's history as more companies had products prequalified. In 2001, only four monovalent product presentations were sold to UNICEF from three producers, with prices ranging from \$0.31 per dose for a ten-dose vial to \$0.68 per dose for a one-dose vial. By 2004, UNICEF was procuring monovalent Hep B from five manufacturers, and more products in multi-dose vials had entered the market. By 2007, most multi-dose vials were selling to UNICEF for between \$0.20 and \$0.25 per dose. One-dose vials ranged from \$0.23 for PAHO, to \$0.27 (Crucell), and \$0.40 (LG Life Sciences) for UNICEF.

### Hepatitis B



Note: The number of manufacturers is based upon those from which UNICEF procured Hep B vaccine in a given year.

### Hepatitis B prices – the highlights:

- The market has matured in the past decade, with lower prices following the presence of greater competition from multiple suppliers.
- Low prices could mean limited profits for manufacturers, possibly leading to the market exit of industrialised country suppliers.
- There is possible room for a secondary market of specialised products, such as single-dose microneedle to be administered by community health workers.

## HIB VACCINES

The Hib vaccine is the newest of the five vaccines contained in pentavalent, and has always been the most expensive component of the five. The conjugate technology necessary for its production contributes to its higher cost.

When PAHO started purchasing monovalent Hib in 1999, the lowest price per dose it could obtain was \$2.18. In comparison, the PAHO price per dose for a DTP vaccine the same year was less than \$0.07.

The PAHO price for monovalent Hib continued to rise during the 2000s, outpacing inflation, possibly due to low demand for monovalent Hib in comparison to pentavalent vaccines – most countries in the PAHO

region having introduced pentavalent.<sup>50</sup> UNICEF also procures very low volumes of monovalent Hib and DTP-Hib vaccines in comparison to pentavalent vaccine—in 2010 UNICEF procured 97.5 million doses of pentavalent, and only 3.7 million doses of DTP-Hib.

It's only after the first emerging country producer, Serum Institute of India, was prequalified that prices paid by PAHO for the monovalent lyophilised Hib product began to fall. The PAHO average weighted price per dose (based on purchases of Serum, GSK and Sanofi products) fell

from \$3.45 in 2009 to \$2.25 in 2010 and further to \$2.00 in 2011. On the other hand, the average price per dose of liquid Hib rose from \$3.20 in 2010 to \$3.60 in 2011, despite the 2010 prequalification of a Cuban manufacturer, Center for Genetic Engineering and Biotechnology.

## PENTAVALENT VACCINES

The high price of Hib has meant that pentavalent price reductions were neither as rapid nor as substantial as anticipated.<sup>51</sup> In addition, with GSK the only player in the market until the mid-2000s, there was no competitive pressure on price. While GSK held a monopoly, pentavalent prices offered to UNICEF never dropped below \$3.10 a dose, and in some years were as high as \$3.65. The arrival in 2006 of products from Crucell, a manufacturer which produces in South Korea, did not bring down prices—in fact, Crucell's pentavalent prices have been typically higher than GSK's every

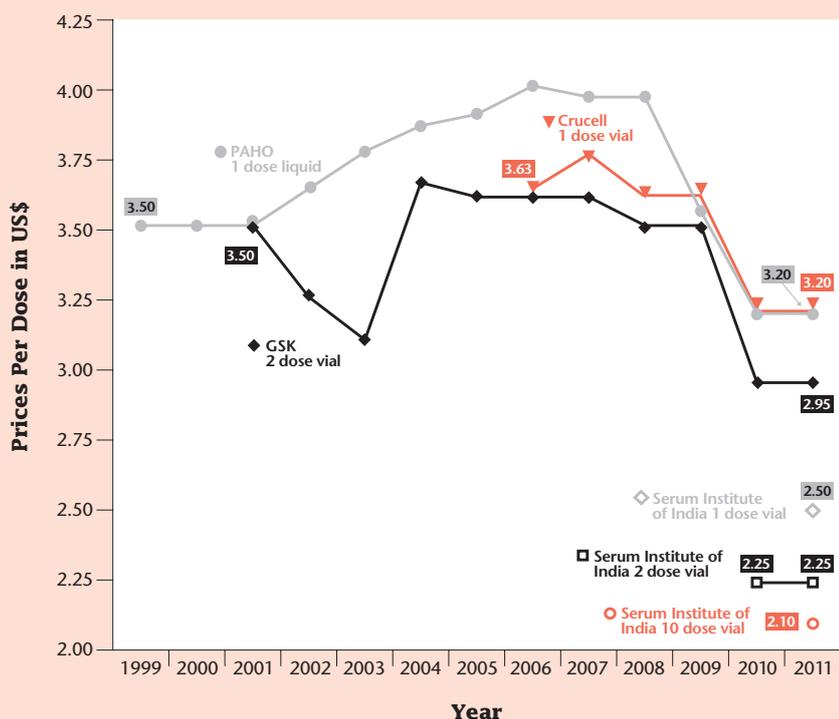
year since 2007. GSK's product is a two-dose lyophilised, while Crucell's product is a single-dose liquid presentation.

It was not until the entrance of emerging-market suppliers that prices gradually started to come down, though in 2008, only one of two new Indian suppliers—Shantha Biotechnics—offered a lower price of \$2.90, while Panacea Biotec took advantage of the oligopoly market by offering a \$3.60 price similar to GSK and Crucell. GSK, Crucell, and Panacea only dropped their prices in response to the Serum Institute of India

coming on the market in 2010 with a pentavalent vaccine priced at \$2.25.

Demand for pentavalent vaccine in 2010 increased significantly, therefore some suppliers were willing to offer additional discounts. Serum announced further pentavalent price reductions for UNICEF, to \$1.75 a dose for its recently prequalified liquid ten-dose vial.<sup>52</sup> Other manufacturers offer only one- or two-dose vials. The impact of having multiple suppliers, particularly those from emerging markets, highlights the significant savings that can be achieved when competition exists.

### Pentavalent prices for UNICEF & PAHO, 1999–2011



**Notes:** UNICEF prices are listed by manufacturer. All product formulations are liquid, with the exception of the GSK and Serum two-dose vial (lyophilised).

### Pentavalent prices—the highlights:

- The market is still developing as new suppliers are being prequalified, e.g. Biological E Limited received prequalification for a pentavalent product in August 2011 (and price data is not yet published).
- The market first suffered from a lack of competition, followed by a lack of vaccine security.
- The number of doses per vial has had an impact on price; multi-dose vials are less expensive on a per dose basis.
- Widespread introduction of HepB and Hib in developing countries has been a centrepiece of GAVI success during its first decade of activity. However, these product introductions will be difficult to sustain unless prices of vaccines containing HepB and Hib reach a level whereby countries can self-pay.

The number of competing suppliers of pentavalent has in recent years been reduced as a result of quality issues. In October 2010, Crucell, UNICEF's largest supplier of pentavalent, announced that batches of its vaccine may have been produced using unsterile equipment

following power outages at their production facilities.<sup>53</sup> Crucell was able to restart production following a WHO investigation. In recent years, Shantha and Panacea have both had their pentavalent vaccines de-listed from WHO prequalification status. The Shantha product, Shan5, was

suspended and subsequently de-listed from WHO prequalification in 2010.<sup>54</sup> Panacea's HepB and Hib-containing vaccines including its pentavalent vaccine, Easyfive, were delisted in 2011 following a WHO site audit that showed inadequate quality management systems.<sup>55</sup>



# Adaptation challenges

Diphtheria-Tetanus-Pertussis, Hepatitis B, Haemophilus influenzae type B and combination vaccines

Pentavalent introduction reduces the number of recommended shots per child that must be administered from nine to three. Fewer doses with a lower volume vaccine presentation also mean that less transport deliveries to health facilities are required, less time spent by health staff administering immunisations,

less discomfort for children and greater convenience for caretakers.

In some countries with limited health care infrastructure and a lack of healthcare workers, in hard-to-reach districts a stable unidose presentation (with a microneedle that has a VVM)

would help expand the reach of EPI programmes. While stable unidose presentations will cost more, they would likely be cost-effective considering reduced logistics and human resource costs as well as reduced disease burden and deaths in the population that has so far remained unvaccinated.

## COLD CHAIN LOGISTICS

Because pentavalent has limited heat stability and only lasts one to two weeks outside of the cold chain at temperatures up to 37°C (although it is recommended that vaccines remain within the cold chain until time of administration), a functioning cold chain is an essential element of successful vaccine introduction.

Ethiopia, for example, which introduced liquid pentavalent in 2007, increased its central refrigeration volume by 106%, and saw the frequency of

vaccine transportation approximately double at national and regional levels. While GAVI partners provide one-time grants to fund the costs of system expansion, increased costs for budget items such as vaccine transportation are and will continue to be borne by the government.<sup>56</sup>

The cold chain requirements for pentavalent were one reason that some countries first introduced a DTP-HepB combination or monovalent HepB, and later switched to pentavalent.

Unlike pentavalent, the DTP-HepB vaccine was available in a multi-dose vial at the time GAVI started to offer countries support, and required approximately the same cold chain capacity as multi-dose DTP vials that countries were already using. Some suppliers now provide pentavalent vaccine in multi-dose presentations, reducing the need for additional cold chain space.

