THE RIGHT SHOT:
BRINGING DOWN BARRIERS TO AFFORDABLE AND ADAPTED VACCINES

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ACCESS CAMPAIGN
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MÉDECINS SANS FRONTIÈRES

Médecins Sans Frontières (MSF, or Doctors Without Borders) is an international, independent, medical humanitarian organisation that delivers emergency aid to people affected by armed conflict, epidemics, healthcare exclusion and natural or man-made disasters.

Each year, MSF teams vaccinate millions of people, largely as outbreak response to diseases such as measles, meningitis, yellow fever and cholera. MSF also supports routine immunisation activities in projects where we provide healthcare to mothers and children. MSF is scaling up its vaccination activities with a particular focus on improving its work in routine immunisation, as well as extending the package of vaccines used in humanitarian emergencies. In the year 2012–2013, MSF had a 60% increase in the number of doses administered in its projects.

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 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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EXECUTIVE SUMMARY

Vaccination is a cornerstone of Médecins Sans Frontières' (MSF) work to reduce illness and death caused by preventable diseases. While global immunisation coverage reached 84% in 2013, in some places vaccination rates have stagnated, leaving behind children chronically unimmunised and unprotected. For more than 40 years, MSF has been at the forefront of vaccine delivery in crisis contexts, and in response to outbreaks of vaccine-preventable diseases. We also conduct routine immunisation in areas where health systems have failed.

Whether vaccinating refugee children in South Sudan, or pregnant women in Afghanistan, MSF has committed itself to prioritising vaccination as a core health service in its operations. In 2013 alone, our programmes delivered more than 6.7 million doses of vaccines and immunological products, and we see the need to ramp up our activities even further.

However, the organisation increasingly faces challenges at the field and global levels in expanding capacity to address immunisation needs. The barriers encountered by MSF, including the rising cost of new vaccines and the lack of vaccine products suited for low-resource settings, are also obstacles for affected countries. As MSF uses newer vaccines more frequently in crisis settings, in line with the recently developed World Health Organization (WHO) guidelines on vaccinating in humanitarian emergencies, the challenges we face in purchasing vaccines at an affordable price have become acute. In addition, countries that are unable to afford these high prices are increasingly voicing their frustration at the inability to protect their children against life-threatening – but preventable – diseases.

This second edition of *The Right Shot* outlines how the prices of 16* fundamentally important vaccines have evolved since their development, in some cases as far back as 2000. The report analyses how prices are affected by the fact that a few multinational companies dominate the market, a lack of competition, various procurement strategies and purchasing conditions, and the business practices of the pharmaceutical industry. The publication consolidates and analyses vaccine price data points from countries, UNICEF, Pan American Health Organization (PAHO), MSF, and pharmaceutical companies. By examining the differences in pricing strategies used by companies based in emerging economies (developing-country manufacturers) and multinational companies (industrialised-country manufacturers), the publication explains how multinational pharmaceutical companies use their first-to-market advantage to reap blockbuster revenues, and are increasingly moving beyond high-income countries in seeking other profitable markets.

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* Human papillomavirus, inactivated poliovirus, pneumococcal conjugate, oral cholera, measles, measles-rubella, measles-mumps-rubella, meningitis A, meningitis C, meningitis ACYW-135, three diphtheria/tetanus/pertussis-containing vaccines, hepatitis B, rotavirus, tetanus toxoid.

It also demonstrates how entry of additional manufacturers with WHO-prequalified vaccines, in particular developing-country manufacturers, stimulates competition and drives down prices.

An overarching challenge that MSF faces in analysing the vaccine market is the lack of data on prices and the notoriously opaque nature of the market; this lack of transparency also inhibits efforts to improve affordability. Price secrecy is ubiquitous in the vaccines market, putting countries and other purchasers at a distinct disadvantage when negotiating with companies.

While Gavi, the Vaccine Alliance, has helped to lower prices of new and underused vaccines for its eligible countries – originally the poorest 73 countries of the world – the cost to fully immunise a child has nevertheless skyrocketed. Even at the lowest global prices, the introduction of the newest vaccines against pneumococcal and diarrhoeal diseases (pneumococcal conjugate and rotavirus vaccines, respectively), and against cervical cancer (human papillomavirus vaccine) has increased the cost of the full vaccines package 68-fold from 2001 to 2014 [see box, page 6], calling into question the sustainability of immunisation programmes after countries lose donor support. Of particularly serious concern is the impact of this drastic increase on most middle-income countries (MICs), which are benefitting neither from lower prices negotiated by organisations such as Gavi, nor from international donor support. Many children living in MICs are not benefitting from new, life-saving vaccines as a result of irrational and unaffordable pricing policies; some of these countries even have lower immunisation coverage rates than Gavi-eligible countries.

Finally, while recent years have seen the introduction of several new vaccines that offer significant potential to reduce childhood deaths, there has been little investment in adapting – or optimising – vaccine products to resource-limited contexts. Most vaccines still need to be refrigerated in a rigid 'cold chain' until the moment they are administered, which is an immense challenge for places without electricity. Multiple doses are needed to fully protect children, and bulky products complicate transport to remote areas. These are some of the obstacles that annually prevent almost 22 million children under one year of age from receiving the basic package of life-saving vaccines. Whether in a small village in rural Congo or a refugee camp in Iraq, vaccine delivery can be extremely difficult and costly to execute. A growing body of evidence, including MSF research, shows that some vaccines can remain effective outside of a strictly regulated temperature range, and rapid steps to re-label vaccines for their true heat stability are needed, along with further investments in better adapted products.

Vaccine commodities themselves account for almost half of the 57 billion US dollars (US$) needed to finance the Decade of Vaccines – the global framework for expanding access to immunisation from 2011 to 2020. In the meantime, many countries, especially middle-income countries, are unable to afford the newest vaccines for their populations, nor can organisations such as MSF provide these vaccines to crisis-affected children, because of the very high price tag. Better solutions that can make new quality-assured vaccines more affordable and adapted to the environments where children are most vulnerable are urgently needed. Efforts to accelerate real competition in the vaccines market will deliver the most sustainable price reductions; in the interim, procurement strategies that benefit as many countries as possible should be pursued. Collective action is needed to improve price transparency and ensure affordable prices for quality-assured vaccines in all countries, so that governments can make the benefits of immunisation accessible to their populations. Shedding more light on the vaccine industry will benefit children everywhere.

> **"MSF faces increasing challenges in offering full immunisation to children in our projects. The rising price of the basic vaccines package means that we can't afford to protect kids living in crisis, and nor can many countries who want to protect their children."**
>
> *Dr Greg Elder, MSF Deputy Director of Operations*

AFFORDABILITY AND VACCINE PRICING

Unaffordable prices hinder countries from introducing new, life-saving vaccines and threaten the sustainability of immunisation programmes. Under the current paradigm, 'affordability' is defined by what countries and donors are willing to pay rather than a rational system that maximises access for all countries and populations.

The support of Gavi, which provides 'Gavi-eligible' countries [see box below] with temporary access to subsidised vaccines at negotiated lower prices, has enabled many of the poorest countries to introduce new and underused vaccines in their immunisation programmes.[1] However, within the next five years more than 25% of Gavi's country cohort will 'graduate', i.e. become ineligible for full Gavi support, and it is estimated that by 2025, 29 of the original 73 eligible countries will have lost Gavi support entirely. These countries will then face the dual challenge of meeting the higher cost of new vaccines and fully self-financing their national immunisation programmes. For example, a highly donor-subsidised price for the pneumococcal conjugate vaccine (PCV) has enabled many Gavi-eligible countries to introduce the vaccine and prevent avoidable childhood mortality. When these countries are no longer Gavi-eligible and required to self-finance the vaccines, they may have to pay up to six times more for PCV, according to what we consider to be a conservative estimate by Gavi.[2]

The challenge of unaffordable vaccines is even more pronounced for the range of so-called 'middle-income countries' (MICs) that have never been Gavi-eligible, nor had access to Gavi's lower prices. Prohibitively high prices are causing many MICs to fall behind the Gavi-supported countries in the rate of introducing PCV in their national immunisation programmes [see Graph 3, page 14]. The US itself is also challenged with high prices: the number of US physicians offering immunisations is reported to be in decline as a result, and one-third of family-practice doctors are considering ceasing vaccinations because of the high prices of vaccines.[3] Beyond countries, non-governmental organisations (NGOs) such as MSF also struggle to access the lowest global vaccine prices, being unable to systematically access Gavi-negotiated prices.

There is no global consensus on the most effective way to improve vaccine affordability. Various actors develop and implement selected strategies, often with different country groupings or at the regional level. Strategies to enhance access to affordable vaccines worldwide are urgently needed; some of these strategies are discussed in this report, and include promoting price transparency and price monitoring mechanisms, pursuing pooled procurement, increasing competition through an expanded manufacturer base, and designing new models of vaccine development. Broader availability of predictable and sustainable access to low-cost vaccines would enable more countries to afford to introduce life-saving vaccines into their health systems.

ELIGIBILITY FOR GAVI SUPPORT

A country's eligibility for Gavi support is determined by its Gross National Income (GNI) per capita. Since 2011, Gavi has implemented a graduation policy, whereby when a country's GNI per capita crosses the threshold of US$1,570, support is phased out over the next five years. During 'graduation', stepped country co-financing requirements increase linearly until countries are required to fully self-finance the vaccine by the end of the five-year period.[1] Gavi's graduation policy is far stricter than the eligibility threshold of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund).

THE RISING PRICE OF IMMUNISING A CHILD

Several new vaccines have been added to the WHO immunisation schedule since 2001 [see Graph 1, page 7]. Using the yearly lowest publicly published prices (available only to some developing countries), in 2001 it cost a minimum of US$0.67 to immunise a child against six diseases (tuberculosis, measles, diphtheria, tetanus, pertussis and poliomyelitis); in 2014, it costs a minimum of US$32.09–45.59* to immunise a child against 12 diseases (tuberculosis, measles, rubella, diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b, poliomyelitis, pneumococcal diseases, rotavirus and, for adolescent girls, human papillomavirus (HPV)). So while the number of diseases against which a child is immunised has doubled between 2001 and 2014, the cost of the vaccines package to fully immunise a child has disproportionately multiplied 68-fold. Moreover, this estimate represents the theoretical best-case scenario, as it is based on the lowest available prices for the UNICEF Supply Division and restricted to a select group of developing countries, usually only Gavi-eligible countries.

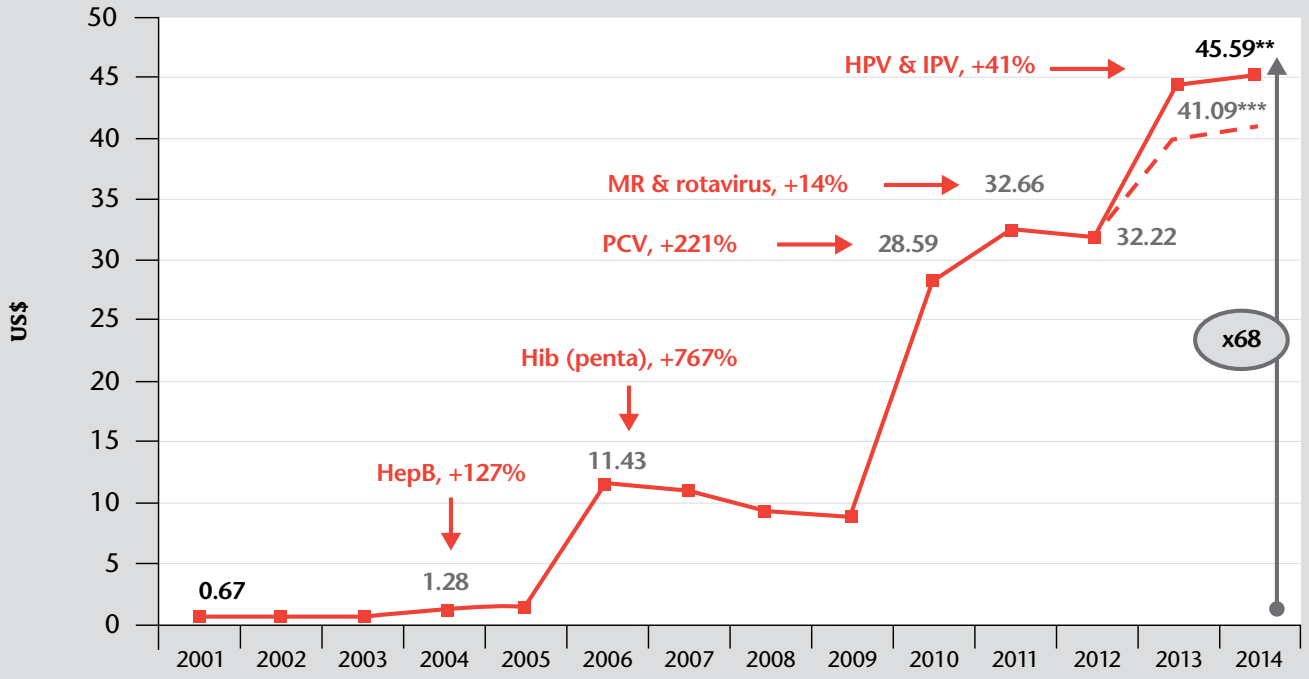
The situation is particularly difficult for developing countries, including MICs, that do not receive Gavi support. For instance, according to the Pan American Health Organization (PAHO) which has historically benefited from access to lower prices due to the PAHO Revolving Fund, 'the cost per child vaccinated was less than US$5 [in 1979], while it is currently approximately US$70 per child immunised, only taking into account the cost of the vaccines [excluding HPV vaccine]'.[4] Many countries outside of the PAHO region are worse off as they procure vaccines on their own and pay much higher prices. In some of these countries, prices can reach more than 20 times the price paid by Gavi/UNICEF: for instance, the HPV vaccine is purchased at EUR75 / US$100 in Macedonia, or 22 times the price paid by Gavi-supported countries.[5] The price increase for the newest vaccines – HPV, pneumococcal conjugate vaccine (PCV) and rotavirus – is such that some MICs have deemed them not cost effective enough to introduce into their Expanded Programme on Immunization (EPI) schedule.[6]

Gavi-graduating countries are preparing to lose both the subsidy to purchase vaccines and access to some lower negotiated prices. Even if countries can maintain their procurement at the lowest price, the end of Gavi subsidies will drastically increase their immunisation budgets. For example, Honduras is currently graduating and will stop receiving Gavi support as of 2016. Honduras will have to then cover the US$5 million currently annually paid by Gavi for new vaccines, which represents a 38% increase in the government's present expenditures for immunisation.[7] Moreover, this cost will increase more if the country introduces the HPV vaccine in the coming years.

Other estimates for how much country immunisation budgets will rise to cover new vaccines are increases of 197% in Sri Lanka between 2012 and 2018, 801% in Congo, and up to 1,523% and 1,547% for countries like Angola and Indonesia, respectively[8] [see Table 1, 'Select Gavi-graduating country co-financing payments for new vaccine costs,' page 13]. Given that vaccines are only part of the cost to fully immunise a child, and that other programme costs must still be added (human resources, transportation, cold chain, infrastructure, other immunisation supplies, etc.), this escalation of vaccine prices seems difficult to absorb for many countries.

* US$32.09 is the price to immunise a boy in 2014; US$45.59 is the price to immunise a girl (includes the HPV vaccine).

Graph 1: Price to immunise a child based on lowest price available to Gavi/UNICEF



** Includes 3 doses of HPV vaccine. *** Includes 2 doses of HPV vaccine.

Sources:
WHO routine immunisation summary tables,[9] Gavi,[10] UNICEF Supply Division,[11] MSF *The Right Shot* 1st ed.[12]

Notes and methodology:
Available in Annex F, together with the timeline on WHO recommendations and Gavi vaccine funding decisions.

ACCESS TO AFFORDABLE VACCINES: WHY PRICE IS A BARRIER TO IMMUNISATION

WHAT IS AN 'AFFORDABLE' PRICE?

Who decides what is affordable and what metrics are used?

Vaccine 'affordability' is currently defined by what countries and donors are willing to pay, and not according to public health need. With poor countries affording new vaccines only because they are heavily subsidised by donors such as Gavi, and many MICs struggling to introduce these same products, the long-term effectiveness of the current global immunisation system is questionable. Although even some Gavi countries continue to face challenges in their ability to pay for new vaccines, Gavi has nevertheless enabled tremendous progress in access to vaccines for many of the world's poorest countries. Attention must now focus on sustainable solutions for all countries.

Gavi is a significant voice in the global debate on vaccine affordability. Gavi is trying to define the lowest available price for the vaccines it purchases, the countries that merit the lowest price and the budgetary responsibility of developing countries that must fully finance their own immunisation programmes once Gavi support ends.

New price reduction developments have been announced for Gavi-eligible countries, each with separate conditions. Gavi's threshold of US$1,570 GNI per capita (revised each year for inflation) suggests that Gavi donors consider this economic indicator to represent a country's ability to fully finance its own vaccines.

Furthermore, a Gavi-commissioned fiscal space analysis generated a model predicting that Gavi-graduating countries would need to allocate only 0.6% of health budgets to independently support the full cost of vaccines.[13] This estimate is within the range of global development targets that have set an expectation that countries will spend up to 10% of their budgets on health (short of the 15% Abuja Declaration) and that vaccine commodities will occupy no more than 1.0% of the total health budget.[13,14] This measurement has been used as justification for the 'affordability' of domestically financed immunisation programmes. However, the underlying assumptions in the Gavi fiscal space analysis prove problematic for broader application, for several reasons.

- The model includes external resources (such as grants from the Global Fund and the World Bank) within the health budget calculation, artificially inflating the resources available to Ministries of Health for reallocation. These donor funds fluctuate according to global economic conditions and priorities, and they should not be considered available for funding vaccination.
- The model uses a static estimate for the number of vaccines introduced. Each additional vaccine will compound the eventual cost of full immunisation for Gavi-graduated countries. The first wave of graduating countries in this analysis have skipped introducing one of the most expensive vaccines – HPV – but future graduating countries may assume the price burden for this vaccine. While 11 of the 16 Gavi-graduating countries in the analysis have introduced two or fewer vaccines with Gavi-support, 73% of the 'intermediate' Gavi-eligible cohort has introduced three or more vaccines.* The estimate that vaccines will cost 0.6% of health budgets is therefore unlikely to hold for countries introducing more new vaccines.
- Gavi-graduating countries do not have secure access to all Gavi-negotiated prices in the medium to long term. Gavi's negotiations with manufacturers for guaranteed price continuity post-graduation are time-limited and company-specific, with procurement caveats that may be legally and programmatically challenging to implement.
- Vaccine investment at country level has increased more slowly than was assumed in original fiscal space analyses. This could be attributed to under-reporting, reallocation of health budgets away from vaccines or simple limits on how much countries can invest in vaccination.[15]

Gavi is trying to define the lowest price, the countries that merit the lowest price and the budgetary responsibility of developing countries.