## PRESENTATIONS: LIQUID VS. LYOPHILISED AND SINGLE-VS. MULTI-DOSE VIALS

The slow uptake of pentavalent was hindered by a number of factors, including the lack of supply capacity, lack of a global recommendation for Hib vaccination, and the lack of a fully liquid vaccine. The early pentavalent vaccines were liquid-lyophilised combination vaccines – the freeze-dried Hib element came in a separate vial from the liquid DTP-HepB combination, and needed to be reconstituted

before being administered to a child. This not only required extra training of health staff, but increased the amount of time required for a health worker to prepare the vaccine for administration – one study showed that a liquid vaccine like DTP took an average of 36 seconds to draw up into a syringe, while reconstituting the lyophilised pentavalent took over twice as long.<sup>57</sup> Additional preparation time

for health care workers means reducing the number of children who can be immunised in a day.

Now that Serum's liquid vaccine in a ten-dose vial has been WHO prequalified, pentavalent is finally attainable at a similar volume-per-dose as a multi-dose vial DTP product, easing the burden on a country's cold chain and delivery system.

## DOSING SCHEDULES

Finally, a key barrier to increasing coverage with these vaccines is the need for three doses over a specified period of time. A 2011 Demographic & Health Survey in Ethiopia showed

that national DTP coverage dropped from 64% with the first dose to 37% with the third dose.<sup>58</sup> The development of a pentavalent combination vaccine that could be

delivered in fewer doses would likely have a dramatic impact on cost as well as coverage, as it would increase convenience for caretakers.

## Hepatitis B birth dose

Infants born to mothers with Hepatitis B are particularly at risk of acquiring the disease through peri-natal transmission, and also more likely to develop chronic disease related to Hepatitis B later in life.<sup>59,60</sup> The recommended “birth dose”, administered within the first 24 hours of a baby’s life, is 90% effective in halting this route of transmission.<sup>61</sup> But without a stable, easy-to-deliver product, it will be difficult to reach children born outside of the healthcare system, which account for over half the world’s births.

Some countries have piloted innovative strategies. In 2002, the Indonesian government worked with the Program for Appropriate Technology in Health (PATH) to train

traditional midwives to administer the HepB birth dose to babies they deliver in homes, using PATH-developed Uniject technology. Midwives were given monthly supplies of single-dose, ready-to-use vaccines in Uniject packaging. Because HepB vaccine is heat-stable for up to 30 days outside cold chain, midwives did not need to refrigerate the vaccines. Uniject technology also did not require midwives to measure the dosage or prepare the vaccine, simplifying administration.<sup>63</sup>

The concept was successfully tested, increasing birth dose rates from 5% to 52%.<sup>64</sup> These results inspired the Indonesian government to implement Uniject administration of the birth dose on a nationwide scale in 2002,<sup>65</sup> producing similar

coverage levels on a national scale by 2004.<sup>63</sup> Positive improvements from similar strategies have also been reported in other parts of Asia.<sup>66</sup>

While single-dose microneedle products are more expensive than traditional Hepatitis B vaccine vials, reduced wastage on a programme level and delivery by community health workers instead of health care professionals offer potential for programmatic cost savings.<sup>67</sup> According to producers, however, the existing Uniject product is problematic due to wastage in the product-filling process. There is need to build on the potential for programmatic success by developing the next generation of single-dose microneedle products.

## Adaptation challenges—the highlights:

- More flexibility built into EPI schedules and broader product presentation would allow countries to create a more customised approach to their immunisation needs, and improve the reach of vaccination programmes.
- There is a need to create links between programmatic challenges and new product adaptation/development, such as the Uniject experience in Indonesia demonstrates.
- Both governments and donors need to be ready to pay higher product prices for easier-to-administer products when this will mean reaching children that are currently unreached. Higher prices could be offset by reduced logistics and human resource costs as well as lower mortality and morbidity in populations that are so far unreached.



❖❖❖ **MEASLES-CONTAINING  
VACCINES, WITH RUBELLA  
AND MUMPS**



# General information

Measles-containing vaccines, with Rubella and Mumps

## WHO RECOMMENDATIONS

- Vaccination against measles has been included in the Expanded Programme on Immunization (EPI) since its inception in 1974.
- Mumps vaccines have been available since the 1960s and are only recommended for use in countries with effective EPI programmes. When countries decide to include mumps in the schedule, it is recommended that it be done in combination with measles and rubella.
- Measles vaccination gained further momentum in 2001 with the creation of the Measles Initiative, supported by WHO, UNICEF, American Red Cross, U.S. CDC, and the United Nations Foundation. From 2000 to 2010, this initiative led to an estimated 74% global reduction in measles-related mortality.<sup>68</sup>
- In 2011, WHO recommended the inclusion of rubella vaccine in EPI programmes. In November 2011, GAVI announced it would open a window of support for countries introducing rubella vaccination. Correspondingly, in 2012 the Measles Initiative integrated rubella into its strategic plan, refocusing its efforts on both measles and rubella elimination.

## PRODUCTS AND MANUFACTURERS

- The first measles vaccine was licensed in the U.S. in 1963 by Merck. In 1968, Merck introduced Attenuvax from the Moraten measles strain. Nine other U.S. and European pharmaceutical companies subsequently marketed products.<sup>69</sup>
- Several manufacturers outside of the U.S. and Europe also produce measles vaccine. Serum Institute of India introduced a vaccine in 1989 that was prequalified by WHO in 1993. Biofarma, an Indonesian pharmaceutical company, was prequalified in 1997. The Governmental Pharmaceutical Organization Merieux Biological Products Company of Thailand gained prequalification status in 2010. With Sanofi Pasteur's product, there are four WHO-prequalified measles producers.
- There are currently two WHO-prequalified producers of Measles-Rubella (MR) vaccine. The Serum Institute of India was prequalified in 2000 and produces one-dose, two-dose, five-dose, and ten-dose vials (lyophilised and water for injection diluent). Crucell's MoRu-Viraten became prequalified in 2004, although it had been marketed since 1986. Crucell, however, recently decided to exit the market for MR vaccines, leaving Serum Institute as the sole supplier.
- The first measles, mumps, and rubella (MMR) vaccine was introduced by Merck in 1971, currently known as M-M-R II. Currently three other manufacturers produce MMR. Products come in one-dose, two-dose, five-dose and ten-dose vials.

## DOSING SCHEDULES AND PRESENTATIONS

- WHO recommends that all children receive two doses of measles vaccine.
- In countries with ongoing transmission, the initial dose should be given as soon as possible after the loss of the protective maternal antibody, ideally at the age of nine months, with the second dose given at least one month after the first dose, ideally at 15 to 18 months of age.
- In countries with low measles transmission, that are near elimination, and where the first dose of MCV is given at age 12 months, the age of the second dose of measles vaccine is left to authorities to determine the best timing to achieve the highest coverage possible.
- The efficacy of one dose of measles vaccine given at nine months of age is approximately 85 to 90%. The efficacy increases to 99% when the first dose is given at 12 months.<sup>70</sup> Children who fail to respond to the first dose of vaccine nearly universally acquire immunity following a second dose.<sup>70</sup>
- One dose of rubella vaccine is recommended. Countries including rubella vaccine in their schedules are recommended to administer combined measles-rubella vaccine, at the same age as the first dose of measles.
- Measles-containing vaccines (MCVs) come in a variety of multi-dose presentations; all presentations are lyophilised with a diluent.



# Prices

Measles-containing vaccines, with Rubella and Mumps

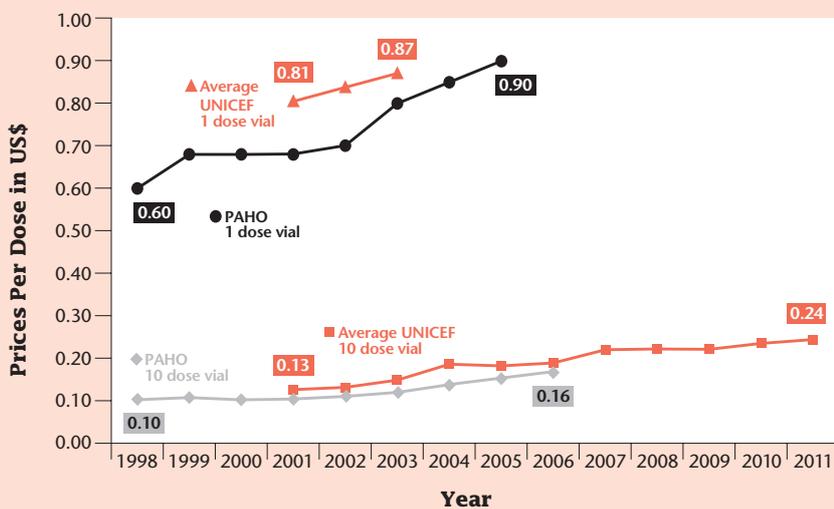
## MEASLES MONOVALENT VACCINE

Despite the number of producers, the price of measles monovalent vaccine has gradually trended up over the past decade, with 2010 prices nearly double or triple those in 2000, before adjustment for inflation. This may be due to decreasing demand for measles monovalent vaccine, as more

immunisation programmes shift to using other MCVs such as MR and MMR. The PAHO region, for example, where many countries transitioned during the late 1990s to MR and MMR vaccines to meet regional disease elimination targets, stopped procuring measles monovalent vaccine after 2006.

The price for measles monovalent vaccines is likely to increase as more countries transition to measles-rubella vaccine, particularly in light of the 2011 WHO recommendation to include rubella in all national immunisation programmes.

### Measles prices, UNICEF & PAHO 1998–2011



### Measles prices – the highlights:

- With multiple emerging country manufacturers, the price of the measles monovalent vaccine is relatively low, despite an upward trend.
- Serum Institute controls bulk of market which is a concern for supply security and future price development.
- As demand shifts to combination vaccines (MR, MMR), prices are likely to continue on an upward trend.
- There is a significant price differential between monodose vials and multi-dose vials; single-dose vials cost six to nine times more than ten-dose vials.

## MEASLES AND RUBELLA VACCINE

While approximately twice the price of measles monovalent vaccine, MR is still a relatively inexpensive vaccine compared to others.

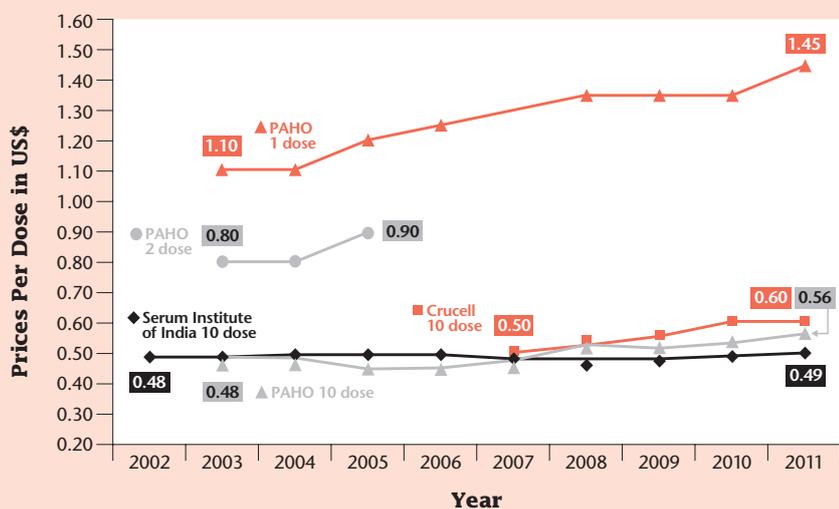
As with the measles monovalent vaccine, multi-dose vials are significantly more affordable: single-dose vials cost more than double that of the ten-dose vials. Despite the lack of robust competition,

both suppliers have offered ten-dose vials at comparable prices and the price has remained relatively stable over the past decade. Crucell has recently, however, decided to exit the measles and measles-rubella market; the impact of this on price is yet to be seen.

With recent WHO recommendations to include rubella vaccine in EPI

programmes, and GAVI promises of financial support, the anticipated increase in demand may prompt additional suppliers to enter the MR market. The low price of the vaccine, however, will likely make it unattractive to developed country-based multinational companies.

**Measles and Rubella prices, UNICEF & PAHO 2002-2011**



### Measles and Rubella prices – the highlights:

- The shift to include rubella vaccination in routine immunisation programs may drive up prices of MR vaccines in the short term as demand increases.
- The impact on price of a recent decision by one manufacturer (Crucell) to exit the measles and measles-rubella market has yet to be seen.
- However, over the middle-term, if more low-cost competitors can be enticed into the market, price reductions should be possible.



# Adaptation challenges

Measles-containing vaccines, with Rubella and Mumps

## COLD CHAIN LOGISTICS

Measles-containing vaccines are relatively heat-stable, although the vaccine needs to be discarded within six hours of reconstitution (or if the VVM expires, whichever

comes first). All WHO-prequalified measles monovalent and measles-rubella vaccines have a VVM of 14, meaning that they can last up to 14 days outside the cold chain at

a temperature of up to 37°C (although it is recommended that vaccines remain within the cold chain until time of administration).

## DOSING SCHEDULES

As breastfed newborn infants are protected from measles virus from maternal antibodies and because newborn's immune systems are not mature enough to mount an appropriate response to measles vaccination before the age of six months, the first dose of measles vaccine is recommended at the age of nine months.<sup>72</sup> As around 15% of children receiving the dose at the age of nine months will not have an adequate response, an additional dose is recommended for all children at least one month after the initial dose.

Unlike DTP, Hib, pneumococcal, and Hepatitis B vaccines which are given during the same timeframe, measles vaccination occurs separately and independent of other vaccinations (with the exception of countries where yellow fever vaccine is in the national immunisation schedule, and also administered at nine months). In countries lacking well-organised routine immunisation services, the challenge to deliver MCV can be daunting.

Two inhalation products are in the pipeline for facilitating measles vaccine administration. A wet mist inhalation

product has shown good efficacy but requires energy to generate aerosols, and the liquid vaccine used in this presentation must be freshly made up before administration. A dry powder administration method which uses a reservoir-mouthpiece filled with vaccine powder aerosol for inhalation is also under development. Initial results of the dry powder administration method in animal studies demonstrate that it can induce an immune response at least equivalent to the traditional injection route. Inhalation products have a high potential for expanding the reach of measles vaccination.<sup>73,74</sup>

### Adaptation challenges—the highlights:

- The unique dosing schedule of measles vaccine requires countries to recapture children at an age when other vaccinations are not given. Adaptation challenges, and not prices, act as the key barrier to wider coverage.
- Though MCV is relatively heat-stable, vaccine must be quickly used after reconstitution or otherwise discarded. Additional support is needed to expedite work on vaccine stability and alternative delivery mechanisms.



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••••• **MENINGOCOCCAL  
MENINGITIS VACCINES**



# General information

## Meningococcal Meningitis vaccines

### WHO RECOMMENDATIONS

- The WHO strategy for vaccination against meningococcal disease varies, according to the epidemiological context of a geographical region or specific outbreak. WHO promotes epidemic preparedness through surveillance, as well as prevention and response to epidemics by vaccination, where appropriate.
- Polysaccharide vaccines can be used for children over two years of age to control outbreaks in countries which have not yet introduced conjugate vaccines. Meningitis conjugate vaccines are preferred.
- Conjugate vaccines offer long-term protection, as well as induce herd immunity, and are therefore recommended preventatively as part of routine immunisation in settings where an appropriate vaccine exists for local serotypes.<sup>75,76</sup>
- Countries with endemic meningococcal disease, such as the 25 countries that make up the African Meningitis Belt, are at particular risk of meningitis, and have recently begun introducing large scale preventative vaccination campaigns with MenAfriVac, a conjugate vaccine against meningitis A.<sup>77</sup>

### PRODUCTS AND MANUFACTURERS

- The first polysaccharide vaccines against meningococcal meningitis groups A and C were developed at the Walter Reed Military Hospital in the U.S. in the late 1960s.<sup>78</sup> Sanofi Pasteur was the first manufacturer to license a monovalent meningitis A vaccine in 1974.
- Bivalent A+C polysaccharide vaccines were developed by Sanofi Pasteur in 1975,<sup>79</sup> and received WHO prequalification in the aftermath of the 1996 and 1997 meningococcal epidemics in Africa. GlaxoSmithKline (GSK) also produced a bivalent polysaccharide A+C. Following a Sanofi decision to temporarily suspend production, in 2006 WHO approached Finlay Institute of Cuba and Bio-Manguinhos of Brazil to ensure an alternative supply. The resulting Bio-Manguinhos vaccine was subsequently WHO prequalified in 2007.<sup>80</sup> Sanofi subsequently resumed sales of their bivalent vaccine to UNICEF.
- Addressing the unreliable supply of vaccines effective against W135 and with funding provided from ICG partners, GSK developed a trivalent polysaccharide with A, C, and W135 serotypes exclusively for use in Meningitis Belt countries. Regulatory approval was rapid and the first products were rolled out in January 2003, followed by WHO prequalification in 2005.<sup>81</sup> In 2010, GSK decided to halt production of this trivalent vaccine.
- The new meningitis A vaccine (MenAfriVac), prequalified by WHO in 2010, is the only WHO-prequalified conjugate vaccine against meningococcal disease. Individual national regulatory authorities have, however, also approved conjugate vaccines for meningitis C, and a tetravalent vaccine against A, C, W135 and Y.
- Tetravalent conjugate vaccines against A, C, W135 and Y meningitis have also been recently introduced in high-income markets. Sanofi Pasteur obtained U.S. FDA approval for a product in 2005,<sup>82</sup> and Novartis in 2010.<sup>83</sup> Novartis is awaiting approval for use of the vaccine in a younger age group. GSK is also awaiting regulatory approval of a tetravalent conjugate vaccine.

### DOSING SCHEDULES AND PRESENTATIONS

- WHO recommends vaccination against meningococcal disease in countries with high or intermediate endemic rates of meningitis, or in epidemic-prone areas. Vaccination is also recommended for defined high-risk groups.
- The dosing schedule is dependent upon the type of vaccine administered (conjugate or polysaccharide).
- Polysaccharide vaccines induce a short-lived immune response—booster shots are necessary every three years—and cannot be used in children under two years. Conjugate vaccines are preferred to polysaccharide vaccines.
- Since 2010, meningitis A conjugate vaccines have been progressively introduced in the Meningitis Belt through large scale vaccination campaigns that target people aged one to 29 years. The product is available in a ten-dose vial, and is administered through intramuscular injection.
- WHO-prequalified meningitis vaccines are available in 10-dose vials and come in lyophilised form.



# Prices

## Meningococcal Meningitis vaccines

Following the largest ever recorded meningococcal epidemics in Africa in 1996 and 1997, which resulted in the deaths of over 25,000 people, in 2000 WHO called for development of meningococcal conjugate vaccines to allow for more preventive responses to meningitis.<sup>84</sup>

The development of meningococcal conjugate vaccines significantly improved the impact of meningitis vaccination by stimulating a longer-

term immune response, eliminating the need for recurring booster shots. The conjugate vaccines could also be used in children as young as nine months—one of the age groups most vulnerable to the disease. These vaccines also contribute to “herd immunity” by halting bacterial transmission from the vaccinated to the unvaccinated, which is not the case for polysaccharides.