* Using country groupings from Saxenian et al., 2011 (country grouping based on 2009 per capita GNI, with 'intermediate' countries having a 2009 per capita GNI of US$996–1,499, and graduating countries 2009 per capita GNI of US$1,500 or more), and vaccine introduction from 'disbursements by program year' from www.Gavialliance.org/results/disbursements/

Progress towards affordable access

While the global community lacks a rational pricing system that serves all countries and populations, Gavi has nevertheless had a key role in reducing prices of vaccines for its group of eligible countries, and the 'Gavi price' is often used as the worldwide lowest reference price. As a result of its negotiations with manufacturers and special agreements, Gavi has managed to secure vaccines at reduced prices – often one-half to two-thirds lower than other known public prices – although these agreements are negotiated on an ad hoc basis and only available to Gavi's limited group of countries.[16]

Pooling vaccine procurement – as is practised through the PAHO Revolving Fund [see box, page 15] – allows some countries to benefit from bulk purchasing and financing mechanisms, and access low prices through high volumes and economies of scale. It also provides manufacturers with predictable and reliable demand forecasts and purchases.

Some manufacturers have been active in defining affordability on their terms, with several companies publicly committing to global access policies for selected new vaccines. For example, under a product development partnership including WHO and PATH, the manufacturer Serum Institute of India – an emerging economy manufacturer – developed the Meningitis A vaccine with a specific affordability target of US$0.50 per dose [see Meningitis Product Card, page 60].

Pharmaceutical companies from industrialised countries claim to have adopted tiered pricing practices to promote access and affordability for developing countries, while achieving large revenues with 'blockbuster' products in high-income economies. However, these tiered pricing policies are largely not publically available and – with minimal data available – often have no clear rationale or relation to a country's economic classification. GlaxoSmithKline (GSK) has been one of the few companies to publicly disclose significant information about its vaccines tiered pricing strategy for developing countries, categorising countries by their ability to pay, commitment to vaccination programmes and volumes purchased [see box 'How do pharmaceutical companies set their vaccine prices?', pages 20-22].[17] In late 2013, GSK also published the latest results of its candidate malaria vaccine (Mosquirix), publicly committing to selling the vaccine at no more than a 5% profit margin.[18]

Some of these efforts will, however, only benefit selected countries and populations while excluding others from accessing vaccines at affordable prices (e.g. Gavi prices are for Gavi-eligible countries only); and even the lowest prices offered by some pharmaceutical companies are likely to be inadequate compared to those achieved by competition between multiple manufacturers. To date, high prices charged to MICs for PCV by GSK and Pfizer under their tiered pricing strategy has led to this group of countries failing to adopt PCV as widely as low-income countries that have benefitted from both lower prices and donor financial support. If sustainable and predictable prices were available more broadly, more countries would likely be able to afford to introduce life-saving vaccines.

AFFORDABILITY IS NOT THE ONLY OBSTACLE TO ACCESSING VACCINES

Low prices are a critical part of sustainable immunisation programmes, but weak health systems are a significant obstacle to successful vaccine delivery. Vaccines 'adapted' for use in resource-poor environments can lower programme costs by reducing associated systems-related needs, such as the constraints of the cold chain. The key vaccine adaptations that MSF teams working in developing countries need include:

- vaccines that are stable at high and freezing temperatures
- simplified administration routes
- fewer doses and more flexible dosing schedules
- reduced volume and bulkiness
- improved efficacy of oral vaccines
- more efficacious antigen combination for low-middle-income countries (LMIC).

Adaptations can also extend the reach of vaccination beyond what is achievable with conventional vaccines. For example, a more thermostable pentavalent vaccine would be available at 97% of health centres, instead of 87% using the current pentavalent vaccine in the cold chain; removal of the pentavalent vaccine from the cold chain would open up space for even more Expanded Programme on Immunization (EPI) vaccines to reach health centres.[19] Supply-chain modelling of different product adaptations can further demonstrate the positive impact of adapted vaccines.

In some circumstances, additional incentives may be needed to develop better adapted products, particularly for adaptations needed for developing countries. Possible options could include development prizes, preferential procurement, fast-tracked regulatory processes, or advanced purchase commitments.

PARTICULARITIES OF THE VACCINE MARKET

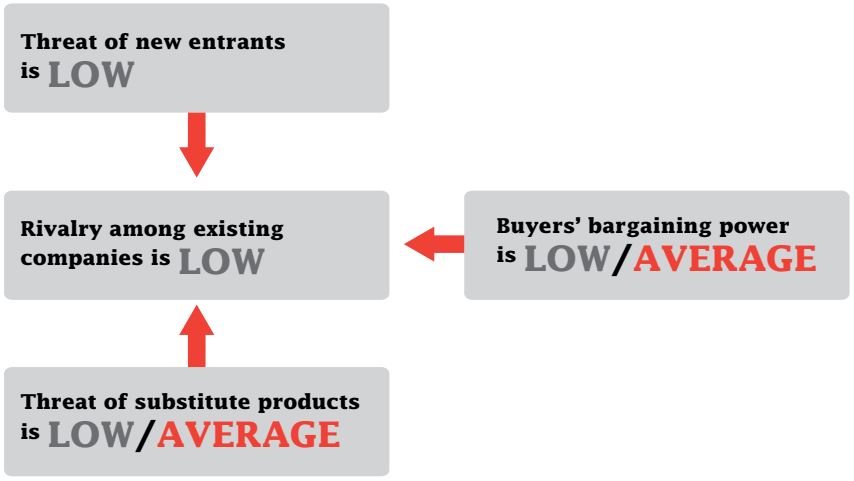
In the vaccine market, the scarcity of publicly disclosed vaccine prices and other essential data undermines the development of effective public health policies. Vaccine prices spiral upward seemingly unchecked and yet some pharmaceutical companies claim that vaccine profits are still insufficient to keep them in the market. Amongst some experts, low prices have been blamed for market collapse, particularly when vaccine manufacturers fled the Expanded Programme on Immunization (EPI) market in the late 1990s. Since then, UNICEF has endeavoured to mitigate risk by brokering multi-year procurement agreements with multiple vaccine manufacturers.[20]

Most pharmaceutical companies do not reveal prices and many require vaccine purchasers to sign price confidentiality clauses that forbid disclosure of pricing information. Information asymmetry prevents countries from effective negotiation to secure lower prices, and compromises their ability to budget appropriately for new vaccine introduction.

An analysis of the new vaccine market can be based on Porter's Five Forces framework.* The MSF analysis [see Figure 1] describes the bargaining power of buyers, the threat of new entrants to the market, the threat of substitute products and rivalry within the industry, concluding that the vaccines market favours manufacturers – not purchasers.

Figure 1: MSF analysis of the new vaccine market

MSF's analysis (based on Porter's Five Forces*) of the international market for new vaccines shows that the industry is extremely attractive but well-protected, thus excluding new entrants while enabling current manufacturers to maintain strong positions and potentially high margins.



- Threat of new entrants is low. Barriers to entry are high, because of capital-intensive and time-consuming research and development (R&D) and intellectual property (IP) restrictions, high sunk and fixed costs (sunk costs are those that, once committed, cannot be recovered – e.g. the cost of equipment that is designed to produce a specific product and cannot readily be diverted to other uses) and the regulatory processes required to obtain and maintain plant and product prequalification.[22]
- Buyers' (countries') bargaining power is low/average. A lack of transparency and knowledge regarding existing products, characteristics and prices limits the capacity of buyers – mostly countries – to make informed decisions.[23] With few manufacturers in the market (often forming duopolies/oligopolies),[24] buyers' bargaining power is limited. Buyers can increase their power by concentrating their demand (e.g. by pooling procurement).
- Threat of substitute products is low/average. Vaccine substitution (within the industry) is possible, but depends on the availability of competitor products and product characteristics. For example, for each of the three newest vaccines (PCV, HPV and rotavirus) there are only two WHO-prequalified products, each resulting in a duopoly; furthermore, the two vaccines are not substitutes for one another because of different product characteristics. When competition exists, originator products can be replaced with cheaper, quality-assured vaccines from low-cost manufacturers.
- Rivalry among existing companies is low. When there are only a few originator companies for a particular vaccine, rivalry is low and companies tend to keep prices high until a lower-cost manufacturer enters the market.[24] When low-cost manufacturers do enter the market, strategies such as tiered pricing allow originator companies to remain competitive against low-cost manufacturers in the low-income-country segment, by securing a high margin in developed markets while reducing their prices in low-income countries.

* Porter's Five Forces is a framework used to analyse the level of competition within a particular industry and inform business strategy development. The five forces analysed (threat of new entrants, threat of substitutes, bargaining power of suppliers, bargaining power of buyers and industry rivalry) define competitive intensity and the attractiveness of a market to potential entrants. For more detail, read the seminal article by Michael E. Porter 'How Competitive Forces Shape Strategy' in the March 1979 *Harvard Business Review*.[21]

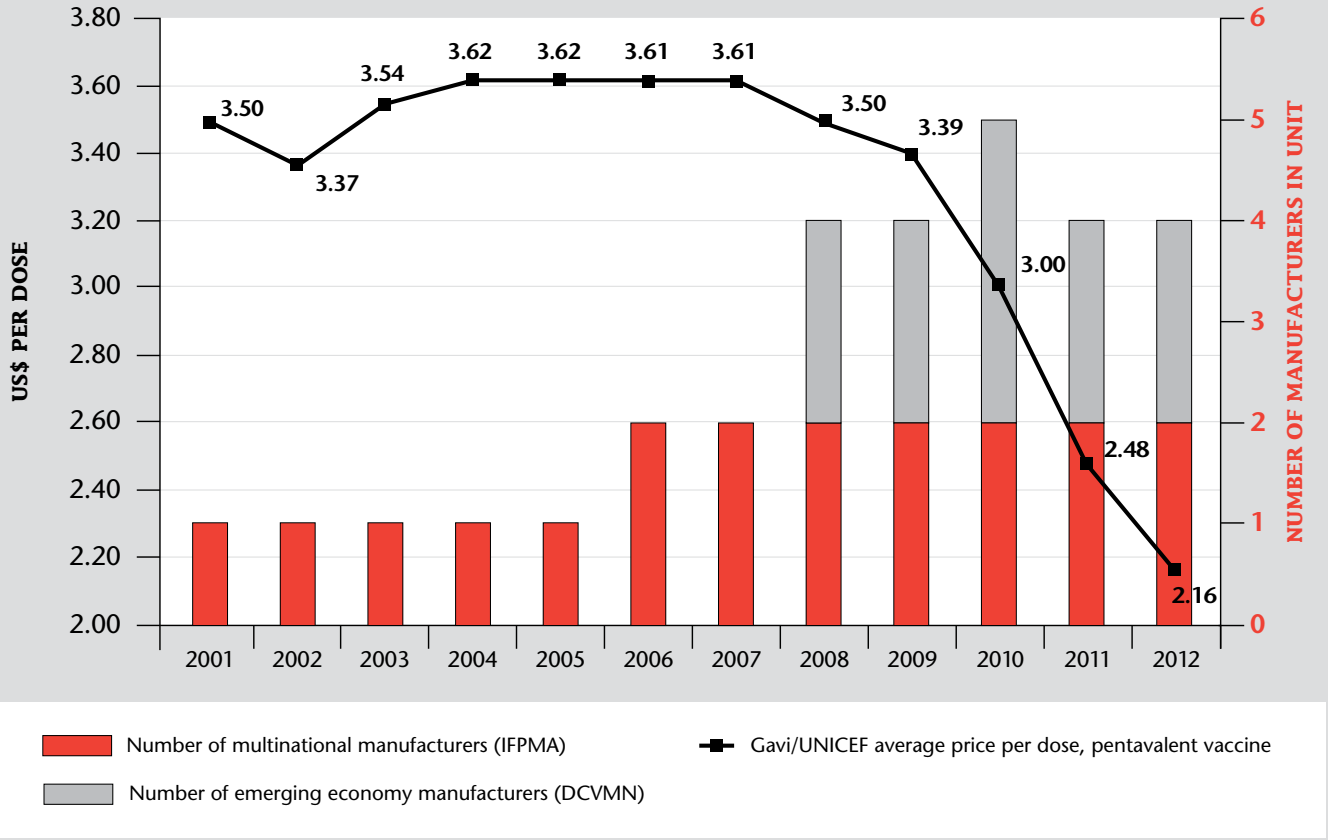
The concentration of vaccine manufacturers, combined with high entry barriers, significantly limits competition in this market, so that manufacturers making new vaccines operate in a highly protected environment.

Clear and precise information on the real costs of developing and manufacturing vaccines, which would also clarify whether industry threats to exit the vaccines market are valid, would facilitate attempts to determine vaccine affordability.

Competition brings vaccine prices down

Prices usually fall when new manufacturers enter the market. For instance, UNICEF purchased the pentavalent vaccine for Gavi-eligible low-income countries from a single supplier at US$3.50 a dose in 2001. In 2012, UNICEF purchased the vaccine from four manufacturers, at an average price of US$2.16 a dose for low-income countries. The entrance of new and low-cost manufacturers since 2008 has contributed to lowering the price per dose by 38% [see Graph 2]. Among the newest and most expensive vaccines, there is currently little competition: the PCV, HPV and rotavirus vaccines each have only two WHO-prequalified manufacturers, creating de facto duopolies for the manufacturing, distribution and pricing of these vaccines.

Graph 2: Number of manufacturers (by type) and price, pentavalent vaccines purchased for Gavi-eligible countries



Sources:
UNICEF Supply Division[25,26]

Notes and methodology:

- For Gavi-eligible countries only.
- Price per dose is calculated by dividing the total value spent by UNICEF to purchase pentavalent vaccines by the total number of doses purchased and donated to UNICEF for each year between 2001 and 2012.
- Volume and value data have been updated with the latest figures from May 2013.
- Manufacturers listed below have supplied pentavalent vaccines to UNICEF at any time between 2000 and 2012: Biological E, Panacea Biotec, Serum Institute of India and Shantha Biotechnics (emerging manufacturers); Crucell/Berna Biotech Korea and GSK (industrialised manufacturers).

NGO ACCESS TO AFFORDABLE VACCINES

MSF is one of several non-governmental organisations that vaccinate children and struggle to access affordable vaccines for their programmes; high prices limit the use of new vaccines such as PCV, HPV or rotavirus, for example, by reducing the number of children that it is possible to target for immunisation.

MSF believes that humanitarian organisations and NGOs should be able to purchase vaccines at the lowest global price – currently the Gavi price – for their medical operations. Gavi is finally publicly supporting this notion.[27] However, MSF and others still cannot systematically purchase vaccines at Gavi prices,[28] and MSF believes the commercial price that Gavi pays is still too high.

MSF has been in negotiations with Pfizer and GSK since 2008 to access PCV at the lowest global price. PCV could protect thousands of refugees and people living in hard-to-reach areas from pneumonia. However, after five years of negotiations, neither Pfizer nor GSK have been willing to sell MSF the vaccine at the lowest global price; both have offered MSF donations instead. Donations have a short-term affordability benefit, but they are unsustainable and often complicated by company-imposed restrictions on geographic or population use and volume limits, and can undermine recipients from transparently communicating about procurement challenges. Furthermore, vaccine donations create long-term harm by undercutting the market and stifling competition, as smaller companies cannot match donation offers, even if such companies offer low prices. Organisations such as WHO, UNICEF and Gavi have institutional policies against accepting donations.[29,30]

In principle, donations are not a strategy that MSF favours as a means of dealing with affordability challenges; however, after many years of failed price negotiations, MSF will make a short-term exception to its non-donation policy and accept a donation for a limited supply of PCV over the next few years. The serious delays in providing life-saving vaccines for children living in crisis have forced MSF to make this pragmatic, though unsustainable, decision.

A sustainable mechanism is urgently needed for MSF and other humanitarian actors to quickly and affordably access new vaccines for the world's most vulnerable children, regardless of where they live.

> **"Refugee children are incredibly vulnerable to vaccine-preventable diseases...and urgently need access to the newest vaccines."**
>
> *Dr Greg Elder, MSF Deputy Director of Operations*

VACCINATING IN HUMANITARIAN EMERGENCIES

Emergencies can quickly disrupt a country's health system – particularly in already fragile states with weak health systems – thereby impacting the country's ability to maintain high immunisation coverage even for basic vaccines. The most recent coverage estimates by WHO demonstrate declining vaccine coverage in countries experiencing emergencies. For example, the coverage rate in Central African Republic fell from 47% to 23% between 2012 and 2013, and in Syria the rate fell from 72% to 41% between 2011 and 2013.[31]

Children caught in emergencies are among the world's most vulnerable, yet are not routinely receiving protection from life-threatening diseases, such as pneumonia and diarrhoea. In refugee camps where MSF works, pneumococcal diseases are a major cause of morbidity and mortality and MSF has recognised the significant potential of the pneumococcal conjugate vaccine (PCV) to protect refugee children's lives. However, policy obstacles and manufacturer refusal to extend Gavi prices to NGOs have prevented rapid implementation of recent WHO guidelines recommending immunisation programmes in humanitarian emergencies.

In 2013, a retrospective survey documented childhood mortality in Yida refugee camp, South Sudan, at levels above the emergency threshold. Having determined that pneumonia was a frequent cause of child deaths in the Yida refugee population, MSF decided to vaccinate children with PCV and pentavalent vaccines. At the time of this decision, MSF had already been in negotiations with GSK and Pfizer for upwards of five years to purchase PCV at the lowest global price. After continued refusals by each company, with donation offers extended to MSF instead, MSF decided to pay US$7 per dose – double the Gavi price – to purchase approximately 24,000 doses of PCV10 from GSK. The high vaccine price forced MSF to scale back vaccination of the originally planned older age range as it could only afford to immunise children aged up to 23 months. The vaccination campaign was carried out in three rounds from July through September 2013.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AFFORDABILITY CHALLENGES FOR GAVI-GRADUATING COUNTRIES

While Gavi currently subsidises vaccine purchases in almost all of its originally eligible countries, more than a quarter of its country cohort is 'graduating'.[8] Some of these countries will lose Gavi support entirely starting from 2016.[32]

Countries receiving Gavi support for new vaccines are required to finance a portion of the vaccine cost with non-Gavi funds; this 'co-financing' requirement is based on a country's GNI per capita. Triggered by reaching the GNI eligibility threshold (currently at GNI US$1,570 per capita), 20 Gavi-graduating countries are experiencing an aggressive increase in co-financing obligations through the graduation process. Some graduating countries have expressed concern that their increasing immunisation costs cannot be sustainably financed as they lose Gavi subsidies. Saxenian et al. have reported on the affordability challenges that some of these graduating countries are already facing.[8] Several have sought external donor support to help finance their immunisation programmes post-Gavi; another will become the recipient of a vaccination trust fund.[8] The expected budget increases for previously-supported Gavi new vaccines are listed in Table 1. The table excludes other non-Gavi-supported vaccines that countries have to also finance.