The development of conjugate vaccines created the potential to carry out

preventive, rather than reactive campaigns against meningococcal meningitis in countries facing recurrent epidemics. But although tetravalent conjugate vaccines (A, C, W-135 and Y) were approved in 2005 and 2010 these products were priced at a level that made them impractical for use in the public sector of Meningitis Belt countries. There was no tiered price for GAVI-eligible countries. The CDC lists the U.S. price as US\$68.12–\$82.12 between 2005–2011.

## THE MENINGITIS VACCINE PROJECT

The Meningitis Vaccine Project (MVP) was established in 2001 by PATH and WHO and received funding from the Bill and Melinda Gates Foundation.<sup>85</sup> After negotiating with several possible industrial partners, the MVP reached an agreement with Serum Institute of India to produce a new monovalent Meningitis A conjugate vaccine. In exchange for price and supply commitments, the Serum Institute benefitted from transfer of technology and know-how. Clinical trials were funded through PATH.

With the cooperation of Synco Bio Partners in the Netherlands, and the Center for Biologics Evaluation and Research of the U.S. Food and Drug

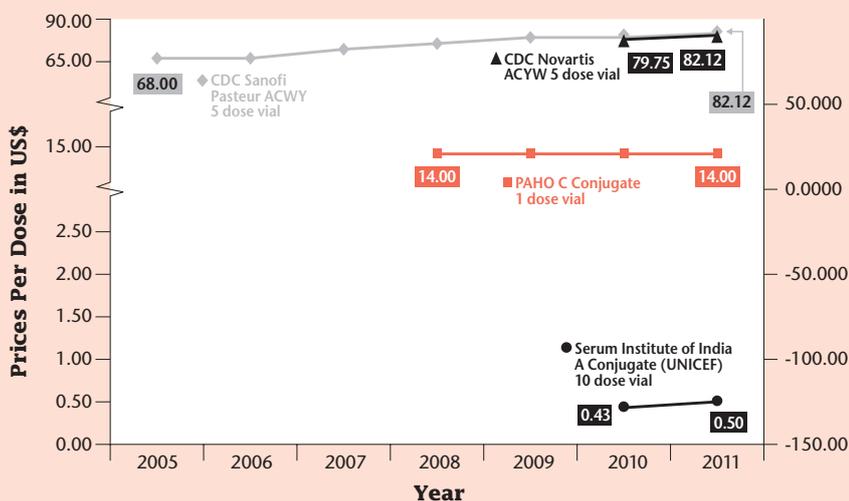
Administration (FDA), the Serum Institute initiated development of the vaccine in 2003. The total R&D costs for this vaccine were estimated to be about \$60 million, not including the cost of the manufacturing plant. The Serum Institute committed about \$15 million to the project.<sup>86</sup>

Following successful clinical trials, the conjugate A product, called MenAfriVac, received Indian regulatory approval and was WHO-prequalified in 2010. MenAfriVac was initially introduced before the 2010–2011 meningitis season in people aged one to 29 years in Burkina Faso, Mali and Niger.<sup>87</sup> The vaccine has successfully halted outbreaks in regions where

it was introduced, and has since been rolled out in other countries in the Meningitis Belt, such as Chad and Nigeria, with other countries planning to follow in coming years. By one estimate, the advent of a meningococcal conjugate vaccine for Africa could avert 7,100 deaths and 14,200 disabilities, and save over \$350 million over 10 years.<sup>88</sup>

UNICEF purchases the vaccine for \$0.50 per dose (2011 price). This is less than half the price of the Sanofi and Bio-Manguinhos bivalent A+C polysaccharide products. The product was almost a decade in the making, and today Serum is the sole supplier.

## Meningococcal Conjugate prices for UNICEF, PAHO & CDC 2005–2011



## Meningitis prices—the highlights:

- Tetravalent (A, C, W-135 and Y) vaccines have been developed by Sanofi Pasteur and Novartis with US FDA approvals in 2005 and 2010 respectively. The US CDC price in 2011 was \$82.12 per dose and there is so far no access programme or publicly communicated tiered price for GAVI-eligible or other developing countries.
- A meningitis conjugate A product was WHO prequalified in 2010 and was priced at \$0.50 per dose in 2011. This product is being rolled out in Meningitis Belt countries.



# Adaptation challenges

Meningococcal Meningitis vaccines

## COLD CHAIN LOGISTICS

MenAfriVac is stable for 30 days outside the cold chain (VVM 30), at temperatures up to 37°C, although all vaccines should be kept in the cold chain until administration. Its heat stability also creates potential

for alternative delivery strategies, such as leaving back-up supplies of vaccine at rural health facilities.

MenAfriVac is still, however, an injectable vaccine. For health centres unable to administer traditional

injections, if single-dose, microneedle formats were available, community health workers could deliver the vaccine ensuring a deeper reach into communities.

## SEROTYPES

One limiting characteristic of the new MenAfriVac is that it protects against only one strain of meningitis. While meningitis A continues to be the predominant serotype found in the Meningitis Belt, particularly in hyper-endemic countries,<sup>89</sup> the geographic distribution of serotypes is not static over time.

Outbreaks caused by W135 meningitis in West Africa in 2001–2002, and in various countries in 2011–2012, demonstrate that serotype prevalence needs to be followed carefully. There will be an ongoing need for new products as serotype disease burden is further documented.

Although additional products are currently available for additional serotypes, prices are prohibitively high. In order to develop these products at more affordable prices, partnerships similar to that of the Meningitis Vaccine Project collaboration need to be pursued.

### Adaptation challenges—the highlights:

- Conjugate vaccines offer potential for more predictable and larger demand from Africa, particularly for potential introduction in EPI.
- Multivalent conjugate vaccines which are needed for Africa are presently available in developed countries, but are priced prohibitively high and thus inaccessible to developing countries.
- The MenAfriVac project demonstrates the potential of “platforms” to facilitate transfer of technology and support all aspects of product development for an adapted, affordable product. The model should be replicated to harness the development potential and production capacity of low-cost producers.



 **PNEUMOCOCCAL  
CONJUGATE VACCINES**



# General information

## Pneumococcal conjugate vaccines

### WHO RECOMMENDATIONS

- In 2007, WHO recommended pneumococcal conjugate vaccine (PCV) for inclusion in national immunisation programmes.<sup>90</sup> The recommendation particularly encouraged PCV use in countries where mortality among children aged under five years is greater than 50 in 1,000 live births, or where more than 50,000 children die annually.
- WHO's policy setting body, the Strategic Advisory Group of Experts (SAGE), is presently reviewing its recommendations on the PCV dosing schedule.

### PRODUCTS AND MANUFACTURERS

- Current WHO-prequalified pneumococcal conjugate vaccines include a new ten-valent and 13-valent vaccine, as well as an older seven-valent vaccine.
- The first PCV to gain regulatory approval in the U.S. and Europe was Wyeth's Prevenar 7 (Wyeth has since been bought by Pfizer). Offering protection against seven pneumococcal serotypes common to industrialised countries, the product was designed to meet the pneumococcal disease burden of higher-income countries, preventing strains responsible for approximately 65–80% of pneumococcal disease in the U.S. and Europe.<sup>90</sup> The vaccine's efficacy in developing countries, however, was uncertain when it first came on the market.
- In 2003 and 2005, Wyeth conducted phase III clinical trials on a PCV9 candidate vaccine that added two serotypes prevalent in Africa. Trials were successfully conducted in South Africa and the Gambia.<sup>91</sup> Despite successful trial results, Wyeth abandoned PCV9 in favour of developing PCV-13, resulting in several years delay of access to a PCV for developing countries.
- WHO prequalification for Prevenar 7 did not occur until the end of 2009, almost a decade after the vaccine was first introduced in the U.S., and two years after the WHO recommendation. The delay in prequalifying the product was due to the presentation which was a pre-filled syringe deemed not suitable for developing countries.
- A new PCV, Synflorix, marketed by GlaxoSmithKline in a one-dose vial, was WHO prequalified in 2009. Synflorix protects against ten pneumococcal serotypes, and had only been approved by European regulatory authorities earlier that year, in April 2009.<sup>92</sup> In March 2010, a new presentation of Synflorix in a two-dose vial also received a WHO prequalification with some special conditions.<sup>93</sup> Since this product does not contain a preservative, which was unique for two-dose vial presentation, WHO recommended that countries using this presentation take special precautions, including increased surveillance. This restriction has meant that Synflorix has so far been introduced in very few GAVI-eligible countries.
- A newer iteration of the Pfizer vaccine, Prevenar 13, protecting against 13 pneumococcal serotypes and designed to replace PCV7, earned U.S. FDA approval in February 2010.<sup>94</sup> Prequalification by WHO followed in August 2010.
- The first GAVI-eligible countries to use PCV were the Gambia and Rwanda. These two countries received a donation from Pfizer of PCV7 beginning in 2009. PCV7 did not meet the set WHO requirements regarding a minimum number of serotypes contained in the vaccine.

### DOSING SCHEDULES AND PRESENTATIONS

- The recommended WHO dosing schedule is in the process of being reviewed by WHO's policy-setting body, SAGE.
- According to 2007 WHO guidelines, there are three acceptable schedules. Three doses of PCV at either six, ten and 14 weeks of age; or at two, four and six months of age; a booster shot at 12–15 months is recommended for the latter.<sup>90,95</sup> Or a two dose schedule before six months of age can be administered; a booster shot at nine to 15 months is recommended in this case.
- PCV products all come in liquid form.