Table 1: Select Gavi-graduating country co-financing payments for new vaccine costs (in US$)

Country	2012	2018	Increase 2012–2018 (%)
Angola	2,267,799	34,542,500	1,523%
Armenia	193,804	1,082,000	558%
Azerbaijan	1,224,450	3,028,500	247%
Bhutan	39,068	133,500	342%
Bolivia	730,675	5,134,000	703%
Congo	563,712	4,513,500	801%
Georgia	239,941	1,710,000	713%
Guyana	36,447	365,000	1,001%
Honduras	1,088,385	3,365,000	309%
Indonesia	2,088,500	32,314,500	1,547%
Kiribati	15,475	60,000	388%
Moldova	154,092	1,116,000	724%
Mongolia	129,985	676,000	520%
Sri Lanka	943,752	1,860,500	197%
Total	7,627,585	89,901,000	1,179%

Source: Saxenian et al.[8]

> **"When Nigeria exits from Gavi support, it needs to be able to get vaccines at Gavi prices or lower to continue to afford them."**
>
> *Professor Muhammed Ali Pate, former Minister of State for Health, Nigeria*

In addition to losing the Gavi subsidies, Gavi graduates have only time-limited access to the lower negotiated Gavi prices, and only for specific vaccines. Without long-term assured price access or new low-cost competitors entering the market, vaccine prices for Gavi-graduates could spike far higher than the current prices – which will already stretch health system budgets – once Gavi subsidies conclude. Gavi has secured an extension of some of its discounts for graduating countries from some manufacturers. These agreements – with Crucell, Sanofi Pasteur/Shantha, GSK and Pfizer – are time-limited and with a variety of conditions, rendering these ad hoc deals, like short-term donations, unsustainable in the long term.[33] Some companies that also supply Gavi, such as Merck (for rotavirus and HPV vaccines), have yet to make similar commitments for Gavi-graduating countries.

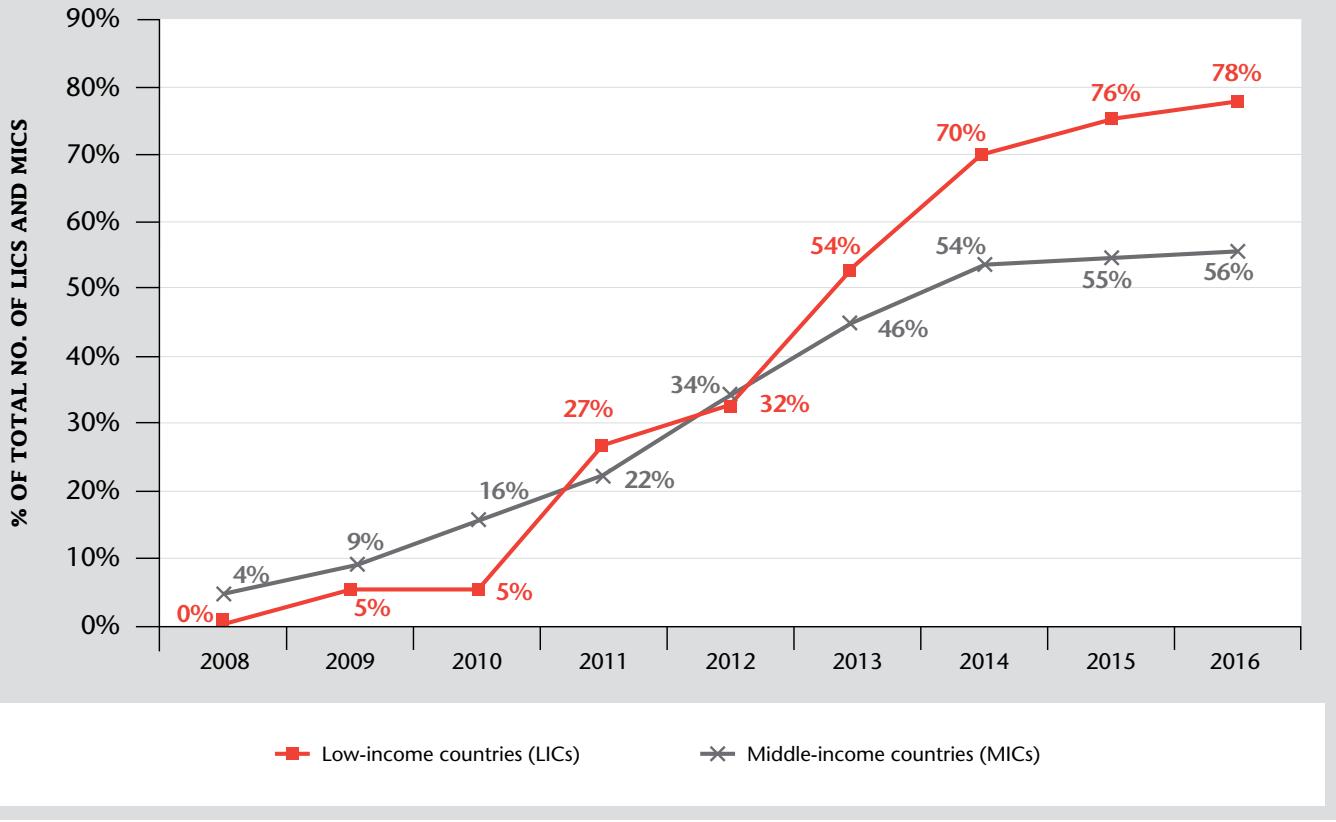
MIDDLE-INCOME COUNTRIES STRUGGLE TO ACCESS AFFORDABLE VACCINES

For countries that are considered middle-income economies – MICs currently number more than 100 – introducing new vaccines is an immense challenge from an affordability standpoint. The MICs, with a combined population of about five billion, a birth cohort of approximately 96 million,[34] and where 75% of the world's poor live,[35] have diverse public health needs and economic realities. Achieving the 'middle-income' economic threshold has paradoxically limited their ability to access new vaccines at affordable prices. Twenty-one of the 54 countries categorised as lower-middle-income (LMIC) are Gavi-eligible; the remainder, and all of the upper-middle-income countries (UMIC) are either unable to access Gavi support or will be 'graduating' soon.[36]

Higher vaccine costs are difficult to absorb in many MIC budgets, as these countries already self-finance a costly immunisation budget. A 2006 study of comprehensive vaccine costs in Vietnam found that the introduction of new vaccines would increase the government's budgetary costs by more than 100%.[37] Given that vaccines are only part of the cost to immunise a child – for instance in Honduras, total vaccine costs for a immunised child are US$39.93, but comprehensive implementation costs US$136.62 – the escalation in vaccine prices has become prohibitive.[38]

Countries excluded by Gavi often have few sources of external support for vaccine introduction. Bilateral price

Graph 3: Proportion of LICs and MICs that have introduced or plan to introduce Pneumococcal Conjugate Vaccines (PCV)



Sources: WHO,[44] World Bank[45]

Notes and methodology:

- Year of introduction (and planned introduction for 2013, 2014, 2015 and 2016) as registered by WHO as of 31 Dec 2012. WHO draws the data from the most recently received Joint Reporting Form. Latest update: 17 Jan 2014
- Classification of countries as low-income (LIC) or middle-income (MIC) is done using 2012 GNI per capita, calculated using the World Bank Atlas method:[45]
  - LICs: GNI of US$1,035 or less
  - MICs (include LMICs and UMICs): GNI of US$1,036–12,615
- Number of LICs in 2012: 37
- Number of MICs in 2012: 100 (47 LMICs and 53 UMICs)

negotiations with vaccine manufacturers place these countries, which may have lower volumes and lack expertise in price negotiations, at a distinct disadvantage. Where certain vaccines have not been introduced into EPI, individuals may purchase them privately, sometimes at prices comparable to those in high-income countries. For instance in 2014, the PCV13 vaccine was available for US$63.74 per dose in hospitals in Morocco, while in France the manufacturer price was US$58.43 per dose. Many children – 77% of the MIC cohort – are vaccinated in countries undertaking self-procurement for some or all of their vaccines; these countries are paying higher prices than pooled procurement could yield.[39] In some of these countries, prices of vaccines can reach more than 20 times the price paid by Gavi/UNICEF. For instance, the HPV vaccine is purchased at EUR75/US$100 in Macedonia, or 22 times the price paid by countries supported by Gavi.[40]

By 2011, low-income countries (LICs) had surpassed MICs in PCV introduction, the annual growth rate of introduction between 2009 and 2016 being 47% for LICs compared to 30% for MICs [see Graph 3, page 14]. Despite the high pneumonia burden, MICs have been slow to adopt this expensive new vaccine [for prices, see the PCV product card, page 72]. By 2016, it is expected that 78% of LICs will have introduced PCV in their routine immunisation programmes, versus 56% of MICs. The high cost is even altering the cost-effectiveness analyses of these life-saving vaccines: Thailand found that, at the current price, PCV was not cost-effective enough to be integrated into EPI.[41]

Economic indicators alone do not encapsulate societal development, nor do economic indicators necessarily correspond to the ability of a country's health system to reach its population with essential health services. Relying solely on crude economic thresholds is too unsophisticated a method for establishing a country's ability to pay. For example, Nigeria is categorised as a LMIC, with a 2013 GNI per capita of US$2,760.[42] Nigeria, however, has a vaccination coverage of 58%, making it the country with the second highest proportion of unimmunised children in the world. Other MICs similarly suffer from poor health service performance and disproportionately high disease burdens. The Republic of South Africa has a vaccination coverage of 65% and an HIV prevalence rate of 17.9%,[43] illustrating that despite its positive general economic achievement the country's public health indicators remain dire. Countries like South Africa benefit neither from donor assistance (for immunisation) nor from pricing mechanisms that can increase affordability and accelerate availability of vaccines for the public. The HPV product card [see page 39] shows how the price of HPV introduction in South Africa is affecting the government budget.

To understand how arbitrary the economic indicators that are used to divide countries are, consider that in 2013 there were 28 countries that have never been Gavi-eligible that had a GNI per capita lower than that of the Gavi-graduating country with the highest GNI.[39]

PAHO'S REVOLVING FUND: A REGIONAL POOLED PROCUREMENT AND FINANCING MECHANISM FOR VACCINES AND RELATED SUPPLIES

The Americas region has a diversity of countries at various levels of economic development and health system performance. Established in 1977[46] as part of the Expanded Program on Immunization (EPI) of the Americas, the Pan-American Health Organization's (PAHO) Revolving Fund is a pooled procurement and financing mechanism for vaccines and related supplies. The PAHO Revolving Fund has been credited with Latin America and the Caribbean's high immunisation rates, disease eradication and elimination successes, early vaccine introduction, and access to some of the lowest vaccine prices in the world.[47] The predictability of supply/demand and the lower prices negotiated have enabled countries in the region to better plan for their immunisation budgets, resulting in higher rates of national financial self-sufficiency; 95% of vaccines costs are financed with national funds. More than 180 million vaccine doses (worth US$512 million) were purchased in 2012 for PAHO's participating 35 countries and six territories.[46]

The Revolving Fund establishes annual and multi-year tenders for vaccines and makes use of a credit line financed by PAHO member states. Historically, PAHO's Revolving Fund has negotiated with manufacturers and obtained the lowest prices by pooling demand and offering the vaccine at the same single price per vaccine for the region, independent of a country's economic classification.

The Revolving Fund has also negotiated with companies to obtain most favoured nation status, whereby manufacturers agree to offer the Revolving Fund the lowest global price for a specific vaccine product. However, this is changing as companies that practise tiered pricing and some international donors dislike the most favoured nation clause and argue that MICs in the PAHO region – such as Brazil or Ecuador – should pay higher prices than those offered through Gavi to the region's poorer countries. While there were originally six Gavi-eligible countries in the PAHO region, five of these countries are currently losing Gavi support through the graduation process.

VACCINE PRICE AND DATA OPACITY

The vaccine pricing landscape is notoriously opaque, and prices paid for the same vaccine vary significantly from one country to another. This is in contrast to the availability of price data for other public health commodities. Prices for HIV antiretroviral (ARV) medicines, for example, are published on the WHO's Global Price Reporting Mechanism, allowing a modest comparison of costs across countries, companies and time – although the lack of generic competition for new ARVs, and the increasing use of tiered pricing for these drugs, is significantly obscuring ARV prices across countries.[48] The opacity of vaccine pricing hinders countries, especially MICs, from introducing new vaccines and raises concerns as to whether Gavi-graduating countries will be able to sustain their full immunisation programmes when they can no longer access the Gavi-negotiated prices.[49]

Without price comparison mechanisms, countries cannot fully understand the vaccine market and are unable to determine if they are paying an affordable price for their vaccines. Governments and policy makers are increasingly using cost-effectiveness analyses to inform decision-making when planning the purchase and introduction of new vaccines.[50,51] However such studies often lack an important element: the price the country will be charged for the vaccine. An evaluation of cost-effectiveness analyses of HPV concludes that, "in the end then, the key determinant of cost effectiveness is the only factor that cannot be evaluated, even though it will be important when deciding on the vaccine to be used in a national prevention scheme."[52]

The growing demand from countries to have access to reliable price and procurement data[23,51] has prompted the international community to start developing initiatives on price transparency, but information remains scarce [see page 18].

WHY ARE THE COST COMPONENTS OF A VACCINE SO OBSCURE?

The cost components for vaccines are challenging to understand, as most associated costs are not publicly available. Vaccine costs should depend upon governments' and pharmaceutical companies' investment choices in research and development (R&D), cost of goods, manufacturing, regulatory approvals and marketing, among other factors; however, little of this information is communicated publicly.

Myths and opacity behind R&D costs

The R&D investment required for a new vaccine varies widely and companies themselves cite wildly different figures. Often the pharmaceutical industry provides R&D investment estimates that are too high; for example PhRMA, Pharmaceutical Research and Manufacturers of America, states that total development costs can reach close to US$1 billion.[53] But in a 2009 article in the journal *Vaccine*, Light et al. estimated that rotavirus vaccine development costs were US$167–508 million for Merck's product and US$150–466 million for GSK's

Table 2: Total worldwide revenues of HPV, PCV and rotavirus vaccines, published by companies (in US$ million)

	Total cumulated sales, in US$ million	Average sales per year, in US$ million	Sales time period
Pfizer, Prevnar 13	15,905	3,976	2010–2013
Merck, Gardasil*	9,896	1,237	2006–2013
Merck, Rotateq*	4,282	535	2006–2013
GSK, Synflorix	2,240	448	2009–2013
GSK, Rotarix	3,038	380	2006–2013
GSK, Cervarix	2,046	292	2007–2013

Table sources: GSK, Merck and Pfizer annual reports 2006–2013; research note.[62]

Notes:

Exchange rate based on Oanda.com and xe.com, using yearly July rates.

* These amounts do not reflect vaccines sales in major European countries made through the joint venture Sanofi Pasteur MSD. However, amounts reflect supply sales to Sanofi Pasteur MSD.

product (in 2008 US$), acknowledging that the Phase III clinical trials were unusually large; GSK cited them as the 'largest infant vaccine trials ever conducted'.[54] This aligns with the findings of André et al. that costs to bring a new vaccine to market ranged from US$200 to US$500 million.[55] While private sector investment in R&D has been overstated, public sector contributions to vaccine development are often under-reported. For the HIV vaccine, in 2012 the public sector contributed approximately 83.4% of the overall investment, with the commercial sector contributing only 3.5% in early-stage research and development.[56] Likewise for one HPV vaccine, two Australian research centres alone are credited with 13% of research and development costs.[57] The US National Institutes of Health and US universities also contributed significant public resources to the development of the HPV vaccine. Such investments are not factored into the end price of the vaccine, meaning that governments are often paying twice for a product: through their R&D investment and by paying high prices.

The opacity of manufacturing costs

Opacity in manufacturing costs is also a challenge to making informed public health decisions. It gives rise to uncertainty regarding some pharmaceutical companies' statements that vaccines are being sold 'at cost' to Gavi-eligible countries. Without independent verification, it is unclear whether profits are still being made off sales to the world's poorest countries. In 2013, the president of Merck Vaccines noted that the price of HPV vaccine at US$4.50 per dose to Gavi represented Merck's manufacturing cost, excluding research, marketing or other costs.[58] A GSK representative also claimed that profit could not be made at their price of US$4.60 per dose to Gavi.[58] As no independent group has been allowed to verify the manufacturing costs cited by Merck and GSK, it is unknown whether this price represents the actual per-dose manufacturing cost.

Nevertheless, Merck and GSK's public statements that the price of their HPV vaccines to Gavi represents the cost of manufacture, at US$4.50 and US$4.60 per dose, respectively, demonstrates the significant profit margin that is derived from sales to other countries, such as the US, where the government is charged US$121.03 and US$103.85 per dose, respectively. MSF is undertaking a study to explore the actual manufacturing costs for HPV vaccine.

Without verifiable information on the real cost of manufacturing and other cost data, it is impossible to accurately assess company profits. Nevertheless, the high prices of these vaccines in developed markets have enabled manufacturers to earn tremendous returns estimated to be at least 12 to 16 times the cost of manufacture (based on the assumption that the Gavi price represents the vaccine manufacturing cost) for Cervarix and Gardasil.[58–61] Revenues as reported by the companies producing the newest vaccines are listed on page 16 [see Table 2, opposite].

THE ADVANCED MARKET COMMITMENT MODEL: MAKING PROFITS FROM DEVELOPING COUNTRY MARKETS

A precedent of deriving profits from developing-country vaccine markets was established by the Gavi Advance Market Commitment (AMC) for pneumococcal vaccines. The AMC concept was proposed as a means of spurring investment in vaccines for diseases concentrated in low-resource countries and of promoting rapid vaccine uptake in the most affected countries.[63,64] It was hypothesised that a donor-subsidised ceiling price and demand quantities would incentivise a range of vaccine manufacturers to open new lines of research that would not have otherwise been developed.

The Gavi AMC for PCV provided a late-stage public- and philanthropic-funded subsidy of US$1.5 billion that to date has benefitted two multinational manufacturers (Pfizer and GSK) that had already committed to producing a profitable vaccine.[65] In a 2012 evaluation of the AMC, Dalberg Global Development Advisors found that one of these manufacturers expanded its manufacturing capacity in response to the AMC (the other had already decided to expand for a global market).[65] Despite the limitation of manufacturers being unwilling to share their costing information, the evaluation nevertheless determined that the two manufacturers were earning returns at or above the 10–20% mark typically referenced as incentivising suppliers in the vaccines/pharmaceutical industry. The AMC manufacturers may ultimately reap profits in excess of 20% from the subsidy.[65] The evaluation's conclusions noted that the AMC did not contribute to the development of the existing PCV products, and that "the substantial revenue potential of the Gavi market therefore may have been enough to attract low-cost manufacturers without additional subsidies [of US$1.5 billion from the AMC]". While a third manufacturer is expected to enter the market in 2019, the AMC was not a critical factor in this investment decision, though a fourth company tripled their research investment in PCV after the AMC announcement.[65] To date, 73% of the AMC donor funds (US$1.095 billion) for Gavi have been committed to Pfizer and GSK.

DESPITE GLOBAL INITIATIVES TO IMPROVE PRICE TRANSPARENCY, PRICE INFORMATION REMAINS SCARCE

Price transparency is rare in the vaccines market, with both countries and pharmaceutical companies often reluctant to share price information.

Some manufacturers have taken steps towards articulating their global pricing strategy; for instance, both GlaxoSmithKline (GSK) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) published tiered-pricing papers in 2013 that provide some information on their pricing strategies for developing countries.[17,66] There is, however, little will to increase transparency about prices themselves, as companies fear price erosion as a result of competition and publicly available price references. For the purposes of preparing this report, MSF contacted nine companies to request information on their vaccine prices; all of the multinational manufacturers declined to share their prices. For more information, see the box 'How do pharmaceutical companies set their vaccine prices?', pages 20-22.