# Prices

## Pneumococcal conjugate vaccines

The CDC first approved use of PCV7 in 2000, purchasing the vaccine for \$44.25 a dose. The CDC price for PCV7 continued to increase over the next decade—in 2009, before the CDC switched to purchasing Prevenar 13, PCV7 was \$71.04 a dose, bringing the total cost to vaccinate a child with three doses to \$213.12.

The WHO 2007 recommendation for PCV occurred before any vaccine was prequalified, and before a vaccine targeting key serotypes in developing countries had been developed.

Access to PCV10 and 13 have been largely supported by a financial mechanism called an Advance Market Commitment (AMC), initially imagined as a tool to stimulate innovation.

Following deliberations in 2007, an expert working group decided to pilot the first AMC for pneumococcal vaccines. But the pilot was not designed to stimulate R&D as the pneumococcal products were already in late stage development. The mechanism would rather be used to stimulate rapid scale-up of production and to speed up introduction of the vaccine in GAVI-eligible countries.

The pneumococcal AMC would only accept products that met certain specifications, pre-defined by WHO in a Target Product Profile (TPP). The TPP set a minimum standard for serotypes. While PCV7 did not meet this criteria, Synflorix and Prevenar 13 did.

The AMC had set an initial target price of PCV at \$2.00 per dose, meaning that this “tail price” would be the maximum long-term price paid to a supplier after the subsidy had been allocated. Finally the AMC locked in a tail price of \$3.50.

By the end of 2011 two firms, Pfizer and GSK, had agreed to sell the AMC 48% of the total number of units to be purchased through the AMC, entitling them each to receive \$360 million in top-up subsidy. The AMC negotiated a significant discount from the US price, but this price was above the price per dose price that could be achieved by emerging country producers selling multi-dose vials.

Prevenar 13 is Pfizer’s second best selling product, grossing \$2.82 billion in the first nine months of 2011.<sup>96</sup>

By 2015, 37 GAVI countries are scheduled to have introduced PCV. Because co-payments by governments for new vaccines are set at \$0.10 to \$0.30 a dose, national budgets are not yet unduly impacted by the AMC procurement strategy. Countries graduating from GAVI support, however, will be required to increase their co-financing payments as they approach graduation, after which they will no longer receive GAVI subsidies.

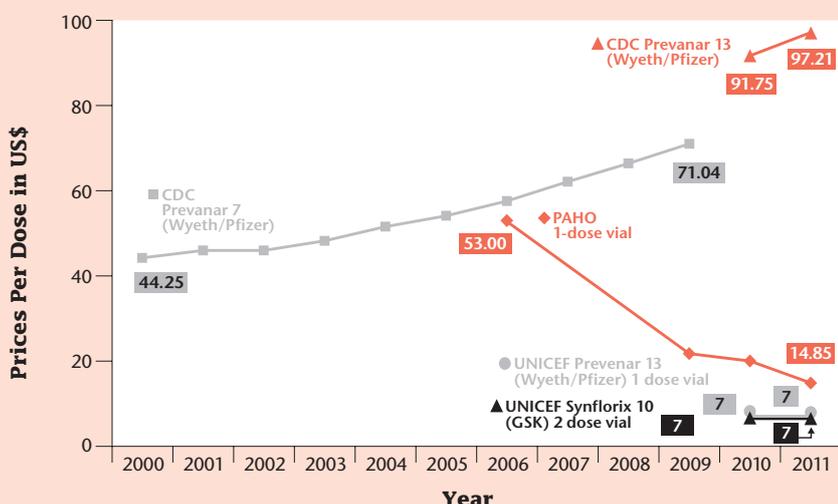
Honduras, for example, will graduate from GAVI support in 2015, though its 2009 average per capita income was only \$1,800.<sup>91</sup> With GAVI’s help, the country has introduced immunisation for both rotavirus and PCV, and currently pays

\$1.09 per child for the two vaccines. Once GAVI support ends (assuming prices remain stable), Honduras will have to pay \$25.50 per child—assuming it pays the PAHO, non-GAVI price, of \$7.50 per PCV dose—to which the cost of other routine immunisations must be added. In 2015, Honduras the country is projected to have a birth cohort of 202,000 children; at \$25.50 per child, vaccinating against rotavirus and PCV would cost an estimated \$5.1 million per year. Honduran authorities are hoping to get GSK’s approval to continue paying the GAVI price, even if the country will no longer be GAVI-eligible.

In addition, the prices GAVI negotiates set a default lowest global price, so if these prices are high, middle-income countries suffer the consequences too. For example, Brazil and Argentina pay more than \$14.00 a dose for PCV (these arrangements include things like technology transfer from the manufacturers and cold chain support). In South Africa, where per capita income is lower than both of these Latin American countries, the government pays \$25.00 a dose. South Africa also receives some support from Pfizer for their EPI programme.

While the AMC is enabling a quick rollout of PCV in GAVI countries, the cost of the AMC may outstrip both donors’ and countries’ ability to pay. From 2010–2025 the cost to GAVI, AMC donors and countries can be expected to range from \$9 to \$11 billion dollars.<sup>97</sup>

### Pneumococcal Conjugate Vaccine prices, UNICEF, PAHO & CDC 2000–2011



Note: The UNICEF Price of \$7.00 includes the AMC subsidy.

### Pneumococcal conjugate prices—the highlights:

- The current UNICEF price of \$7.00 (including AMC top up of \$3.50 per dose) is a substantial reduction from the US CDC price. However, this price is considerably higher than the \$2.00 target that competing companies have set.
- Because of lack of access to know-how, licences for production technology and an AMC mechanism that has favoured existing producers, there is not yet competition from low-cost producers, and none expected until 2016 at the earliest.



# Adaptation challenges

Pneumococcal conjugate vaccines

## DOSING SCHEDULES

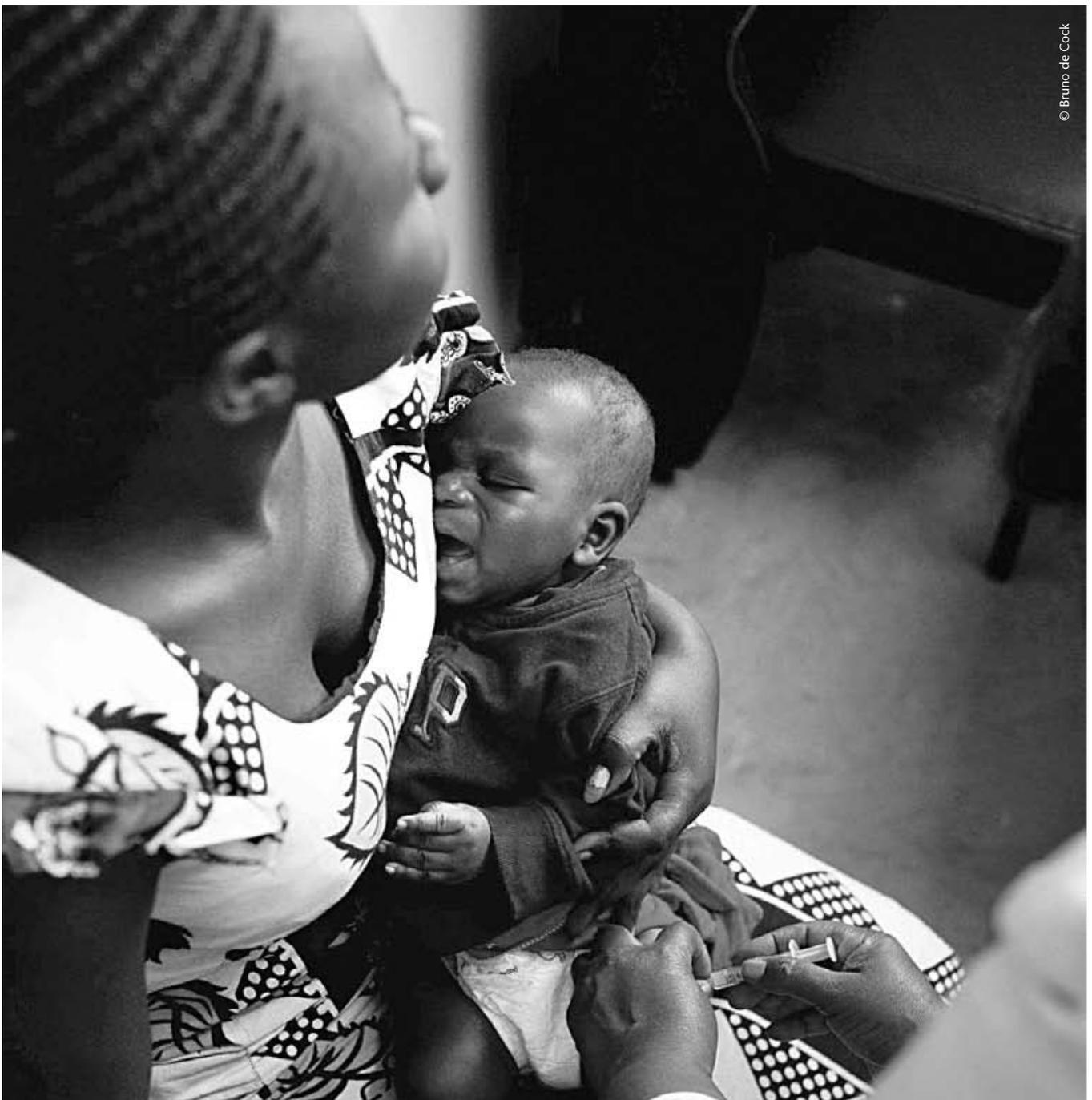
The dosing schedule of PCV aligns with the pentavalent vaccine, which allows countries to integrate PCV into existing programmes. PCV also has high heat stability; it can be used in a controlled temperature cold chain for 30 days at temperatures up to 37°C. The stability of this product gives some flexibility to EPI managers.