On the buyers' side, the PAHO Revolving Fund[67] has been publishing its prices for many years, but data are limited to the weighted average price by product presentation; the information does not include the manufacturer price per product, nor volumes purchased, and historical prices are difficult to access. In 2011, UNICEF Supply Division for the first time retroactively published ten years of price information for all its low-income country vaccine purchases.[11,68] UNICEF's move to increase transparency was a milestone in vaccine price discussions, further adding to the information base that has enabled the comparison of prices across various regions and by countries at different levels of economic development; those data sets inspired publication of the first edition of the this report.[68]

On country-specific data, some national websites provide public- and private-sector vaccine prices, but the sites are typically difficult to navigate and lack descriptive information about the products and price components, limiting the usefulness of the data and accurate cross-country comparisons (see Annex A for methodology and difficulties encountered). To develop the Vaccine Product Cards in this report, we sought country price points to conduct analyses across different economic development levels. As concluded by S. van Dongen in a comparative analysis of websites reporting medicine prices in 2010, the utility of identified national price data was limited by missing information such as the components of each price, and the comprehensiveness of the price information.[69]

Reasons cited by countries and companies for concealing vaccine prices include the fear that data could be wrongly interpreted and concern about parallel trade.[70] These concerns have for instance pushed the once publicly accessible Common European Drug Database (CEDD, called Euripid since 2010), which was created "to make prices of pharmaceuticals easily available for the public of Europe",[71] to now restrict its access to officials from its member countries.

The availability of pricing information for other public health commodities such as ARVs for HIV,[72] contraceptives and artemisinin combination therapy (ACT) for malaria, indicates that vaccine price opacity does not need to exist. An analysis of six medicine price-information mechanisms showed that positive effects on access to medicines – such as uptake of higher-quality medicines, improved contract negotiation outcomes, changes in national pricing policies and lowered prices – are seen when mechanisms that increase data quality and price transparency exist.[73] As vaccines are largely purchased by governments in the public sector using tax payer monies, it is reasonable for citizens to have access to the prices paid and to expect government and industry accountability for the prices negotiated.

> **"To the extent that we know what other countries are paying, that would strengthen our arm [in negotiations with companies]."**
>
> *Dr Yogan Pillay, Deputy Director General, Department of Health, South Africa*

Developments in vaccine price data availability and price monitoring

Outside of the prices published by the PAHO Revolving Fund and UNICEF, there are few initiatives to enhance price transparency.[74]

At country level, initiatives exist to enhance decision-making based on cost and price analysis. ProVac – a programme-costing model developed by the PAHO region in 2006 – was born out of the need to strengthen economic evaluation and increase the use of economic evidence to inform national EPI decision-making. While not a price transparency mechanism per se, ProVac enables countries to share economic evaluations and costing studies, which benefit vaccine pricing decisions in other countries.[75,76] The ProVac initiative has provided evaluation support to 14 countries in the PAHO region for introduction of HPV, PCV and rotavirus vaccines. Following the success of the initiative, PAHO received requests for ProVac support from countries outside of the region. Since

its founding, ProVac has compiled data from more than 130 countries to assist national decision-makers.

At a global level, the importance of price transparency is gaining momentum as countries increasingly articulate high prices as a barrier to vaccine access. Almost half of the US$57 billion budget of the Decade of Vaccines (DoV) – the global framework for expanding access to immunisation from 2011 to 2020 – will be absorbed by the cost of vaccine commodities alone, and in 2012 MSF advocated price monitoring over the course of the DoV. At the 2013 World Health Assembly, a proposed framework for monitoring, evaluation and accountability of the Global Vaccine Action Plan (GVAP) included the addition of a report on trends in vaccine prices, with the development of indicators to monitor prices over the decade.[74] Monitoring prices is now considered a measure of success for the GVAP, "a challenging task, but an important priority".[77]

In 2012, UNICEF Supply Division launched a middle-income country pooled procurement pilot mechanism for new vaccines, with one objective being increased price transparency. As part of the pilot, UNICEF asked manufacturers to share prices for countries participating in the mechanism and reference pricing for countries electing to self-procure.[78,79] In the initial forecasting, 19 countries (with a birth cohort of 7.2 million) expressed interest in joining the initiative.[78] At the time of this publication, UNICEF had not announced any awarded contracts from this pilot. No information on why this procurement mechanism has so far not worked has been made public. It has been argued that few manufacturers responded to the tender, as they were unwilling to provide public reference prices, which companies see as potentially undermining their capacity to sell at higher prices to other markets; another hypothesis is that companies did not see clear commitments from countries to purchase the vaccines.[77,35]

The most promising initiative in the price information domain could be the WHO Vaccine Product, Price and Procurement (V3P) project, a mechanism that can have a critical role in fostering international data transparency [see box below].

Increased price transparency will help to fill the data gap and reduce the current asymmetry of information between purchasers and suppliers. When manufacturers claim to use differential pricing that offers the 'right' price to a country, they use publicly available information on countries to classify them and justify a price at which to sell their vaccines. But as manufacturers maintain total opacity on their R&D, production costs and prices, it is significantly more complicated for countries to negotiate fair prices that can be defended against industry's oft repeated statements that prices paid do not sustain future investments in R&D and do not even cover their operating costs.

THE WHO VACCINE PRODUCT, PRICE AND PROCUREMENT (V3P) PROJECT

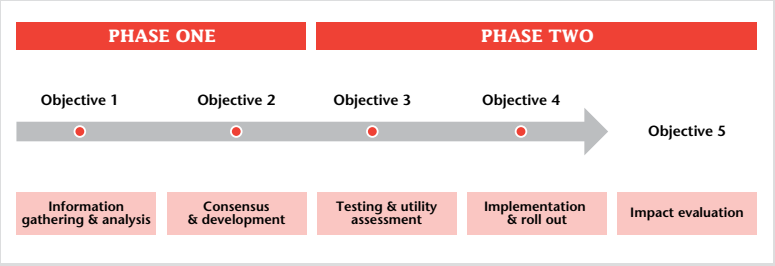
Launched in 2011, the WHO Vaccine Product, Price and Procurement (V3P) project aims to develop a mechanism to collect, assemble and disseminate "reliable, accurate and neutral information and data on vaccine product, price and procurement, allowing for increased price transparency and more informed decision making in the vaccine implementation and procurement processes".[80]

The mechanism should be used collaboratively by countries, especially self-procuring low- and middle-income countries and Gavi-graduating countries, with the end product a web-based tool linked to the database, similar to the WHO Global Price Reporting Mechanism (GPRM)[72] on HIV drugs. The project has started collecting pricing data and had a soft launch with select country data in June 2014 [Objective 4 from Figure 2].

The V3P could be critical to achieving improved international price transparency. As it moves into implementation, sustained WHO and government political will and commitment to share price information will be key to the development and success of the V3P mechanism. For more information, visit the V3P website: www.who.int/immunization/programmes_systems/procurement/v3p/platform/en/

Figure 2

Phases of the V3P project



Equipping countries with accurate and reliable price information would assist decision making and lead to quicker and more sustainable adoption of new vaccines.[51]

Additionally, having access to the terms and conditions by which other countries manage to secure lower prices (e.g. manufacturer, product, presentation, procurement terms, volumes, duration of contract) would assist governments in better understanding product options available and how to lower the cost of introducing vaccines.[49,51]

HOW DO PHARMACEUTICAL COMPANIES SET THEIR VACCINE PRICES?

In an effort to better understand vaccine pricing, we contacted nine pharmaceutical companies* and asked them to share their prices and pricing strategies for this report. Findings are presented below, including companies' responses.**

TRANSPARENCY

- Vaccine prices are difficult to find. Companies usually do not publish them, considering the information to be proprietary and confidential. Pricing reports published by the MSF Access Campaign, such as Untangling the Web of Antiretroviral Price Reductions, use price information voluntarily shared by pharmaceutical companies or listed in searchable public databases, but our efforts to secure vaccine price information from companies were far less successful.
- Out of the nine companies contacted:
  - four shared their prices (Bio Farma, Biological E, Panacea and Serum Institute of India);
  - seven shared some information regarding their pricing strategy or vision (the four listed above and Crucell, GSK, Merck and Pfizer);
  - one did not reply within the requested time period (Sanofi Pasteur).
- Large multinational companies are not inclined to improve price transparency as it is perceived to increase price referencing and thus weaken their negotiating position with governments and other purchasers. One company cited price transparency as increasingly compromising its ability to offer low prices to the poorest countries.
- Emerging manufacturers from developing countries were more transparent and willing to share their prices and other pricing strategy and product information.

PRICING STRATEGY

Pricing strategies are influenced by the particularities of each market and the power of its actors. Please refer to the page 10 analysis of the new vaccines market and the forces active in the industry.

In the vaccines market, two groups of manufacturers emerge, each with distinct pricing strategies. While each manufacturer will have its own particular strategy, two broad models can be identified:

- Cost-plus pricing strategies
- Value-based and differential pricing strategies

GROUP 1: COST-PLUS PRICING STRATEGIES[82] PRICE IS MAINLY FIXED ON COSTS (E.G. COSTS OF PRODUCTION)

- The emerging manufacturers we contacted largely do not apply differential pricing strategies, selling their vaccines at similar prices to all countries, with price variation mainly attributable to differences in Incoterms,*** transportation costs and regulatory costs.
- This strategy allows manufacturers to compete on price and use their low cost structure and ability to reduce costs to sell vaccines at a much lower price than other manufacturers.

* Details on company contacts available in Annex B.
** Research methodology presented in Annex A.
*** See definition of Incoterms in Annex C.

GROUP 2:
VALUE-BASED AND DIFFERENTIAL PRICING STRATEGIES[82]
PRICE IS FIXED ON THE BASIS OF WHAT BUYERS ARE WILLING/ABLE TO PAY

- This strategy is especially used in non-competitive markets (e.g. for newer vaccines) where manufacturers do not have to compete on price.
- In this strategy, the price of the product is not evidently linked to costs; the manufacturer seeks the best price that the buyer is willing to pay, even if it means applying different prices to different buyers. This differential pricing or market segmentation strategy is often referred to as 'tiered-pricing'.
- Multinational manufacturers that replied to our request reported that they apply differential pricing strategies; however when asked for more information, most provided little or no or detail on how their tiered pricing policies are defined. Company responses follow:
    - Crucell, a subsidiary of Johnson & Johnson, applies a tiered-pricing strategy, aligned with Johnson & Johnson's Credo,[83] and believes that tiered pricing is the best solution in markets with limited suppliers, and that preventing companies from tiering prices would lead to higher vaccine prices in developing countries. However, little information is publicly available on how tiers and prices are set.
    - GSK operates a tiered-pricing approach, describing it as "based on a country's development level and ability to pay". GSK does not share further pricing information but has published a publicly available position paper on tiered pricing that details its seven-tier approach to differential pricing.[17]
    - Merck details its pricing position as "a worldwide differential-pricing framework that takes into account many factors including countries' level of economic development, public health priorities, volume and duration of procurement and economical value for the local health care system". However, little information is publicly available on how tiers and prices are set.
    - Pfizer does not share its pricing policy with third parties, but supports principles of tiered pricing, as developed in the 2012 IFPMA position paper on tiered pricing.[66]

EFFECT ON PRICES

These two different pricing strategies are reflected in vaccine prices.

- Pricing strategies influence the price set by manufacturers for a similar product. Companies from Group 1 above compete on prices, and usually offer their vaccines at a lower price than manufacturers from Group 2 [see Table 3, overleaf]. As originator manufacturers claim that their cost structure typically does not allow them to compete on low-price competitive markets, they might decide to exit the market when prices become too low (e.g. Crucell exited the measles-rubella UNICEF market in 2013, citing the fact that pricing trends were incompatible with the company's strategy), or to concentrate on high-margin and more profitable markets (e.g. newer vaccines, high-income markets).
- Pricing strategies influence the price paid across buyers. Manufacturers from Group 1 tend to offer their products at a similar price to all countries, while manufacturers from Group 2 apply value-based and differential pricing strategies. In Graph 4, page 22, we see that the highest price paid (that could be identified through public information sources) for PCV by a MIC is 1,471% higher than the price to Gavi countries.

Table 3: Comparison between the highest and lowest available price to UNICEF for selected vaccines for low-income countries (Gavi-eligible countries only), in US$ per dose

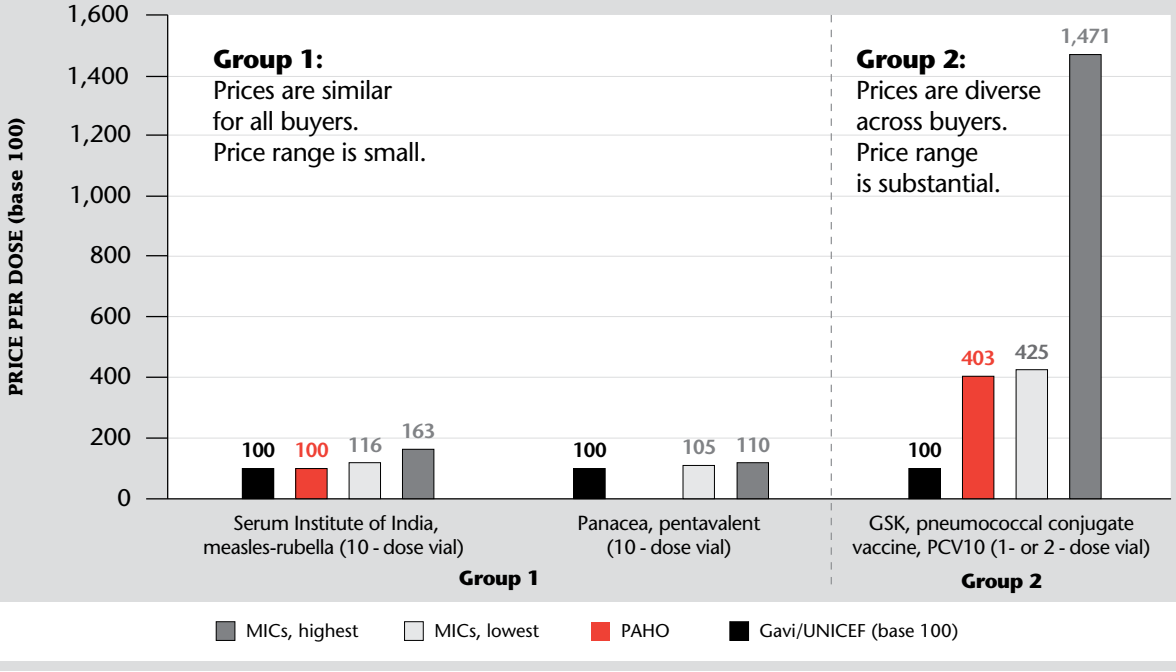
Vaccine	Lowest price	Highest price	% difference
PCV, 2014 and forecasts	SII*	GSK	73%
	$2.00	$3.40 – 3.50	
MMR (10-dose), 2014	SII	Sanofi Pasteur	84%
	$1.02	$1.89	
Measles (10-dose), 2014	Bio Farma	Sanofi Pasteur	105%
	$0.22	$0.45	
DTP (10-dose), 2012	Bio Farma	Sanofi Pasteur	175%
	$0.16	$0.44	
Rotavirus, 2014 and forecasts	Bharat Biotech**	Merck	400%
	$1.00	$5.00	

Table sources: UNICEF SD,[11] Bloomberg News 2013[84]

*Price commitment from Serum Institute of India (SII) to produce PCV and sell it at US$2 per dose.[84]

**Price commitment from Bharat Biotech to produce a rotavirus vaccine (Rotavac) and sell it to the public sector at US$1 per dose.[85]

Graph 4: Examples of vaccine price differences between countries, illustrating distinct pricing strategies (see also box on pages 20 & 21)



Sources: UNICEF Supply Division,[86] PAHO Revolving Fund,[67] country price analysis (see Annex A for details on methodology and sources), communication with manufacturers.

Notes and methodology:

- Data are for 2013 or 2014.
- Group 1: companies operating cost-plus pricing strategies.
- Group 2: companies operating value-based and differential pricing strategies.
- If the Gavi / UNICEF price for the Serum Institute of India (SII) vaccine was US$100, the highest price observed for the same product in a MIC would be US$163, or 1.63 times the UNICEF price. For GSK's PCV10, the highest price observed in a MIC is 14.71 times the price offered to Gavi / UNICEF.
- For SII and Panacea, price range for MICs was obtained through communication with the companies.
- For GSK, prices represent the lowest and highest national prices found via public information.
- Sources and definitions detailed in Annex A.

EXISTING SOLUTIONS TO IMPROVE AFFORDABILITY AND THEIR LIMITS

POOLED PROCUREMENT INITIATIVES AND ASSOCIATED CHALLENGES

Existing solutions to improve vaccine affordability

Pooled procurement of vaccines – a strategy whereby several countries aggregate their individual volume needs, to their mutual benefit – can help to reduce prices by leveraging economies of scale and streamlining heavy procurement processes by centralising vaccine tenders, contracts and payment. It is an effective strategy to lower vaccine prices for the purchaser and lessen procurement capacity requirements for countries.[87] For example, countries with small populations may have difficulty negotiating affordable prices because of their limited profitability for suppliers and resulting lack of market power.

'Pooling' demand from multiple purchasers benefits both purchasers and suppliers. Larger vaccine volumes mean greater negotiating power for purchasers, such as governments, while pooled procurement provides manufacturers with more predictable volumes for manufacturing plans, allows improved forecasting and reduces transactional costs through simplified contracting and purchasing processes. Pooled procurement is used by the PAHO Revolving Fund, UNICEF Supply Division (SD), by Gavi through the UNICEF SD, by the Vaccine Independence Initiative for the Pacific Islands (also managed by UNICEF SD), and the Gulf Cooperation Council.

Countries and organisations that practise pooled procurement vary in their characteristics. For example, Gavi's eligibility policy (country GNI per capita <US$1,570) means that its pooled procurement is based upon economic indicators. As part of its market-shaping strategic goal, Gavi uses pooled procurement via UNICEF SD to negotiate lower prices on behalf of the donors that pay for new and underused vaccines for Gavi-eligible countries.[88] The PAHO Revolving Fund uses pooled procurement for a geographic zone, whereby any country in the Americas region can use its procurement mechanism to access the prices negotiated by the Revolving Fund secretariat [see box: PAHO's Revolving Fund, page 15]. Countries of the PAHO region primarily self-finance their own immunisation budgets, with more than 95% of the cost of vaccines bought through the Revolving Fund paid by national funds. The Revolving Fund has, however, been under pressure to alter its principles of regional solidarity and the availability of one price for all countries [see box overleaf: Two public health organisations with different price models].

UNICEF Supply Division developed the pilot Middle Income Country New Vaccine Procurement Initiative in 2012, in response to growing concern for Gavi-graduating countries and for other MICs left out of any other existing pricing or pooled procurement structures. The initiative was established to pool demand among MICs for the three newest and most expensive vaccines – PCV, HPV and rotavirus vaccines – and aggregate forecasts for companies.[78] No awarded contracts from this pilot have been published, however, and information on why the mechanism has so far not worked is not public; it is likely that few manufacturers responded to the tender, as they were unwilling to provide public reference prices. For more information on this mechanism, see 'Developments in vaccine price data availability and price monitoring', page 18.

The Gulf Cooperation Council, established in 1978, includes six participating countries that pool their vaccine needs, aggregating demand and standardising specifications across countries.[89,90] Countries in the group use the mechanism differently, with some countries using it occasionally while others use it to supply the majority of their vaccines.

At the request of its member states, the WHO Eastern Mediterranean Region (EMRO) began work on a Pooled Vaccine Procurement (PVP) initiative in 2011.[39] The initial phase of the initiative received interest from Egypt, Iraq, Jordan, Lebanon, Libya, Morocco, Syrian Arab Republic and Tunisia, and was ready to supply interested MICs with pentavalent vaccine, PCV, rotavirus vaccine and HPV vaccine as of October 2013.[91,92] As of mid-2014, tenders had not yet been released for the PVP initiative.

In a 2010 analysis on pooled procurement mechanisms for vaccines, the World Bank and Gavi highlighted the value of pooled procurement mechanisms as:

- predictability (stable flow of funds)
- equitability (especially for participating low-income and small countries that would otherwise probably pay higher prices)
- efficiency (more efficient use of resources and lower vaccine cost)
- feasibility (requires investment and agreement on procurement legislation)
- sustainability (long-term vision).[47]

TWO PUBLIC HEALTH INSTITUTIONS WITH DIFFERENT PRICE MODELS

Gavi/UNICEF and the PAHO Revolving Fund both use pooled procurement strategies to leverage economies of scale for price negotiations with manufacturers, but each has a different philosophy on what is considered an affordable price. Gavi advocates tiered pricing,[93] and uses donor support and its mandate of purchasing new and underused vaccines for only selected developing countries as the basis for its negotiations with manufacturers. Gavi promotes the concept that the lower prices it receives should be subsidised by higher-income countries, which should be expected to pay more. The PAHO Revolving Fund operates on principles of regional solidarity and the philosophy that pooled procurement should lower prices for all purchasers, thereby establishing one price for any country that wishes to use the mechanism. PAHO therefore does not treat countries of different economic levels differently, and instead passes the benefit of its bulk negotiations onto any country in the region that wishes to participate in the mechanism.

The principles governing each mechanism and its associated policies have, however, affected the implementation options of the other. While both PAHO and UNICEF have established 'lowest price clauses' (LPC) with companies in their procurement contracts, it has been PAHO that has faced international pressure to issue exemptions to this agreement.[94] The LPC clause – otherwise known as the most-favoured nation (MFN) clause – contractually requires manufacturers to provide the lowest global price to that purchasing entity; if a lower price is provided to another country, procuring agency or third party, then the company must reduce the price to the same level for the original purchaser. The LPC is disliked by companies that practise tiered pricing and market segmentation in an effort to extract as much profit as possible [see box: 'How do pharmaceutical companies set their vaccine prices?,' pages 20-22].

Companies generally do not wish to offer MICs in the PAHO region – such as Brazil or Ecuador – the same price as that offered to the poorest countries, such as those financed by Gavi. Some companies have even side-stepped the LPC by developing different product presentations specifically for the Gavi and PAHO markets. For example, in the case of PCV and HPV vaccines, GSK created a two-dose vial specifically for sales to Gavi while continuing to offer the single-dose vial for the PAHO market at a higher price.

PAHO has been facing significant pressure from pharmaceutical companies, Gavi and Gavi donors that support tiered pricing strategies, such as the Bill & Melinda Gates Foundation, to abandon its lowest price clause. The pressure increased in 2009 when the price for PCV vaccine was being negotiated under the Gavi Advance Market Commitment. In a bid to pressure the PAHO Revolving Fund to provide an exemption to the LPC so that Gavi could purchase PCV for a lower price without companies being required to lower the price for PAHO countries as well, PAHO was forced to waive its LPC for the prices offered to Gavi/UNICEF through the AMC. Since then, PAHO has issued two additional exemptions for the procurement of rotavirus and HPV vaccines by Gavi/UNICEF. Expressing concern over the higher prices paid by the region for these newer vaccines, in October 2013 PAHO's member states agreed to a PAHO Directing Council resolution reaffirming the principles of the Revolving Fund and requesting a review of the waivers provided so far.[94] In its reaffirmation, PAHO noted that past LPC exceptions had been provided in good faith, but that prices for the Revolving Fund did not significantly decline subsequent to the granted LPC exemptions.[95]

In 2014, Sanofi-Pasteur and Gavi announced new prices for inactivated poliovirus vaccine (IPV)[96] through a four-tier pricing system. In refusing to lower the price for its IPV vaccine to the PAHO Revolving Fund, and with PAHO's resistance to grant another waiver, Sanofi-Pasteur decided to cease supplying PAHO region countries with its IPV vaccine.

Price negotiations for HPV vaccine between the two suppliers (Merck and GSK) and the PAHO Revolving Fund continue. At the time of publication, an affordable price had not been agreed upon between the companies and the PAHO region. Manufacturers, aspiring to extract greater profits from MICs markets, have deployed various tactics to undermine the principles of solidarity of the regional purchasing mechanism. The PAHO Revolving Fund remains under immense pressure as companies move towards pricing strategies that aim to maximise profit in MICS. For more information

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on HPV prices, see HPV Product Card, page 39.

As countries 'graduate' from Gavi support and begin to assume the full cost of new vaccines introduced with substantial Gavi donor subsidies, and to face the unpredictable prices that will be set by some companies, they will find themselves in a similar situation to other MICs – including PAHO region countries – that struggle to afford the escalating prices of new vaccines. With Gavi advocating a tiered pricing approach and expecting to receive the lowest global prices for its purchases, while the PAHO Revolving Fund continues to work for the best possible price for member states in its region by pooling country volumes, these two public health institutions have found themselves at a crossroads of different models for pricing and vaccine affordability. In the absence of a global solution that benefits the countries served by both Gavi and PAHO, pharmaceutical companies are moving forward country by country, trying to divide and segment markets and to lock in the highest prices they can secure from governments.

TIERED PRICING GAINS MOMENTUM DESPITE NEGATIVE EFFECTS ON ACCESS

Tiered pricing, also known as differential pricing, is presented by multinational pharmaceutical companies and some global health actors as the solution for improved access to vaccines. Under the tiered pricing approach, companies charge different prices in different markets for the same product: in theory the highest price is set in higher-income countries, and relatively lower prices in lower-income countries. The premise of tiered pricing is that companies offer price discounts to countries of lower economic status because they cannot afford to pay the same price as high-income countries, such as the US; however, the expectation is that as countries become richer, the price charged to them increases. Intuitively and to the general public, tiered-pricing may sound like a rational approach for establishing prices across a range of countries at different levels of development.

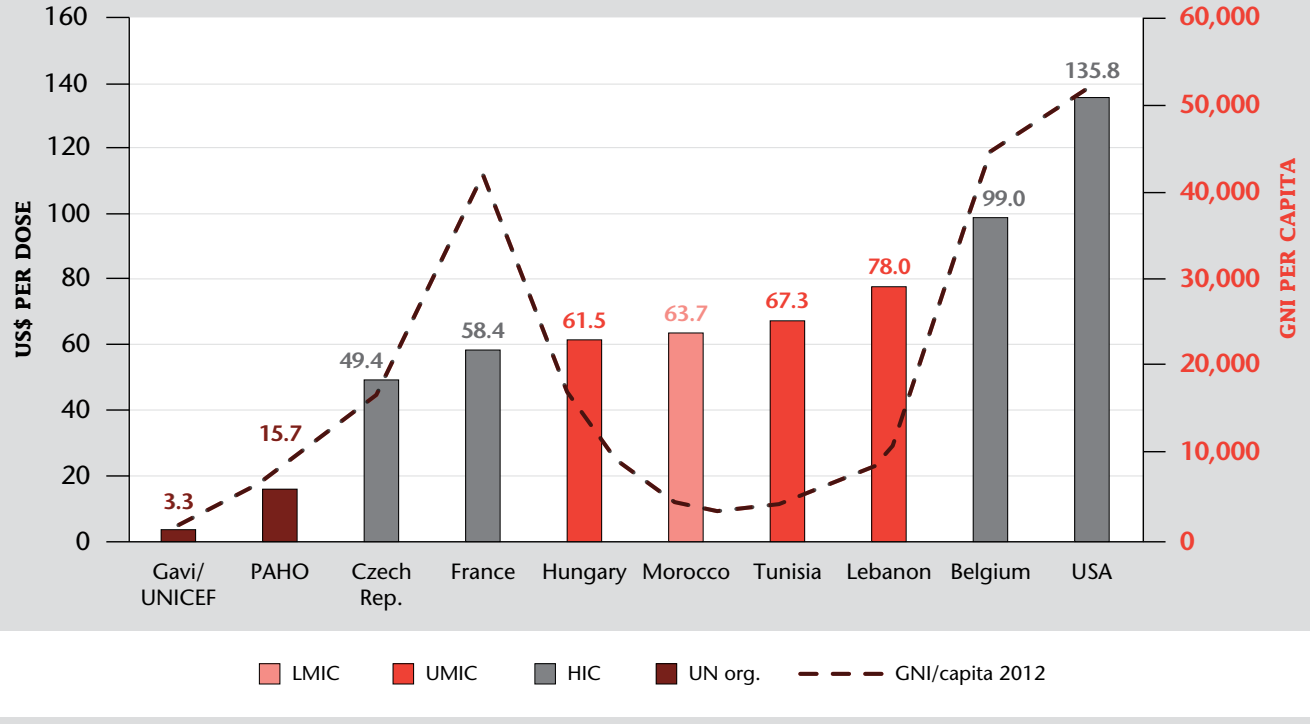
In practice, however, tiered pricing is a pharmaceutical company-promoted strategy that allows manufacturers to set prices as high as the purchaser will tolerate, frequently without considering public health needs and impact, and in fact acting as a market segmentation strategy that can delay the entrance of competition.

Pharmaceutical companies are not transparent in their tiered pricing policies which are usually implemented by companies unchecked and without appropriate government oversight. What few data points are available on tiered pricing strategies show that, aside from Gavi prices, pharmaceutical companies with a monopoly or duopoly in the newer vaccines (GSK, Pfizer, Merck) are pricing these vaccines with no clear rationale or relation to a country's economic classification level, as illustrated by the prices paid by countries for Pfizer's Prevnar 13 [see Graph 5, overleaf]. Morocco, a LMIC, is paying more for Prevnar 13 (PCV13) than France, Hungary and the Czech Republic, all countries with higher economic levels. Likewise, Tunisia and Lebanon are paying more than France for the vaccine, despite having substantially lower GNI levels.

A few companies have taken steps to better articulate the rationale of their tiered pricing business strategy – GSK, for example, published a statement on a seven-tier pricing system in October 2013, noting the inclusion of criteria beyond country economic development – but most multinational companies decline to give further details on how their prices are set, which countries are covered by each tier and how prices are set within tiers. Even though GSK has articulated its tiered pricing strategy, it has not publicly disclosed prices charged in each tier, which tier countries are assigned to and the precise formula the company applies to establish tiers, country classification and prices charged. Companies cite the concern that any transparency regarding their pricing formulas threatens their advantage in the market; they also bemoan any initiatives to increase availability of country price data for fear that it will be used by other countries for reference in price negotiations.

Tiered pricing allows manufacturers to set prices at whatever the market will tolerate, without considering public health needs.

Graph 5: Pfizer's Pneumococcal Conjugate Vaccine (PCV13) price per dose for countries by GNI per capita, 2014



Sources: World Bank,[45,97] Gavi,[14] country price analysis (see Annex A for details on methodology and sources)

Notes and methodology:

- Manufacturer price for all countries except for Morocco and Tunisia, where the price used here is the price to hospitals. See Annex A for more information on definitions and sources.
- GNI per capita for PAHO was estimated at US$7,500.[98]
- GNI per capita for Gavi is the threshold for graduation (US$1,570).[14]
- GNI per capita for countries is based on World Bank Indicators 2012.[45,97]

ROBUST COMPETITION STIMULATES PRICE DROPS, BUT DUOPOLY PERSISTS FOR NEWER VACCINES

Genuine and sustainable price decreases will be stimulated by real competition in the market. The vaccine market differs substantially by antigen; some antigens like the pentavalent vaccine have healthy markets which benefit from proper competition among a broad manufacturer base, while others like the rotavirus, PCV and HPV vaccines are duopolies. As has been seen in the pentavalent market, the entrance of additional manufacturers – a total of seven companies now sell prequalified pentavalent vaccines – has led to steep price declines. In 2008, when Shantha Biotech entered the pentavalent market it undercut the previous lowest price (offered by GSK) by 17%. The introduction of other company products (with more affordable multidose vial sizes) in 2011 and 2012, specifically from emerging manufacturers,[99] further lowered the price: the lowest price available decreased by 56% , from US$2.70 per dose in 2010 (Shantha Biotech, one-dose presentation) to US$1.19 per dose in 2013 (Biological E, ten-dose presentation). However, with only two manufacturers for each of the new and much more expensive vaccines – PCV, rotavirus, HPV – and the inability to use the two available products interchangeably, companies are enjoying near monopolies.

There are a variety of strategies that governments, donors, vaccine manufacturers and others can employ to promote vaccine competition. Reducing the barriers to entry and facilitating diversity in the manufacturing supply by promoting technology transfer to new manufacturers are critical tools to accelerating competition. Simplification of the regulatory processes for product prequalification – while maintaining the highest level of quality assurance – would also facilitate and speed up market entry for lower-cost follow-on and adapted vaccines. Simplification could come from the WHO prequalification programme (PQP) itself and from initiatives to harmonise regional regulations, such as the African Vaccine Regulatory Forum (AVAREF).[100] Vaccine manufacturing companies can also shorten the approval process by responding swiftly to WHO PQP and national regulatory authorities' queries.

Steps to accelerate the entrance of additional manufacturers to harness the price decreases delivered by real market competition – rather than relying on the tiered pricing strategy promoted by multinational pharmaceutical companies – will be critical in promoting availability of affordable vaccines. In the absence of competition, transparency initiatives to avail price and procurement information for use by countries and procurement agencies in their negotiations with pharmaceutical companies are critical. Aggregating volumes through pooled procurement to leverage market weight by country groups will also be a powerful tool in reducing the price of vaccines.

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OPPORTUNITIES TO STIMULATE COMPETITION: CHINESE MANUFACTURERS ENTER THE GLOBAL MARKET

The most effective driver to increase vaccine affordability is competition between manufacturers. Entry of additional manufacturers to the global market will help to bring down prices and ensure adequate supply to meet global needs.

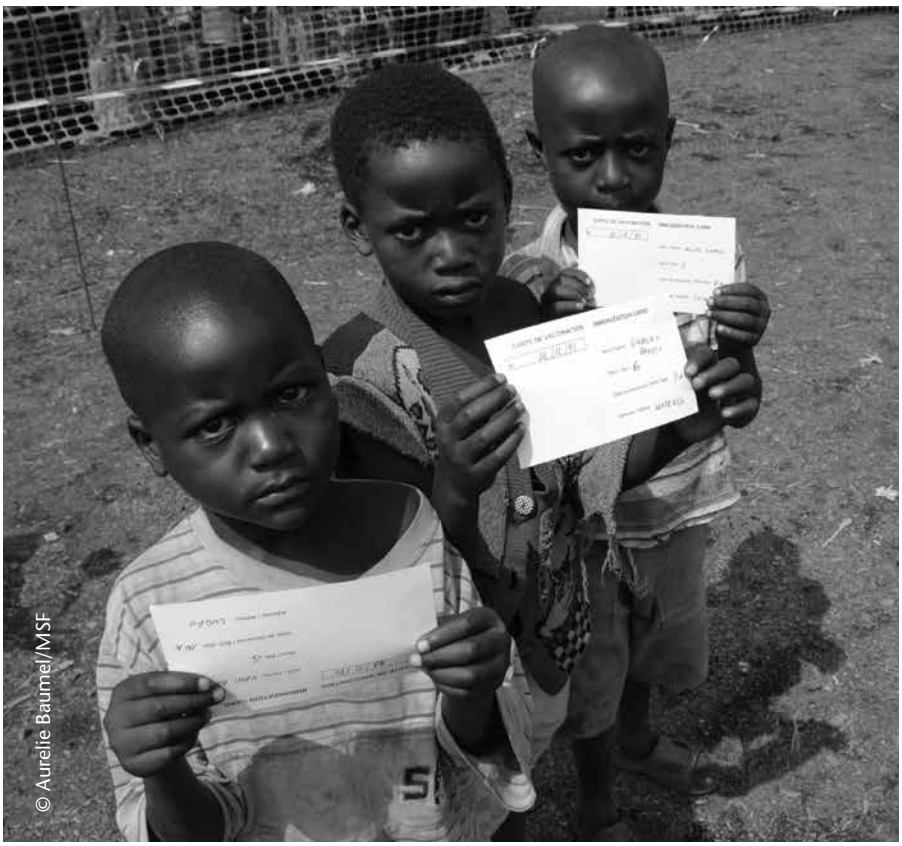
The emergence of Chinese vaccine manufacturers in the global market – with the first WHO-prequalified vaccine by a Chinese company, Chengdu Institute of Biological Products (for Japanese encephalitis vaccine), achieved in 2013 – could stimulate a new era of competition in a market that has traditionally been dominated by a handful of multinational companies.

Chinese manufacturers have been supplying their domestic market for decades. The China Food and Drug Administration (CFDA) reports that China has 34 vaccine manufacturers; four of these are international joint ventures and seven are state run. In March 2011, WHO certified China's National Regulatory Authority (CNRA) for meeting WHO standards for regulatory oversight. This milestone, repeated in July 2014 when WHO renewed the CNRA certification, means that Chinese companies can submit prequalification applications to WHO for international review.

China's largest company is state-owned Sinopharm's subsidiary China National Biotechnology Group (CNBG), which comprises seven manufacturers, including the Chengdu Institute of Biological Products. CNBG reports selling approximately 800 million vaccine doses a year, supplying more than 85% of the vaccines used in China's national immunisation programme.

Chinese companies have a range of vaccine products at different stages of development, including products where a duopoly currently keeps prices high in the international market, such as PCV, rotavirus and HPV vaccines. In addition to contributing follow-on products, Chinese companies are developing entirely new vaccines, such as the vaccine against hepatitis E by Xiamen Innovax Biotech.

The promise of increased competition, new products and improved supply security that Chinese companies represent could be a game changer for the global market. International stakeholders should do their utmost to promote this potential by creating the right legal and policy enabling environments, working to resolve any barriers to market entry, such as regulatory or patent barriers, and accelerating the entrance of these products in the international market.



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> **"We introduced two new vaccines recently...and because there are only two suppliers for each vaccine, there's no competition and we pay a premium."**
>
> *Dr Yogan Pillay, Deputy Director General, Department of Health, South Africa*

VACCINE ADAPTATION

In resource-poor contexts, conventional vaccine profiles can complicate vaccine delivery. Vaccine adaptations – optimising profiles for resource-limited environments – can extend outreach and improve immunisation coverage. Key vaccine adaptations include vaccines that do not require constant refrigeration, provide full protection with fewer doses, include serotypes most appropriate for local disease burden, or can be administered by community health workers through simplified delivery systems.

PROGRESS IN VACCINE ADAPTATION

Few better-adapted vaccines have reached clinical development. Many promising adaptations in preclinical development require partnerships with vaccine manufacturers to reach clinical trials.