It is important to note that the pneumococcal AMC did not stimulate companies to conduct research or development to adapt dosing schedules and/or presentations of the vaccine. Work is still needed to explore the possibility of fewer required doses.

The research arm of MSF, Epicentre, is piloting a novel PCV approach in a

cluster randomised trial that will look at the feasibility and impact of vaccinating a population from birth to 14 years with one dose of PCV13. This trial is expected to start by the last quarter of 2012.

Simplified administration methods, such as through pre-filled microneedles, should also be developed for contexts with limited healthcare workers.



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 **ROTAVIRUS VACCINES**



# General information

## Rotavirus vaccines

### WHO RECOMMENDATIONS

- The first rotavirus vaccine was prequalified by WHO in 2007. In 2009, following efficacy studies with rotavirus vaccines in developing countries, the WHO Strategic Advisory Group of Experts on Immunisation (SAGE) recommended that rotavirus vaccines be included in all national immunisation programmes as part of a comprehensive strategy to control diarrhoeal diseases.<sup>98</sup>
- Rotavirus vaccines have experienced mixed uptake in developed countries. It is widely recommended but not always integrated into routine vaccination programmes. The vaccine first was introduced in PAHO countries in 2006. Developing countries outside the Americas have been slow to introduce the vaccine—Sudan was the first, with GAVI support, in 2011<sup>99</sup>—but GAVI plans to finance the vaccine's purchase for over 40 countries by 2015.<sup>100</sup>
- At the April 2012 meeting of WHO's policy setting body, SAGE, the dosing schedule for rotavirus vaccine was revised to remove previously recommended age restrictions. At the time of this publication, the official WHO recommendation had not yet been published.

### PRODUCTS AND MANUFACTURERS

- The first rotavirus vaccine, Rotashield, developed by American Home Products (formerly Wyeth-Ayerst Laboratories), came on the market in the U.S. in 1998, but was withdrawn following reports of vaccine-related intussusceptions.<sup>101</sup> The benefits of Rotashield introduction—in terms of lives saved—would have outweighed the effects of adverse events in developing countries,<sup>102</sup> but the product was permanently retired.
- Two new rotavirus vaccine products came on the market in 2006—GlaxoSmithKline's Rotarix and Merck, Sharpe and Dohme's Rotateq. Rotarix was first WHO prequalified in 2007 and Rotateq in 2008. Later versions of Rotarix were prequalified in 2009. Available vaccines offer protection against several, though not all, forms of rotavirus infection.

### DOSING SCHEDULES AND PRESENTATIONS

- Two doses of GSK's Rotarix and three doses of Merck's Rotateq are recommended, with the first dose administered at six to 15 weeks of age, and subsequent doses at four to ten week intervals.
- When WHO first recommended inclusion of rotavirus vaccine in all national immunisation programmes, the recommended dosing schedule was restricted to certain age groups to decrease the risk of intussusceptions. For both the GSK and Merck products, the first dose was to be administered by 15 weeks of age, while the final dose had to be administered by 32 weeks of age (approximately eight months). In April 2012, WHO's SAGE recommended to remove the age restrictions based upon evidence which showed that the risk of intussusceptions was outweighed by the additional lives that could be saved with rotavirus vaccination. The specific SAGE recommendation was not available at the time of this publication.
- Rotarix and Rotateq are both administered orally. GSK offers Rotarix in various one-dose presentations—a liquid dose available in an applicator or plastic tube, and a lyophilised vaccine with diluent. Merck's Rotateq is a liquid vaccine available in a one-dose tube.



# Prices

## Rotavirus vaccines

Rotavirus constitutes a significant burden of disease among children in all parts of the world. However, the first rotavirus vaccines were developed for wealthier markets and emerging markets such as in Latin America. Global sales in 2010 were over \$349 million<sup>103</sup> for GSK<sup>104</sup> and \$519 million for Merck.<sup>105</sup> Merck sold almost exclusively to wealthy markets, while 43% of GSK sales came from emerging markets.<sup>104</sup>

Since the first PAHO introduction in 2006, both products' prices in the region have remained at about \$15.00 for a full rotavirus immunisation course—less than ten percent of the price in wealthy markets. PAHO member states purchasing the vaccine almost exclusively introduced GSK's Rotarix, which requires fewer doses and is more heat-stable than the Merck vaccine.<sup>106</sup> The only PAHO countries to introduce the Merck product—Guyana and Nicaragua—were both GAVI countries, and in Nicaragua, the vaccine was supplied through a Merck donation in 2010.

Developing country introduction outside Latin America began in 2011. In September 2011, GAVI approved

an additional 16 country applications for rotavirus vaccine introduction. In addition to introduction in Sudan, GAVI has also supported rotavirus vaccine introduction in Nicaragua, Bolivia, Guyana and Honduras.

There have been calls for further research to determine the efficacy of both rotavirus vaccines against the dominant circulating rotavirus genotypes in developing countries, particularly in Africa.<sup>108</sup>

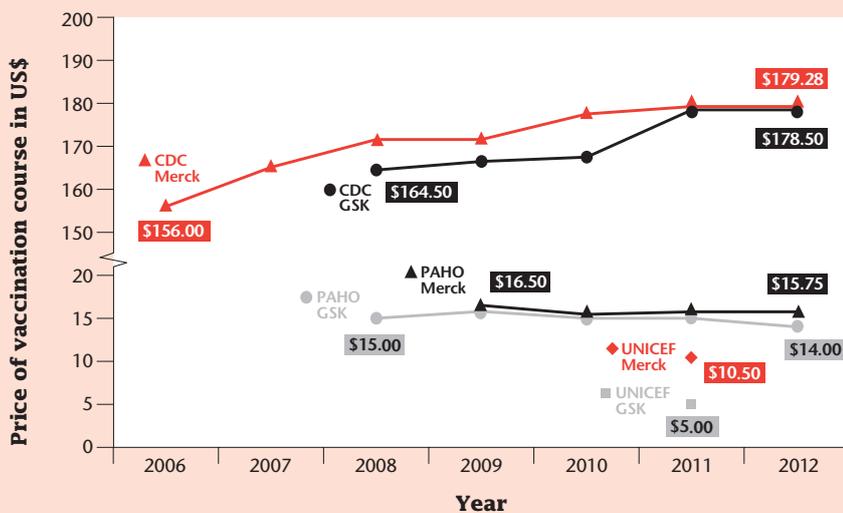
In June 2011, both GSK and Merck announced substantial rotavirus vaccine price reductions for GAVI-eligible countries. GSK reduced its price per dose from \$7.50 to \$2.50 (\$5.00 per course), and Merck reduced its price from \$5.00 a dose to \$3.50 (\$10.50 per course), following sales of 30 million doses. The contractual terms associated with the GSK rotavirus agreement include provisions for volume guarantees, denomination of contracts in euro currency and advance payment. These terms apply to part of a five year contract. The contracts with both Merck and GSK cover about 50% of GAVI demand for rotavirus vaccine for

the period 2012–2016.<sup>109</sup> These price reductions enhanced rotavirus vaccine affordability for GAVI, which plans to purchase for more than 40 countries by 2015.<sup>110</sup>

Two vaccine manufacturers in India, Serum Institute and Bharat Biotech, have rotavirus vaccines in development. Clinical trials are being supported by funding from the Gates Foundation, and the products are expected to reach the market within three years. The introduction of these new vaccines should result in lower prices—Bharat has announced it plans to price its vaccine at \$1.00 a dose, and hopes to bring the product to market by 2014.<sup>111</sup>

While the development of rotavirus vaccines has followed a traditional path—widespread introduction at lower prices for developing countries only after companies earn significant revenue in wealthy markets—increased demand from GAVI and a gradually more competitive market should make the introduction of rotavirus vaccines more affordable for GAVI-eligible countries.

### Rotavirus prices, UNICEF, PAHO & CDC 2006–2012



Notes: Price is for a full course of vaccination with two doses of GSK's Rotarix and three doses of Merck's Rotateq. UNICEF prices are those announced at the June 2011 GAVI pledging meeting.

### Rotavirus prices—the highlights:

- In exchange for advance payments, firm volume commitments, and a euro-denominated contract, GSK has offered UNICEF a significantly lower price than its competitor Merck.
- Lack of competition, particularly from emerging market producers, has so far meant unrealised potential for further price reductions.



# Adaptation challenges

Rotavirus vaccines

## COLD CHAIN LOGISTICS

No Vaccine Vial Monitor (VVM) technology has been approved for the Merck vaccine—the product insert reads that the vaccine should be discarded after 12 hours if exposed to temperatures of 26–30°C; it can be used for up to 48 hours if at 9–25°C.<sup>124</sup> This is not practical in many GAVI countries, particularly in more rural areas where it is difficult to maintain a cold chain. In an attempt to remedy this limitation, Merck is exploring the development of a heat-stable, low-volume, less expensive version of their rotavirus vaccine through Hilleman Laboratories, a joint venture

sponsored by the Wellcome Trust and Merck, based in New Delhi, India.<sup>113</sup>

Both existing rotavirus vaccine products are high-volume compared to other traditional or routine immunisations—Rotarix and Rotateq presentations used by GAVI require a minimum of 17.1cm<sup>3</sup> and 46.3cm<sup>3</sup> per dose, respectively.<sup>114,115</sup> In comparison, the lowest cold chain volume for a GAVI pneumococcal vaccine is only 4.8cm<sup>3</sup> per dose.<sup>116</sup>

Bulkiness, combined with the vaccines' moderate-to-low heat stability, places

a burden on countries to expand and maintain adequate cold chain capacity for rotavirus introduction. WHO estimates that national-level cold chain capacity is adequate for both rotavirus and pneumococcal introduction in only half of all GAVI-eligible countries. Only 63–67% of GAVI countries have adequate capacity to introduce either pneumococcal or rotavirus vaccine. This does not account for cold chain capacity at regional or district level, where storage space and access to electricity is more limited.