A 2013 landscape analysis conducted by MSF on all EPI vaccine adaptations in clinical trials found 13 vaccine presentation advances (including ten oral rotavirus candidates in the pipeline), one packaging adaptation, and 16 delivery-device innovations. Most of these adaptations have been developed through product development partnerships.[101]

While donor support to vaccine research has been significant, there has been a lack of follow-through to enable these technologies to ultimately reach the places where they are needed most.[102] For vaccine manufacturers, changing the standard presentation, packaging and delivery for vaccines incurs additional risk. Without clarity on market uptake, developing a business case for adapted vaccines remains challenging.[103] Early policy guidance on antigen-specific procurement can shape adapted vaccine development at the point when the incorporation of these optimisations will have the lowest marginal cost. Stronger 'pull' mechanisms can also incentivise greater investment in vaccine adaptation to bring these products to market.[104]

The largest vaccine purchasers – such as UNICEF Supply Division – have the opportunity to shape adapted vaccine development by having their procurement policies indicate the 'value' of adapted vaccine attributes in their purchasing decisions. Quantification of adapted vaccine benefits, with cost-effectiveness and systems cost measures, and indication of country preferences for vaccine technologies, can encourage further investment in better products.[102]

Vaccine adaptation has been gaining prominence on the global immunisation agenda. In 2007, WHO and PATH created Project Optimize, which defined an ideal vaccine supply chain and supported efforts to implement these changes. Along with partners, Project Optimize re-established the Vaccine Presentation and Packaging Advisory Group (VPPAG), which has developed a generic preferred product profile (gPPP) for vaccines that includes recommendations for formulation, presentation, labelling and packaging for vaccines intended for use in low- and middle-income countries. The WHO is planning to publish an updated generic product profile.

In 2012, the WHO member states adopted the Global Vaccine Action Plan (GVAP) as the international framework under the Decade of Vaccines for expanding access to immunisation. The GVAP monitoring and evaluation plan includes indicators for relabelling vaccines to allow a controlled temperature chain [see overleaf] and targets for vaccine delivery devices.

> **"We would like a whole new range of vaccines that are simpler to use, are heat-stable, and have simpler schedules, making it easier for us to vaccinate kids."**
>
> *Dr Greg Elder, MSF Deputy Director of Operations*

CONTROLLED TEMPERATURE CHAIN

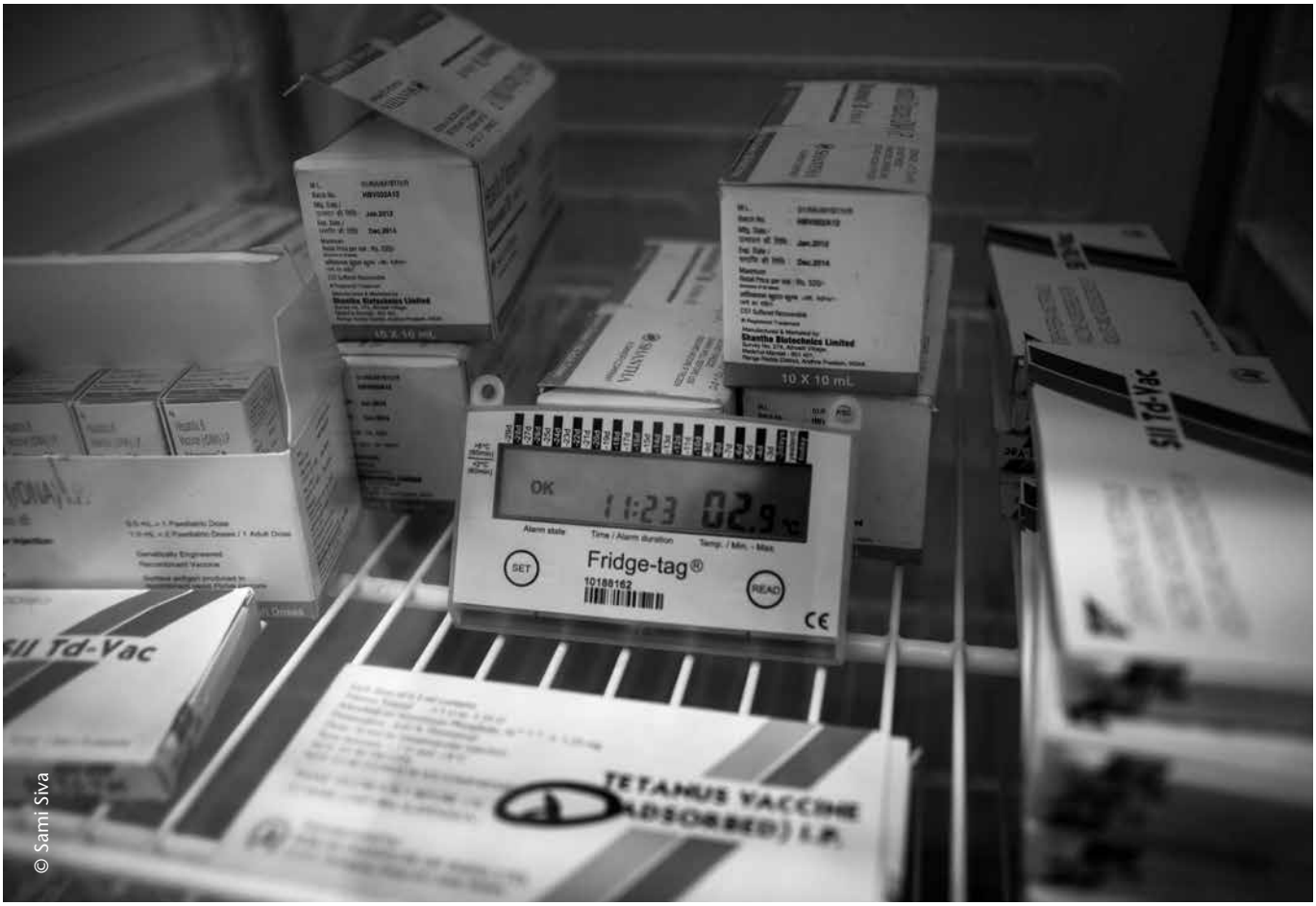
Keeping vaccines cold remains a major constraint on their delivery [see box: Cold chain challenges, opposite], as half of the healthcare facilities in the poorest countries have no electricity supply and only 10% have a reliable electricity supply.[98] Many vaccines, however, are fairly heat-stable; labelling and using vaccines according to their true temperature stability would result in a controlled temperature chain (CTC) or 'flexible cold chain', whereby vaccines can be used outside the traditional strict cold chain.[105] This approach has considerable benefits, including cost savings, preventing vaccine damage caused by accidental freezing, and most importantly, making it easier to reach children living in remote places who would otherwise remain unvaccinated. Relabelling a vaccine for CTC does not require changes to the vaccine itself; the relabelling process is likely to need only inexpensive stability studies, with the exception of a few antigens where clinical bridging studies would be required.

Implementing vaccination in CTC

There are two options for vaccines in CTC: routine immunisation and outreach activities, such as vaccination campaigns. Outreach can include outbreak response, mobile immunisation clinics for remote areas, and immunisation campaigns. Outreach activities typically require only several days of heat stability. In contrast, routine immunisation would require heat stability for at least one month, given the current vaccine delivery systems.

Despite the clear benefits for CTC in vaccination campaigns, the benefits have not yet been fully realised. Only the Meningitis A vaccine (MenAfriVac) has been relabelled and used in a CTC for campaigns. In 2012, the Ministry of Health in Benin implemented the first CTC pilot using 155,000 doses of MenAfriVac in 150 remote villages in Banikoara.[106,107] Following the pilot, 98.7% of supervisors and 100% of vaccinators involved preferred the CTC approach to traditional campaign immunisation which requires the cold chain.[108]

Vaccination campaigns using CTC could dramatically reduce immunisation costs. In a recent publication, Lydon et al. modelled the costs of implementing a MenAfriVac campaign in CTC and compared it with the actual costs in a MenAfriVac campaign in three regions of Chad in 2011. They found that CTC implementation at the district level would have saved more than 20% of the cost of the vaccine doses for the campaign.[109] Considering these were some of Chad's most densely populated and accessible districts, the cost savings of CTC may be even greater in more remote regions.



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COLD CHAIN CHALLENGES

Vaccination rates are often poor in low-resource environments; one of several reasons is that health facilities lack access to the physical infrastructure needed to properly store and manage vaccines. Inadequate supply and logistics systems prove a barrier to transporting vaccines to the most remote areas of a country, and the burdensome cold chain means that the most low-resource areas, lacking electricity, may not be able to properly store vaccines. In the poorest countries, it is estimated that half of the health facilities effectively have no electrical supply, while a mere 10% have reliable electricity.[98]

For outreach and supplementary immunisation activities (SIAs), the logistical challenges mount. In a 2010 measles vaccination campaign targeting 500,000 people in Chad, MSF had to freeze 22,000 ice packs in just 11 days.[110] For a recent measles vaccination campaign in Guinea, Sophie Dunkley, an MSF epidemiologist, explains the logistical challenges: "At the base, where we hold our stock, we have 17 fridges full of the vaccines. We also have the 17 freezers to make and store the 5,000 ice packs we need. The ice packs go into a big cold box that is taken out to the vaccination sites. But even there, we then have to transfer the vaccines from the big cold box into smaller cold boxes, because at each single stage we have to protect the vaccines so that they remain effective. It's a nightmare".

For vaccination campaigns, there is an increasing interest in eliminating the need for cold chain for vaccines stable beyond the standard 2–8°C range for several days or even weeks. Use of a CTC for vaccination outreach has been effective in immunising more people, reducing logistical burdens and reducing costs. A recent CTC campaign with MenAfriVac in Benin halved the logistical costs while achieving safe and widespread immunisation.

MSF is also conducting research on the potential use of vaccines in CTC. In 2013, MSF and Epicentre, its research arm, together with partners, carried out a two-phase study to determine the stability and continued efficacy of the tetanus toxoid vaccine produced by the Serum Institute of India under CTC conditions.[111] In the initial phase of the study, laboratory tests confirmed that the vaccine retained its chemical and biological properties when kept at ambient temperatures of up to 40°C for up to 30 days. The second phase was a clinical study undertaken in Chad, in the Moïssala district, to see how effective the vaccine remained in practice, under similar conditions. The participants – 2,128 women of childbearing age – were each assigned to one of two groups and received two doses of the tetanus toxoid vaccine. Women in the control group received vaccine kept in a strict cold chain; those in the second group received vaccine kept out of the cold chain (up to 40°C for up to 30 days). Participants in both groups reached adequate levels of protection against tetanus. These results strongly suggest that the Serum Institute of India's tetanus toxoid vaccine maintains its efficacy under CTC conditions.

Campaigns with vaccine used in CTC can increase immunisation coverage and save lives, but the onus rests on manufacturers to initiate relicensing of their vaccines for CTC flexibilities. Many vaccine companies have existing stability data generated during their clinical trials, but have not undertaken the relabelling process with regulatory authorities, thus denying countries the opportunity to implement simpler and more effective vaccination outreach.

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SOLUTIONS TO FOSTER INNOVATION: BUILDING A BETTER VACCINE

Current vaccine adaptation technologies have been underused, even as early-stage innovation increases. The fundamental question remains: is the global health community prepared to prioritise better vaccines that may be more expensive to develop and manufacture initially but will allow savings in the long run and, more importantly, allow more children to benefit? Key ways to incentivise adapted vaccine development are listed in Table 4.

Kristensen and Chen have outlined ways to advance vaccine technologies better suited to resource-poor environments. Their paper lists actionable points for all major stakeholders;[102] these include increased specificity in Generic Preferred Product Profiles (gPPPs) for desirable product attributes, funding for early-stage research on vaccine technologies, capacity to pay premiums for higher value products, and quantifying the benefits of vaccine adaptation, particularly additional immunisation coverage and reduced system costs for these technological advances.

Another example of an incentivising mechanism is the European Commission's Vaccine Prize, which in 2013 issued a call for innovations that can ease cold chain challenges through vaccine formulation, preservation and transportation. The prize, of 2 million euros, was awarded in 2014 to a German company that has developed a stabilising technology to protect vaccines against elevated temperatures and accidental freezing.[112] This European Commission prize fund, however, does not include important access conditions nor adequate intellectual property provisions.

> **"We have 17 fridges full of the vaccines. We also have the 17 freezers to make and store the icepacks... at each single stage we have to protect the vaccines so that they remain effective. It's a nightmare."**
>
> *Sophie Dunkely, MSF Epidemiologist, measles vaccination campaign, Guinea, February 2014*

Table 4: Benefits and examples of incentive options to develop adapted vaccines

Incentive option	Benefits	Past examples
Include off-the-shelf adaptation requirements in the gPPPs* for new vaccines	Provides incentives for using inexpensive or off-the-shelf technology including freeze-stable excipients and stability studies for CTC	Auto-disable (AD) syringe requirement in UNICEF procurement
Enable countries using procurement agents – such as UNICEF Supply Division – to purchase vaccines according to their product characteristics preferences	Provides a pull mechanism that incentivises vaccine manufacturers to incorporate value-adding components into vaccines	Country vaccine preference through UNICEF SD (e.g. high demand for the rotavirus vaccine two-dose schedule)
Foster public-private partnerships with critical access provisions and price considerations built into the vaccine target product profile	Provides risk-sharing, technical know-how, and funding needed to overcome market failures for investing in vaccine adaptation	Meningitis Vaccine Project

* gPPPs: Generic Preferred Product Profiles

CONCLUSION AND RECOMMENDATIONS

Improved vaccine access has averted deaths and serious illness across the world, but the benefits of immunisation are still not available to all. Selected initiatives have improved affordability and adaptability of vaccines, but the focus of the past decade has been primarily on low-income countries. With financial subsidies and negotiation of lower prices by Gavi, low-income countries have introduced new vaccines at a faster rate than others; this puts into sharper focus the large group of countries and organisations that have yet to benefit from the newest vaccines because of a lack of strategies to ensure affordability for all. With the mounting concern over the sustainability of immunisation programmes in countries losing Gavi support and the growing voice of countries and organisations left out of pricing and procurement mechanisms, there is an urgent need for deliberate steps to improve vaccine affordability worldwide.

Affordability and prices - ensuring vaccines are affordable for all will require action, including:

- **Accurate and publicly available information on research and development (R&D) and manufacture costs:** availability of information on the R&D and manufacturing costs of new vaccines, and public investments made towards those costs, will enable countries, collectively or individually, to negotiate affordable prices.

  Governments that contribute public funding to vaccine development need first to make that information readily available to the public, and demand that their investments be recouped for improving the public's health through affordable prices to purchasers; and second, to win the argument with donors and the vaccine industry about 'the right price' for a vaccine, i.e. that is not value-based but based on cost plus reasonable profit.

  Pharmaceutical companies should publicly disclose their investments in vaccine development and clarify what costs are attributed to R&D and manufacture, and what is needed to sustain participation in the market.

- **Increased price transparency:** vaccine price data are scarce, with little information to inform purchasing negotiations and policy makers. There is a need to bolster existing mechanisms, and invest in additional mechanisms, to share price data.

  Procurement entities such as UNICEF and the Gulf Cooperation Council, among others, should publish all of their available price data. Gavi and other global health actors that are stewards of public funds should champion price transparency, and commit to continued publication of prices. Forthcoming procurement bodies should incorporate price transparency principles into their procurement models from the outset.

  Governments, which are the primary purchasers of vaccines, should share their information via price data mechanisms, such as the WHO Vaccine Product, Price, Procurement (V3P) project.

  Donor governments and philanthropic entities like the Bill & Melinda Gates Foundation, which contribute funds to norm-setting bodies such as WHO and development assistance mechanisms such as Gavi, should insist on vaccine price transparency. Entities, such as the Gates Foundation, which have conducted their own vaccine market analyses, including cost of manufacturing, and who are actively involved in price negotiations, should make this information publicly available.

- **Monitoring and accountability of vaccine prices:** standard indicators to effectively monitor vaccine prices across purchasing entities (countries, procurement agents) are needed with accountability measures in place.

  WHO and UNICEF should build on the work started on vaccine price indicators in the Decade of Vaccines/Global Vaccine Action Plan monitoring, evaluation and accountability framework, to ensure that indicators are continuously improved. Price indicators should also be tracked across a broader set of countries.

  Pharmaceutical companies should more clearly articulate their pricing strategies, including components used in determining prices for purchasers, and be held accountable to at least meet their own standards. Currently tiered pricing often has no clear rationale or relation to a country's economic classification level.

  Governments and other vaccine purchasers, such as Gavi/UNICEF, should be held accountable for

prices negotiated, particularly as public monies are used for the purchase. Governments should establish national price regulations, including price controls (e.g. reference pricing, controlled mark-ups, maximum retail prices, etc.)

- **Increased use of effective procurement strategies, such as pooled procurement, multi-year contracts, competitive tenders:** a variety of strategies and policies should be pursued to increase the effective use of procurement strategies, including investment in capacity building and to improve forecasting so that tools such as pooled procurement and multi-year contracts can be used to lower prices.

  Countries should commit to working together to achieve economies of scale through pooled procurement mechanisms. Exploring unifying characteristics – such as regional groupings or other common interests – to combine their vaccine volumes will enable more powerful price negotiations.

  WHO, UNICEF and other technical agencies should provide support to countries wishing to improve vaccine procurement competencies and establish pooled procurement mechanisms. WHO regional offices, in particular, should support countries to come together and explore pooled procurement options.

  Donors, such as developed countries and philanthropic entities like the Bill & Melinda Gates Foundation, should provide resources for countries to convene and work towards establishing effective procurement strategies, including pooled procurement. Donors should allow countries to self-determine the principles of those strategies and not create nor endorse policies that will undermine the capacity of governments to implement them.

- **Support for increased competition and entry of lower-cost manufacturers:** entry of new manufacturers, particularly those with lower manufacturing costs, needs to be accelerated through technology transfer, access to licences and key technology know-how.

  Gavi and other global health actors supporting immunisation should invest in measures to stimulate competition and broaden the vaccine product base, with a focus on emerging country manufacturers.

  Donors that support R&D, such as countries and philanthropic entities, should invest funding in innovative research and development models, and steps that increase competition, particularly among lower-cost manufacturers with the goal of ensuring that the resulting vaccines are manufactured at the lowest possible cost and reach all populations in need.

  WHO should provide technical, policy and political support to overcome barriers to product development, and support emerging manufacturers including through regulatory processes to facilitate prequalification applications.

Measures to improve vaccine product characteristics – or adaptations – to immunisation needs in resource-poor settings are ongoing but moving at a slow pace. These innovations are not commonly developed because the populations living in resource-poor settings do not represent a large commercial market. To date, only a handful of adapted vaccines tailored to developing country needs is available.

Adaptation - stimulating research and development of adapted vaccines will require action, including:

- **Identification of adaptation preferences by countries:** country-level practitioners and programme managers know best what adaptations will improve their immunisation programme performance; they need to be in the driving seat for setting priority adaptations.

  Countries with challenges facing their immunisation programme performance should voice their needs in a global forum and insist that the products specifically supported by donors best meet their context needs.

  Procurement agencies, such as UNICEF, should develop a methodology for surveying vaccine adaptation preferences of the countries they support and prioritise products that meet their needs.

- **Demonstrate utility of adaptations:** vaccine adaptations have been shown to improve immunisation coverage, but more evidence must be generated to 'make the case' for investment.

  Donors, such as developed countries and philanthropic entities like the Bill & Melinda Gates Foundation, should invest funding in modelling vaccine adaptations to show their efficacy and the need for them.

  WHO and other technical agencies supporting immunisation programmes in low-resource countries should quantify the contribution of vaccine adaptations to improving coverage.

Setting a clear vaccine adaptation agenda: establish consensus-based, early-stage target product profiles (TPPs) that include key vaccine adaptations to guide researchers, product developers, and manufacturers.