## DISEASE EPIDEMIOLOGY

Rotavirus has a number of different genotypes. The two WHO-prequalified vaccines, Rotarix and Rotateq, are made of one and five rotavirus genotypes, respectively; the genotypes included in both products are the predominant

rotavirus strains found in industrialised countries. Research on rotavirus genotypes in developing countries is evolving. Initial research results indicate that the diversity of genotypes found in some sub-Saharan countries

may require a refined rotavirus vaccine that is more appropriate for local rotavirus epidemiology.<sup>118,119</sup> As new data emerges, it will be important that vaccines be modified to be most efficacious for those contexts.

## DOSING SCHEDULES

Both WHO-prequalified vaccines have a minimum age of primary vaccination of six weeks, and a maximum age of first dose at 15 weeks. Rotavirus vaccine delivery could fit in with a routine immunisation schedule that is administered on time, however, a child first seen for immunisation at later than 15 weeks of age will miss out on receiving rotavirus vaccines. With the current WHO rotavirus guidelines, the maximum age for administering the last dose of either rotavirus vaccine should be 32 weeks. The time window for achieving a full immunisation course is especially limited for the Merck product, which requires three, rather than two doses.<sup>120</sup>

A tangible example of this challenge is Brazil, where WHO lists the national DTP3 coverage rate at 98%,<sup>121</sup> but the percentage of children receiving a full course of rotavirus vaccines has lagged

approximately 20% behind other routine immunisations every year since 2007.<sup>122</sup>

Most rotavirus dosing guidelines are based on clinical trials that occurred in developed countries, where there is access to vaccination services. Preliminary analysis has indicated that the additional lives saved by broadening the age range for rotavirus vaccination would outweigh the hypothetical risks of intussusception.<sup>123</sup> Further research to explore more flexible dosing schedules for rotavirus vaccines would be highly beneficial for countries planning to introduce the vaccine in the future. At the same time, it is important to note that the majority of rotavirus cases are in children under one year of age, and thus any proposed change in dosing schedule should consider the age group which has the greatest disease burden.

### Adaptation challenges—the highlights:

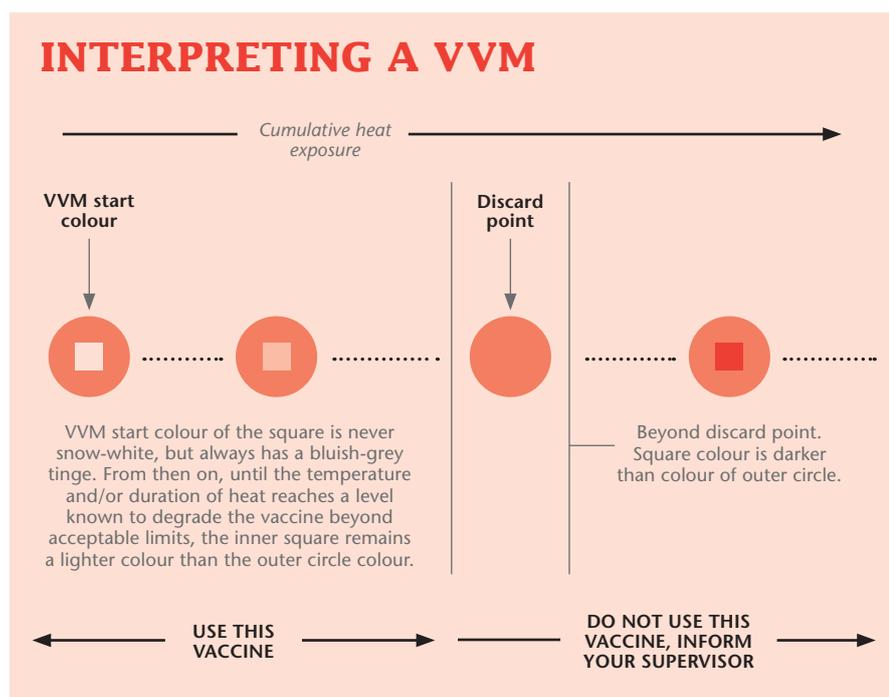
- The Merck product is impractical in places where cold chain is weak. There is great need for more heat-stable rotavirus vaccines.
- Restrictive dosing schedules have an impact on coverage—research into more flexible schedules is needed.
- Further research on efficacy for the predominant rotavirus serotypes in developing countries is needed.
- Continued efforts at volume reduction through novel presentations and introduction of a multi-dose vial would help ease introduction in developing countries.

# ANNEX 1: VACCINE VIAL MONITORS (VVM)

A Vaccine Vial Monitor (VVM) is a heat-sensitive and time-sensitive label affixed to a vaccine vial that indicates whether a vaccine can be used, or if it has been damaged through exposure to excessive heat over time.<sup>112</sup> The label

consists of an inner square inside a coloured circle. The square will start off a lighter colour than the circle, but gradually darkens over time if the vaccine is exposed to heat. The vaccine can be considered safe

for use so long as the square remains a lighter shade than the outer circle. Once the square is the same shade, or a darker shade than the outer circle, the vaccine is no longer safe for use, and must be discarded.



VVMs were first introduced in 1996, following almost 20 years of development. Today, almost all vaccines supplied through UN procurement agencies include a VVM. The VVM is useful for vaccine delivery in two very important capacities:

(1) VVM give health workers the ability to visually and easily assess a vaccine's appropriateness for use, without any detailed information on the vaccine's cold chain or transport route.

(2) The ability to assess heat exposure with a VVM helps prevent viable vaccines from being thrown away or wasted if the cold chain fails for short period of time at a service delivery point.

## HOW DOES THE VVM VARY FOR DIFFERENT VACCINES?

Four categories of VVM identify the different levels of heat stability a vaccine presentation may fall under. Vaccines that prevent the same type

of disease but originate with different manufacturers, or have different presentations, may have different VVMs. The chart below illustrates the

different VVM categories and the length of time vaccines in each category can be exposed to levels of heat before reaching their discard point.

**TABLE 1: VVM REACTION RATES BY CATEGORY OF HEAT STABILITY**

Category (Vaccines)	No. of days to end point at +37°C	No. of days to end point at +25°C	Time to end point at +5°C
VVM 30: High Stability	30	193	> 4 years
VVM 14: Medium Stability	14	90	> 3 years
VVM 7: Moderate Stability	7	45	> 2 years
VVM 2: Least Stable	2	N/A*	225 days

\*VVM (Arrhenius) reaction rates determined at two temperature points.

# WHAT IS THE VVM FOR SOME IMPORTANT VACCINES?

The following chart lists the VVM for several new vaccines from their respective manufacturers in their different presentations. Countries and organisations that engage in

vaccine procurement should consider the VVM, along with factors like price and cold chain volume, when making procurement decisions and assess whether a vaccine is the proper

stability, given a country's distribution system and the typical heat exposure a vaccine will face.

VVM Comparison Chart for Pneumococcal Conjugate, Meningococcal, and Pentavalent Vaccines					
Pneumococcal Conjugate Vaccines					
Manufacturer	Vaccine Trade Name	Presentation	VVM	Shelf Life	
Pfizer	Prevenar 13	1 dose vial	Type 30	24 months at 2–8°C	
GlaxoSmithKline	Synflorix	2 dose vial	Type 7	36 months at 2–8°C	
Meningococcal Vaccines					
Manufacturer	Vaccine Trade Name	Vaccine Type	Presentation	VVM	Shelf Life
Serum Institute of India Ltd	MenAfriVac	Meningococcal A conjugate	10 dose vial (active) + 10 dose ampoule (diluent)	Type 30	24 months at 2–8°C (active); 24 months at 25°C (diluent)
Pentavalent Vaccines: Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type B					
Manufacturer	Pharmaceutical Form	Presentation		VVM	Shelf Life
Crucell Korea	Liquid	1 dose vial		Type 14	36 months at 2–8°C
GlaxoSmithKline	Liquid+lyophilised	1 dose vial (DTP-HepB) (liquid) + 1 dose vial of Hib (lyophilised)		Type 14	36 months at 2–8°C
GlaxoSmithKline	Liquid+lyophilised	2 dose vial (DTP-HepB) (liquid) + 2 dose vial of Hib (lyophilised)		Type 14	36 months at 2–8°C
GlaxoSmithKline	Liquid	1 dose vial		Type 14	36 months at 2–8°C
Panacea Biotec	Liquid	1 dose vial		Type 14	24 months at 2–8°C
Serum Institute of India Ltd	Liquid+lyophilised	10 dose vial DTPw-HepB (liquid) + 10 dose vial Hib (lyophilised)		Type 7	24 months at 2–8°C
Serum Institute of India Ltd	Liquid	1 dose vial		Type 7	24 months at 2–8°C
Serum Institute of India Ltd	Liquid	10 dose vial		Type 7	24 months at 2–8°C
Serum Institute of India Ltd	Liquid+lyophilised	1 dose ampoule DTPw-HepB (liquid) + 1 dose vial Hib (lyophilised)		Type 7	24 months at 2–8°C
Serum Institute of India Ltd	Liquid+lyophilised	2 dose ampoule DTPw-HepB (liquid) + 2 dose vial Hib (lyophilised)		Type 7	24 months at 2–8°C
Serum Institute of India Ltd	Liquid	2 dose vial		Type 7	24 months at 2–8°C