WHO, as a body that sets global health norms, should convene the relevant stakeholders to set a clear agenda of priority vaccine adaptations to guide donor investments and the work of researchers, product developers and manufacturers. Implementing countries should be a leading constituent in this forum.

Funding for innovative technologies and incentivising strategies: innovation needs to be fostered through direct investments (push funding), prizes or other funding mechanisms. Resources available for immunisation programmes must be used to their utmost potential to incentivise development of better adapted products.

Donors, such as developed countries, developing countries with a strong interest in using adapted vaccines, and philanthropic entities like the Bill & Melinda Gates Foundation, should help to design innovative models for vaccine technologies and invest funding to realise their development. In supporting immunisation programmes, all governments that contribute funding should insist that their funding be strategically used to incentivise adapted products. Any adaptations that emerge from such investments should not lead to unaffordable prices or the creation of additional barriers, especially intellectual property barriers, that would prevent increased use of such vaccines.

Gavi should become more involved in upstream product development, investing funds in product adaptations and innovative models that deliver better vaccines for the countries it supports. With its substantial resources, Gavi should design preferential procurement strategies – such as more shares or premiums to better products – that incentivise adapted product development.

Clarify and streamline the regulatory process: while maintaining high quality-assurance standards, the regulatory pathway for innovative and adapted vaccines and delivery devices should be clarified.

WHO and other regulatory bodies, such as national and regional entities, should clarify and, where possible, streamline, regulatory requirements for vaccine adaptations and delivery technologies. Guidance on criteria for seeking WHO prequalification with adaptation attributes, such as extended thermostability, should be communicated clearly to product developers.

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PRODUCT CARDS
Summary and introduction

The nine following product cards presented here and summarised overleaf bring together for the first time key information on important monovalent and combined vaccines. Each vaccine product card itemises disease burden, WHO recommendations, administration schedule(s), product characteristics, product pipeline, access challenges, pricing and affordability. Where possible, historical price information is analysed.

The lack of price transparency and product availability is a barrier to improving and scaling up access to vaccines, and there has been no single source of information providing details on both product characteristics and prices.[23] While other initiatives (e.g. the Vaccine Product, Price, and Procurement (V3P) project) are evolving, we have created this unique compendium which, by providing a clear overview of these vaccines in one place, intends to support decision making at country level and to broaden the discussion on price comparison and price opacity.

Vaccine prices: a note on terminology used in the product cards

For the purpose of our analysis, vaccine price data have been subdivided into four main price types:

- **Government price (Gvt):** price paid by the government for national immunisation programmes.
- **Hospital price (Hosp./Hospitals):** price paid in hospitals and public institutions.
- **Manufacturer price (Manuf.):** price of the vaccine before it enters the wholesale and retail distribution network; does not include wholesale or retail margins, but may include taxes and transportation fees.
- **Retail price (Retail):** price as paid by the population, inclusive of taxes, transportation fees, and margins; sometimes referred to as 'private sector' price.

All prices except the 'government price' are official prices available outside of government immunisation programmes. In some countries, health insurance will cover the cost of the vaccine purchased in the private market, representing a cost to public health insurance schemes. In other countries, where the vaccine is not reimbursed by health insurance, the 'retail price' is a direct burden on a family's budget.

DISCLAIMER / METHODOLOGY

- Except where stated otherwise, the vaccines presented are WHO prequalified (WHO PQ).
- Prices presented are based on the lowest publicly published prices available on the UNICEF Supply Division website, except where otherwise noted.
- Description of development pipelines does not intend to be exhaustive, but summarises publicly available information on products in Phases II and III of clinical trials.
- Between-country price comparison is based on the latest price data available at the time of the analysis (usually from 2013 or 2014). For more details on the pricing methodology, please refer to Annex A.

Vaccine	Industrialised manufacturers (IFPMA*) and emerging manufacturers (DCVMN**) of WHO prequalified vaccines[113]	Presentations available		Lowest price per dose, 2014 (UNICEF prices, US$)†	Pipeline outlook (products in Phase II or III clinical trials)‡
		Single-dose	Multiple-dose		
Human papillomavirus (HPV)	Industrialised: 2 (GSK, Merck) Emerging: 0	Yes	Yes (GSK 2-dose)	4.50–4.60	
Inactivated poliovirus (IPV)	Industrialised: 4 (Bilthoven Biologicals BV, GSK, Sanofi Pasteur, Statens Serum Institute) Emerging: 1 (Serum Institute of India/Bilthoven Biologicals)	Yes	Yes	0.75–2.80	 (Some combination vaccines in development)
Measles	Industrialised: 1 (Sanofi Pasteur) Emerging: 3 (Bio Farma, GPO-Merieux, Serum Institute of India)	Yes	Yes	0.22–0.45	
Measles-rubella (MR)	Industrialised: 0 Emerging: 1 (Serum Institute of India)	Yes	Yes	0.55	
Measles-mumps-rubella (MMR)	Industrialised: 3 (GSK, Merck, Sanofi Pasteur) Emerging: 1 (Serum Institute of India)	Yes	Yes	1.02–3.25	
Meningococcal	Industrialised: 2 (Sanofi Pasteur, Novartis) Emerging: 2 (Bio-Manguinhos, Serum Institute of India)	Yes	Yes	0.53–0.58 (2013, MenA only)	 (Several tetravalent vaccines not WHO PQ or in development)
Pentavalent (DTP-HepB-Hib)	Industrialised: 2 (Berna Biotech [Crucell], GSK) Emerging: 4 (Biological E, LG Life Sciences, Panacea Biotec, Serum Institute of India)	Yes	Yes	1.19–2.95	 (1–3 new manufacturers within next 3 years; hexavalent products in development)
Pneumococcal conjugate (PCV)	Industrialised: 2 (GSK, Pfizer) Emerging: 0	Yes	Yes (GSK 2-dose)	3.30–7.00	 (Not expected before 2017)
Oral cholera (OCV)	Industrialised: 1 (Crucell) Emerging: 1 (Shanta Biotech)	Yes	No	1.85–4.75	
Rotavirus (RV)	Industrialised: 2 (GSK, Merck) Emerging: 0	Yes	No	2.50–5.00	
Tetanus toxoid (TT)	Industrialised: 2 (BB-NCIPD, Sanofi Pasteur) Emerging: 4 (Bio Farma, Biological E, Serum Institute of India, Shantha Biotechnics)	Yes	Yes	0.05–0.09	

*IFPMA: International Federation of Pharmaceutical Manufacturers and Associations.
**DCVMN: Developing Countries Vaccine Manufacturers Network.
†Lowest and highest price offered to UNICEF, across all presentations and conditions. The lowest price is usually accessible only to countries eligible for support from Gavi, the Vaccine Alliance.
‡Based on public information about vaccine development pipelines; number of products in Phase II or III of clinical trials: ● : >3; ◐ : 2 or 3; ○ : 0 or 1.

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Human Papillomavirus Vaccines (HPV)

WHO recommendations & general information

- Cervical cancer is estimated to cause 266,000 to 275,000 deaths globally per year[114–116] and is projected to be responsible for 474,000 deaths per year by 2030. More than 95% of those deaths will be in low- and middle-income countries, in many of which cervical cancer is the leading cause of cancer-related deaths among women and a leading cause of death overall.[117–119]
- Human papillomavirus (HPV) is sexually transmitted and is the primary cause of cervical cancer.[114,120] Persistent infection by oncogenic HPV is a prerequisite for developing cervical cancer, and at least 13 viral genotypes are known to be carcinogenic.[121] Viral type 16 is the dominant oncogenic type in all regions and, with viral type 18, accounts for about 70% of all cervical cancers worldwide.[121]
- In 2009, WHO recommended inclusion of HPV vaccines in national immunisation programmes for administration to girls aged 9–13 years prior to onset of sexual activity. WHO also recommended taking into consideration national public health priorities, programmatic feasibility and cost-effectiveness before inclusion of HPV vaccines in a country's immunisation schedule.[121]
- A combined analysis of two Phase II trials of the quadrivalent (types 6, 11, 16, 18) HPV vaccine found that the vaccine was 99% effective in preventing HPV infection (assessed by absence of cervical intraepithelial neoplasia grade ≥2 or adenocarcinoma in situ) when administered before virus exposure.[121] The quadrivalent vaccine offers added value by protecting against genital warts, as 90% of these are caused by infection with HPV types 6 and 11. There is evidence for significant vaccine-induced cross-protection with other cancer-causing serotypes.[122] The quadrivalent vaccine has been shown to substantially reduce disease incidence of genital warts in countries with high coverage rates.[123]
- As of February 2014, 66 countries had introduced HPV vaccines in their national immunisation programmes and pilot programmes were underway in an additional 40 countries.[117]
- In late 2013, the bivalent HPV vaccine received European Commission approval[125] for a reduced two-dose schedule (at 0 and 6 months) for girls aged 9–14 years.[115,126,127] In 2014 the quadrivalent product received European Commission approval[128,129] for a two-dose schedule (at 0 and 6 months) for girls aged 9–13 years.
- In April 2014, on the basis of research indicating that alternative dosing schedules could be as effective as existing schedules,[130] the WHO Strategic Advisory Group of Experts recommended switching to a two-dose schedule for girls provided that vaccination was started before 15 years of age.[115,128,129,131,132]

Vaccine[124]	Age at 1st dose	Doses in primary series (interval between doses)	Booster
Quadrivalent HPV	9–13 years	2 doses for girls <15 years (minimum 6 months between 1st and 2nd dose) If the interval between the two doses is <6 months, then a 3rd dose should be given at least 6 months after the 1st dose	Not recommended
Bivalent HPV			
Quadrivalent or bivalent HPV: delayed start*	Applicable for girls ≥15 years	3 doses (minimum 1–2 months between 1st and 2nd dose; minimum 4 months between 2nd and 3rd dose)	Not recommended

*This schedule is also recommended for immunocompromised individuals.

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
Cervarix Bivalent HPV (types 16 and 18) vaccine	GSK	July 2009	Liquid, 1-dose and 2-dose vials*	4.60	VVM 30 Single dose Box, 1 vial: 57.7 cm^3 Box, 10 vials: 11.5 cm^3 Box, 100 vials: 4.8 cm^3 Two doses Box, 1 vial: 28.8 cm^3 Box , 10 vials: 5.7 cm^3 Box, 100 vials: 9.7 cm^3
Gardasil/Silgard Quadrivalent HPV (types 6, 11, 16 and 18) vaccine	Merck	May 2009	Liquid, 1-dose vial	4.50	VVM 30 Box, 1 vial: 75 cm^3 Box, 10 vials: 15 cm^3

PIPELINE PRODUCTS

- Merck has the nine-valent vaccine V503 in Phase III of development.[133,134] V503 targets nine HPV subtypes (6, 11, 16, 18, 31, 33, 45, 52 and 58) and is being developed in collaboration with CSL (Australia).
- Xiamen Innovax has a recombinant bivalent vaccine targeting HPV 16 and 18 in Phase III.[135,136]
- Other companies, including ISA Pharmaceuticals, Genexine and Transgene, have vaccines that use a mono-therapy approach to target HPV 16 in Phase II.[137–139]

CHALLENGES

- Lack of routine health services for adolescent girls in many countries poses a challenge to vaccine delivery for the target 9–13 age group,[115] and this is particularly the case in middle- and low-income countries with regard to HPV vaccination.[120] As HPV vaccine is likely to be provided outside of clinics, more user-friendly products such as needle-free formulations – for example, vaccine patches – may prove helpful.[140]
- Sociocultural attitudes and beliefs in different countries and communities can have a negative impact on vaccine acceptance among parents, especially when the specific vaccine target population is adolescent and teenage girls, who need to be vaccinated before the onset of sexual activity.[114,141,142]
- Merck, together with WHO and the Program for Appropriate Technology in Health (PATH), is exploring the stability of Gardasil in the controlled temperature chain (CTC).[127] Pending regulatory reviews and processes, Gardasil could carry CTC labelling by early 2015 indicating that it is stable at temperatures up to 42°C for four days.[143] This is especially important because HPV vaccines are likely to be delivered at schools and other locations outside traditional cold chain-supported environments.

*Two-dose preservative-free liquid is a novel presentation for UN-supported Expanded Programme on Immunization (EPI) programmes and requires specific training and management for its roll-out and administration.

Prices and affordability

The HPV vaccine market is a duopoly, the two suppliers being Merck and GSK. Together with the pneumococcal conjugate vaccines (PCV) and rotavirus vaccines, HPV vaccines are among the newest and most expensive vaccines, presenting affordability challenges that hinder access.

In 2013, Gavi entered into agreements to purchase the HPV vaccines from Merck and GSK at the reduced price of US$4.50 and US$4.60 per dose, respectively. HPV manufacturers announced that at these prices they did not intend to make a profit, explicitly stating that they were selling their respective vaccines to Gavi 'at cost'.[58]

Ongoing research shows that the manufacturing cost of the vaccine could be much lower. As of May 2013, Merck had already earned more than US$8.6 billion in revenues from sales of its HPV vaccine since it was first approved in 2006.[59,61,144] Taking into account the 111 million doses of Gardasil sold worldwide as of May 2013[145], at a manufacturing cost of US$4.50 a dose, the company made more than US$8 billion in profit (excluding the cost of research and development) on HPV vaccine sales over seven years.

HPV VACCINE IN SOUTH AFRICA: ADDRESSING HIGH PRICE CHALLENGES

Sub-Saharan Africa has the highest cervical cancer prevalence (24%)[146] and mortality rate in the world. In South Africa, cervical cancer is the second most common cancer among women (prevalence of 21%).[147] Additionally, HIV-positive patients are more likely to be infected with multiple HPV types (16, 18, 35, 45) and have an increased risk of more aggressive, pre-cancerous lesions at a younger age.[148] Therefore, in May 2013, the South African Minister of Health, Dr Aaron Motsoaledi, announced South Africa's intention to provide the HPV vaccine for free to all girls in grade 4 at public schools and over the age of nine years, covering around 520,000 girls with a two-dose schedule.[149]

South Africa does not qualify for Gavi subsidies, but negotiated a price of 157 rand (approximately US$13) per dose of Cervarix, GSK's HPV vaccine. Adding HPV vaccine to the South African immunisation schedule increased the cost of fully vaccinating a girl in South Africa by about 18%, from more than 1,115 rand to more than 1,363 rand per girl.* The price per dose negotiated by the National Department of Health is on a par with the lowest prices currently paid by some middle-income countries or regional bodies, including the PAHO Revolving Fund. While this was a significant achievement for South Africa, the cost per dose of the vaccine is still approximately three times greater than the price paid by Gavi. Moreover, if the vaccine is to be offered to a broader age range of girls in the future, or eligibility is to expand to include male students, the current cost is not sustainable. Countries like South Africa – middle-income countries with relatively small markets and not benefiting from pooled procurement mechanisms – struggle with escalating costs. If South Africa paid less for the vaccine itself, the country could instead use funds to further strengthen the vaccination programme's operational capacity and broaden age or gender eligibility.

South Africa contributes funds to Gavi, but fails to benefit from Gavi's market-shaping role. The South African government should demand access to Gavi's lower negotiated prices and use its voice to champion access issues for other MICs. Increasingly, the world's unvaccinated children are located in middle-income and non-Gavi eligible countries; without a policy change at Gavi, these children will continue to be unprotected.[150]

MSF participation in South Africa's HPV campaign

An HPV campaign was conducted in the Western Cape from 10 March to 11 April 2014. MSF partnered with the Department of Health in Khayelitsha sub-district to implement the campaign, including providing clinical training for health workers, support for data collection and advocacy activities to promote vaccination. MSF also produced educational radio sessions and articles for local newspapers on the HPV vaccine and prevention of sexually transmitted infections, cervical cancer, and sexual violence. Results of the campaign in Khayelitsha showed that 2,121 girls in 35 schools received the vaccine, out of a reported 2,425 grade 4 girls; the vaccine coverage was thus 87%, with 436 (21%) of girls vaccinated by the MSF vaccination team during a 'mop-up' campaign.

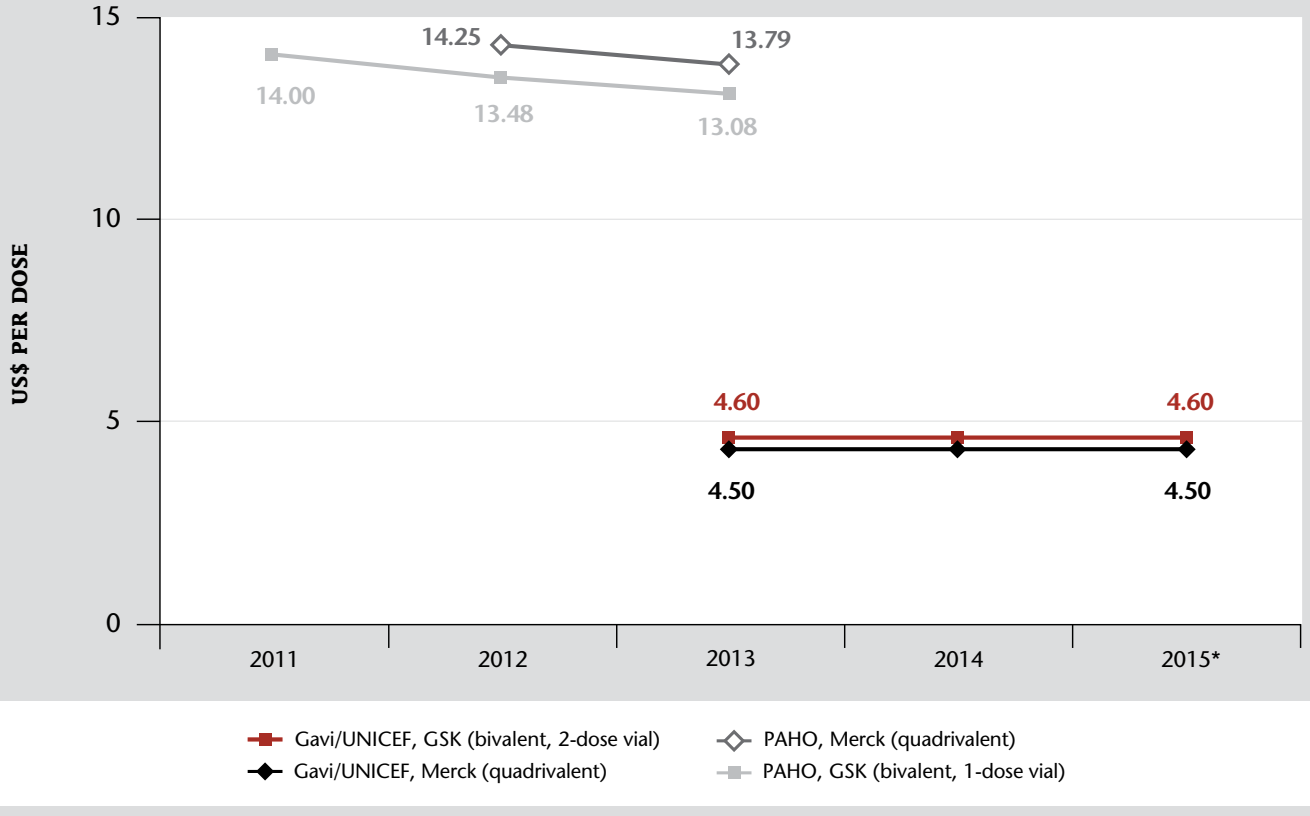
*Cost projections based on prices provided in May 2014 by the National Department of Health to MSF. These prices are not inclusive of VAT or delivery charges. Vaccines include two doses of rotavirus, four doses of DTaP-IPV-Hib, three doses of HBV, three doses of PCV, two doses of measles and two doses of Td, to which the price of the HPV is added. Prices were not provided for the two doses of OPV or single dose of BCG that are also included in the South African EPI.