## FOR MORE INFORMATION:

Please consult the following from the WHO for more details on the history and specifics of Vaccine Vial Monitors: [http://www.who.int/immunization\\_standards/vaccine\\_quality/vvm\\_10years\\_index/en/](http://www.who.int/immunization_standards/vaccine_quality/vvm_10years_index/en/)



# ANNEX 2: THE CHILDHOOD ROUTINE IMMUNISATION SCHEDULE

Antigen	Age of first dose		Doses in primary series
BCG (tuberculosis)	As soon as possible after birth		1
Hepatitis B (HepB)	As soon as possible after birth (within 24 hours)		3–4
	6 weeks (with DTP1)		
	10 weeks (with DTP2)		
	14 weeks (with DTP3)		
Oral polio vaccine (OPV)	As soon as possible after birth		3–4
	6 weeks (with DTP1)		
	10 weeks (with DTP2)		
	14 weeks (with DTP3)		
Diphtheria–Tetanus - Pertussis (DTP)	6 weeks		3
	10 weeks		
	14 weeks		
Haemophilus influenzae type B (Hib)	6 weeks (with DTP1)		3
	10 weeks (with DTP2)		
	14 weeks (with DTP3)		
Pentavalent (DTP-HepB-Hib)	Same dosing schedule as DTP		3
Pneumococcal conjugate (PCV)	Option 1	6 weeks (with DTP1)	3
		10 weeks (with DTP2)	
		14 weeks (with DTP3)	
	Option 2	6 weeks	3
		Must wait 4 week minimum	
		Booster dose at 9–15 months	
Rotavirus	Option 1 (Rotarix)	6 weeks minimum (15 week maximum)	2
		Must wait 4 week minimum (no later than 32 weeks)	
	Option 2 (Rota Teq)	6 weeks minimum (15 week maximum)	3
		Must wait 4 week minimum	
		Must wait 4 week minimum (no later than 32 weeks)	
	Measles	9 months (4 week minimum to 2nd dose)	
Rubella	9 months (with measles)		1

**Notes:** Based upon the WHO Recommended Routine Immunisations for Children ([http://www.who.int/immunization/policy/Immunization\\_routine\\_table1.pdf](http://www.who.int/immunization/policy/Immunization_routine_table1.pdf)). See website for more specific technical guidelines. This graph does not include the HPV vaccine, as the WHO recommendation is for use in adolescent girls, nor antigens which are region or high-risk population specific (such as meningitis A conjugate vaccine, yellow fever, etc).



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# GLOSSARY

**Administration**—Method of vaccine delivery. Can be injection, oral, inhalation/dry powder, microneedle, etc.

**Advance Market Commitment (AMC)**—The GAVI Alliance advance market commitment is a financing model that incentivised pharmaceutical companies to manufacture pneumococcal vaccines for developing countries by providing a subsidy.

**Antigen**—A substance that causes the immune system to produce antibodies.

**Birth dose**—A dose of vaccine given just after the birth of a child, or shortly thereafter.

**Bivalent**—A vaccine which is formulated against two antigens or two serotypes of a related group of similar infectious agents.

**Booster dose**—An additional vaccine dose given some time after initial immunisation to re-expose the body to the antigen and increase immunity.

**Cold chain**—A temperature-controlled supply chain where a product needs to be kept at or below a specified temperature during the transport, storage and handling of the product.

**Cold chain volume (per dose)**—The volume per dose that a vaccine, with its packaging, needs for transportation and storage in a cold chain.

**Combination vaccine**—Two or more antigens administered in a single product that prevent different diseases and reduce the number of shots that need to be administered.

**Conjugate vaccine**—A vaccine that is formulated by linking an antigen derived from the pathogen to a protein molecule.

**Coverage**—The percentage of a target age group who have received particular vaccines. Different methods are used to calculate coverage.

**CPT**—'Carriage Paid To (named place of destination)'. A commercial term (incoterm 2010) meaning the seller pays for carriage. Risk transfers to buyer upon handing goods over to the first carrier.

**Dosing schedule**—see Vaccination schedule.

**DDP**—'Delivered Duty Paid (named place of destination)'. A commercial term (incoterm 2010) meaning the seller is responsible for delivering the goods to the named place in the country of the buyer, and pays all costs in bringing the goods to the destination including import duties and taxes. This term places the maximum obligations on the seller and minimum obligations on the buyer.

**Emerging market supplier**—A producer and/or innovator of a vaccine from developing countries, including India, Brazil and China.

**Expanded Programme on Immunisation (EPI)**—The World Health Organization programme, initiated in 1974, that aims to ensure all children are covered by a list of recommended vaccines.

**FCA**—'Free Carrier (named place of delivery)'. A commercial term (incoterm 2010) meaning

that the seller hands over the goods, cleared for export, into the disposal of the first carrier (named by the buyer) at the named place. The seller pays for carriage to the named point of delivery, and risk passes when the goods are handed over to the first carrier.

**GAVI-eligible country**—A country that is eligible to receive financial support from the Global Alliance for Vaccines and Immunization (GAVI Alliance). Support covers different forms and eligibility is restricted to countries with a Gross National Income per capita of US\$1,520 or less; currently 57 countries are classified as GAVI-eligible.

**Herd immunity**—A form of immunity that occurs when the vaccination of a significant portion of a population (or herd) provides a measure of protection for individuals who have not developed immunity.

**Immunisation schedule**—see Vaccination schedule

**Immunisation**—Immunisation, or vaccination, is the administration of antigenic material (a vaccine) to stimulate the immune system of an individual to develop adaptive immunity to a disease.

**International Coordinating Group (ICG)**—an inter-organizational group, including WHO, UNICEF, MSF and others, which supports prevention and epidemic outbreak response to meningitis. ICG members help manage meningitis vaccine stock, following regional epidemiological trends and outbreaks. <http://www.who.int/csr/disease/meningococcal/icg/en/>

**Liquid Vaccine**—A vaccine in liquid form.

**Lyophilised vaccine**—A vaccine that comes in the form of a freeze-dried powder that must be mixed with a liquid (reconstituted) before it can be administered.

**MenAfriVac**—The Meningitis A conjugate vaccine produced through the partnership of WHO and PATH and the Serum Institute of India.

**Monovalent**—A vaccine which is formulated against a single antigen or a single serotype of a related group of similar infectious agents.

**Multi-dose vial**—A vial of vaccine that contains more than one dose of that vaccine.

**Multivalent**—A vaccine which is formulated against two or more antigens or serotypes of a related group of similar infectious agents.

**Pentavalent**—A multivalent vaccine which immunises against five antigens. Used in this report to refer to the multivalent vaccine immunising against diphtheria, tetanus, pertussis, hepatitis B, and Hib disease (DTP+Hep B+Hib).

**Presentation**—The manner in which a vaccine is available for use, including as single or multi-dose vials, pre-filled syringes, or mono-dose injection devices.

**Polysaccharide vaccines**—Vaccines that are composed of long chains of sugar molecules that resemble the surface of certain types of bacteria; they

are available for pneumococcal disease, meningococcal disease and Haemophilus influenzae type B. **Prequalification**—a product which meets various quality and safety standards as certified by WHO. [http://www.who.int/immunization\\_standards/vaccine\\_quality/PQ\\_vaccine\\_list\\_en/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html)

**Price per dose**—The cost of the vaccine per single dose.

**PAHO Revolving Fund**—A cooperation mechanism established in 1977 for the joint procurement of vaccines, syringes and related health supplies for PAHO Member States. All participating Member States have access to the same products, offered at an average single price independent of the country's size or economic situation. Participants contribute three and a half percent of the net purchase price to a common fund that is used as working capital. <http://www.paho.org/revolvingfund>

**Routine immunisation**—The list of vaccines that are recommended for all children according to the country/region.

**Serotype**—A distinct variation within a species of bacteria or viruses or among immune cells of different individuals.

**Tail price**—A pre-determined maximum price that manufacturers agree to sell a vaccine at or below, after the donor funds that provided an initial subsidy have run out. The term is associated with the Advance Market Commitment.

**Technology transfer**—The process of transferring skill, knowledge, technologies, methods of manufacturing, samples of manufacturing and facilities to ensure that scientific and technological developments are accessible to a wider range of users who can then further develop and exploit the technology into new products, processes, applications, materials or services.

**Tetavalent**—A vaccine which is formulated against four antigens or four serotypes of a related group of similar infectious agents.

**Trivalent**—A vaccine which is formulated against three antigens or three serotypes of a related group of similar infectious agents.

**Vaccination schedule**—A series of vaccines, including the timing of all doses, and intervals between doses, that is recommended. Every immunisation programme has a vaccination schedule. WHO has a recommended global vaccination schedule.

**VVM**—Vaccine Vial Monitor.

**Wastage**—The number of vaccine doses not used and needing to be discarded. Wastage can be caused by discarding open vials with remaining vaccine after an immunisation session has ended, or by discarding doses damaged in unopened vials for other reasons (ex. cold chain failure, broken vials, expired vaccine, etc).

**WHO prequalification**—see prequalification.

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