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

- At US$13.08–13.79 a dose, the Pan American Health Organization (PAHO) pays more than three times the price offered through UNICEF to Gavi-eligible countries [Graph 6].
- In 2014, there has been no price published by the PAHO Revolving Fund at the time of publication. After prices for the HPV vaccines sold to Gavi/UNICEF were announced in 2013, PAHO started negotiations with manufacturers to try to lower the price for its member states, on the basis of the most favoured nation (MFN) clause included in all its contracts with suppliers. The clause stipulates that prices offered by manufacturers to PAHO should be the lowest available global price. After having granted several waivers for previous vaccines purchased by Gavi at lower prices (e.g. for PCV and rotavirus vaccines), the countries of the PAHO region adopted a resolution in 2013 to announce the review of past exceptions made to its MFN clause,[96] in an effort to safeguard its access to the lowest prices. Negotiations on HPV vaccines were ongoing at the time of publication.

Graph 6: Price evolution of Human Papillomavirus Vaccines (HPV) for PAHO and Gavi/UNICEF



Sources:
PAHO Revolving Fund, UNICEF Supply Division

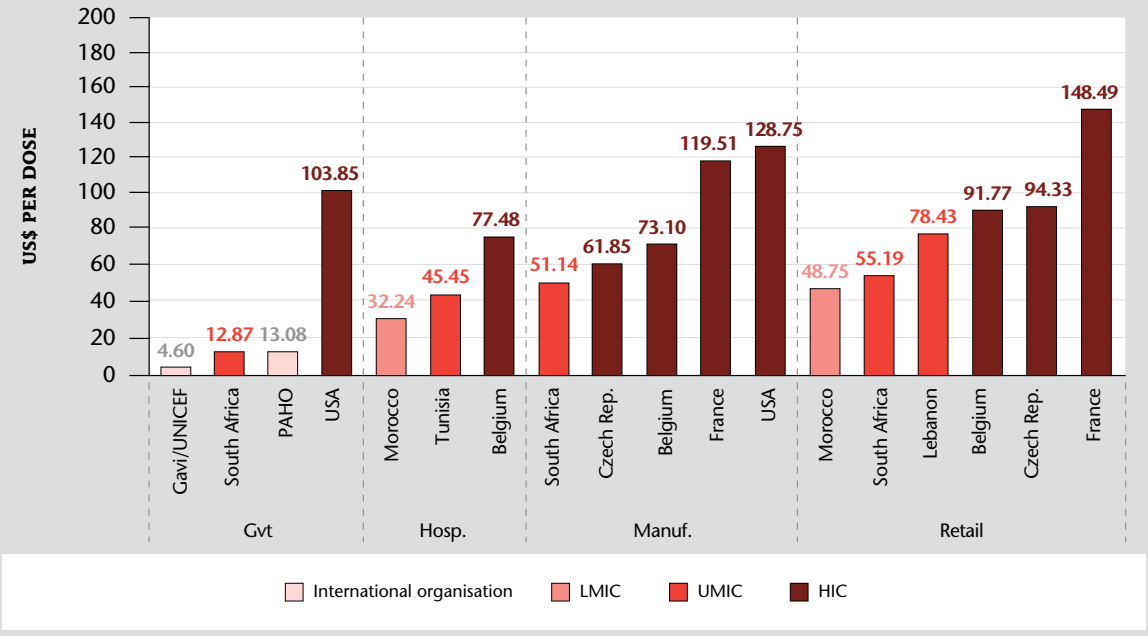
* Forecasted data. Prices remain the same for Merck's vaccine between 2015 and 2017.

PRICES IN COUNTRIES

- The high price of HPV vaccine has been a barrier to its introduction in several countries that do not benefit from the support of Gavi. Several studies show that for the vaccine to be cost-effective the price per dose should be drastically reduced. In a study done in Thailand, HPV vaccination as a single intervention was deemed cost-effective when the cost per vaccinated girl was ≤US$10 (approximately US$2 per dose).[151] In another study, from Latin America, the vaccine was again deemed cost-effective in 26 of the 33 countries studied when priced at US$10 per vaccinated girl.[152] Looking at prices of HPV vaccine in middle-income countries [Graphs 7 and 8, opposite], the price per dose in 2013–2014 is at least 6.5 times higher than the cost-effective price calculated in these studies.
- The recently announced two-dose schedule for HPV[142] will help lower costs by one-third, even though prices will have to be further reduced to improve access in most middle-income countries. The change in schedule is expected to reduce the Gavi budget for HPV vaccines by approximately US$100 million over the next strategic period.[153] South Africa started its school-based HPV vaccination programme in 2014 with a two-dose schedule (at around US$13 per dose, one-fifth of the price in the private sector).[149]
- In Brazil, HPV vaccine is supplied through a partnership between Merck and Instituto Butantan, via an investment of 1.1 million Brazilian reals (US$462 million*) to purchase 36 million doses over five years (15 million doses should be distributed the first year, starting in March 2014).[154] 2014 is the first year in which Instituto Butantan has distributed batches of HPV vaccine; after five years of supply by Merck, it will produce its own version. As seen in Graph 7, and thanks to a technology transfer agreement, Brazil pays one of the lowest global prices for HPV (about 30 reals per dose, or US$12.83*). However, restrictive terms in the technology transfer agreement could limit the opportunity for Brazil to benefit from real competition if emerging manufacturers enter the global market with cheaper products during the contract period.
- GSK has implemented a tiered pricing strategy for Cervarix, based on the price data [Graph 7, opposite], that is closely related to the gross national income (GNI) per capita of the countries where it is sold. The company appears to be using tiered pricing as a strategy to expand access in these markets. MSF remains highly concerned that tiered pricing results in unaffordable vaccine prices. Merck's Gardasil, when compared with GSK's Cervarix in different countries, is more expensive and shows less correlation between price and country GNI. The Flemish region of Belgium, as a result of a special offer by Sanofi Pasteur MSD (selling Gardasil in Europe) through a public tender in 2010, secured the HPV vaccine for its school immunisation campaign at the price of EUR20/US$26.56) per dose, making it one of the world's lowest registered prices for the vaccine. Some of the special conditions for this price (about 105,000 doses per year for five years, to vaccinate 35,000 girls in their first year of secondary school)[156] are known. Based upon the known prices on offer for Gardasil, Merck is not using tiered pricing as a corporate strategy to expand access but rather as a strategic tool to set prices that allow the company to capture market share and maximise its revenues.

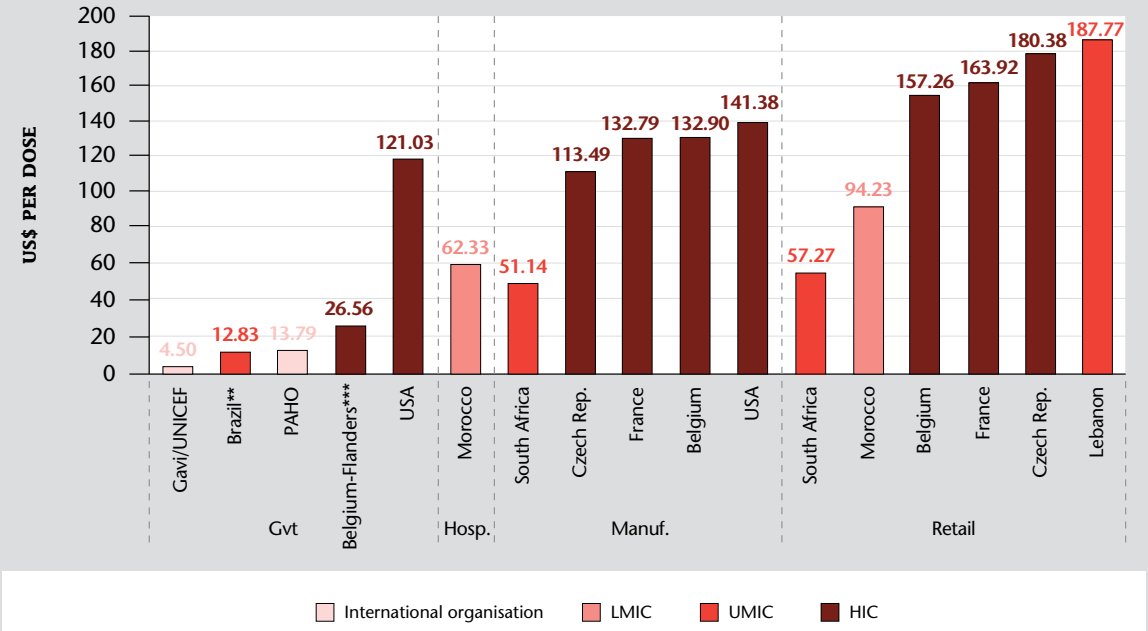
*The exchange rate quoted (1 Brazilian real = US$0.42) is the monthly average exchange rate from OANDA current in January 2014, when the contract was published.[155]

Graph 7: Prices for GSK Human Papillomavirus Vaccine (HPV) in several countries, by income group and price type, 2013/2014*



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

Graph 8: Prices for Merck Human Papillomavirus Vaccine (HPV) in several countries, by income group and price type, 2013/2014*



**Via Fundacao Butantan and technology transfer agreement with Merck. January 2014 monthly exchange rate from Oanda.
***Special price obtained by the Flemish region through public tender.

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

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Inactivated Poliovirus Vaccines (IPV)

WHO recommendations & general information

- Poliomyelitis (polio) is an acute viral infection consisting of three distinct serotypes (1, 2 and 3). Before the introduction of the Expanded Programme on Immunization (EPI) in 1974,[157,158] the disease was the leading cause of disability among children.
- WHO member states resolved at the 1988 World Health Assembly to eradicate polio by the year 2000. At the time global polio incidence was estimated to be around 350,000 cases per year.[157] Sustained immunisation activities reduced polio incidence by >99% between 1988 and 2012,[157] and there were 223 and 403 reported cases of polio in 2012 and 2013 respectively.[157] In 2013, India, and with it the entire WHO South-East Asia region, was declared polio free. The only remaining polio-endemic countries are Afghanistan, Nigeria and Pakistan.[159,160] For the year 2014, as of 30 April, there had been 68 reported polio cases worldwide, with Pakistan accounting for 54 of them.[161]
- The WHO recommends that all children worldwide should be fully vaccinated against polio and that countries using only the oral polio vaccine (OPV) should include at least one dose of inactivated polio vaccine (IPV).[157]
- IPV was first used in the 1950s. Current formulations of IPV are highly immunogenic, with 94–100% seroconversion rates for all three polio serotypes.[157] The addition of the functionally trivalent IPV has been recommended to mitigate against potential re-emergence of polio serotype 2, following the withdrawal of type 2-strains from OPV (making it bivalent). IPV is less effective than OPV in inducing mucosal immunity among previously unvaccinated children, but administering both formulations in immunisation campaigns has resulted in uniformly high antibody titres against all three poliovirus types.[157,158]
- Recent research shows that fractional doses of IPV can be administered intradermally with specialised adapters to auto-disposable syringes or jet injectors. Use of fractional doses allows a lower dose to be given without reduction in immunogenicity and can provide overall cost savings.[162,163] Research also underlines the potential for combining fractional IPV doses with hexavalent vaccine formulations.[164]

Recommended schedules	Age at 1st dose	Doses in primary series (interval between doses)	Booster
3 doses OPV + 1 dose IPV (OPV plus IPV)*	OPV: birth dose	OPV: 1st dose at 6 weeks (4 weeks between doses 1, 2 and 3) IPV: dose at 14 weeks	No booster
1–2 doses IPV+ ≥2 OPV (Sequential IPV OPV)**	IPV: 14 weeks IPV: 2 months OPV: after last IPV dose	IPV: 2nd dose at 3–4 months OPV: 2nd dose 4–8 weeks after 1st dose	No booster
3 doses IPV (IPV only)†	2 months	4 weeks between 1st and 2nd doses, and between 2nd and 3rd doses	If primary series is begun at <2 months, booster recommended at ≥6 months (becomes a 4-dose schedule).

*WHO no longer recommends OPV-only schedules. The OPV plus IPV schedule is applicable to polio-endemic countries and those with high risk of importation.[124]
**Applicable to countries with 90–95% immunisation coverage, low importation risk and where vaccine-acquired polio is a significant concern.[124]
†Applicable to countries with sustained high immunisation coverage and lowest risk of wild poliovirus importation and transmission.[124]

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)	
Inactivated polio vaccine (IPV)	Bilthoven Biologicals BV*	Dec 2010	Liquid; 1-dose vial	2.80	VVM 7	
					Akylux tray of 360 vials = 15.7 cm^3	
Inactivated polio vaccine (IPV)	Serum Institute of India/Bilthoven Biologicals	N/A	Liquid; 5-dose vial**	2.00[165]	N/A	
Poliorix Inactivated polio vaccine	GSK	Aug 2012	Liquid; 1-dose and 2-dose vials‡	N/A	VVM 7 (1-dose vial)	VVM 14 (2-dose vial)
					Carton, 1, 10 or 100 vials (1- and 2-dose vials)	
Imovax Polio Inactivated polio vaccine	Sanofi Pasteur	Dec 2005	Liquid; 10-dose vial‡	1.04†	No VVM	
					10 vials of 10 doses = 2.46 cm^3	
IPV Vaccine SSI Inactivated polio vaccine	Statens Serum Institut	Dec 2010	Liquid; 1-dose vial	N/A	VVM 7	
					Carton, 1 vial = 101.4 cm3	
					Carton, 10 vials = 26.8 cm3	
					Carton, 50 vials = 12.9 cm3	

PIPELINE PRODUCTS

- DTP-HepB-IPV-Hib (PR5I): paediatric hexavalent vaccine in Phase III of development from Sanofi Pasteur.[173]
- DTP-HepB-IPV-Hib (V419): paediatric hexavalent vaccine in Phase III from Merck.[134]
- DPT-IPV (TAK-361S): tetravalent vaccine in Phase II from Takeda and Japan Polio Research Institute.[174]
- Sabin IPV (sIPV) products from Panacea, Takeda and Intravacc (Netherlands Vaccine Institute) in varying phases of development.[175,176]

CHALLENGES

- On 5 May 2014, WHO declared the international spread of polio to date in 2014 to be a Public Health Emergency of International Concern and an "extraordinary event" posing a "public health risk to other states for which a coordinated international response is essential".[161,177,178] WHO identified Pakistan, Cameroon and Syria as states posing the greatest risk of wild poliovirus exportation, and a further seven countries (including Afghanistan and Nigeria) as infected with wild poliovirus but not currently exporting. WHO recommendations include vaccination of all country residents, visitors and travellers and maintenance of the recommended measures for a period of 12 months with no evidence of transmission.[161,177,178]
- There are significant supply bottlenecks relating to IPV. With five-dose and new versions of the 10-dose vials only made available from mid- to late 2014, current availability of one- and two-dose vials will be heavily constrained.[169]
- To expedite supply of IPV, UNICEF recommends that countries provide timely information on preferred vial size, acceptable alternatives, and national licensing requirements and their anticipated timetable for introduction.[167,169,179]

*Acquired by Serum Institute of India in July 2012.

** 5-dose vial presentation from Serum Institute of India/Bilthoven was put forward for the UNICEF bid tender although not WHO prequalified.[166] It is anticipated to be prequalified and available for procurement by the end of 2014.[167–169]

† Price listed is the Gavi price, converted from euros to US dollars.[170] Currently UNICEF procures Imovax Polio from Sanofi Pasteur for non-Gavi countries at three different price tiers that are based on adjusted Gross National Income per capita (see 'Prices and affordability' section, opposite).[171] This arrangement does not cover all middle-income countries, prices for which are country- and supplier specific.[169]

‡ All multidose opened vials must be discarded not more than six hours after opening (WHO multidose open-vial policy).[172]

Prices and affordability

THE GLOBAL POLIO ERADICATION INITIATIVE

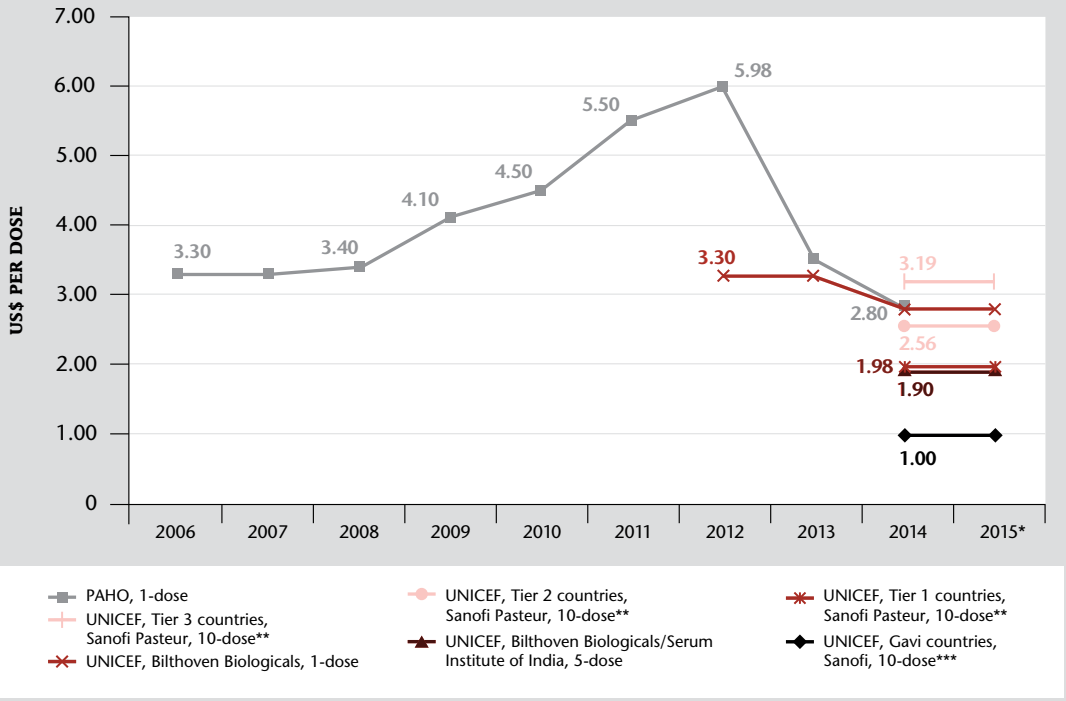
The Global Polio Eradication Initiative (GPEI) was created in 1988, following a resolution passed at the World Health Assembly. GPEI is a public–private partnership with the goal to eradicate polio worldwide. Thus far more than US$8.2 billion has been spent on polio eradication. Efforts intensified after 2008 and since 2012 WHO has declared ending polio a "programmatic emergency for global public health", as a result of which the Polio Eradication and Endgame Strategic Plan 2013–2018 was developed.[157] The plan includes the phasing-out of OPV and progressive introduction of IPV into routine immunisation schedules as a key element of eradication and post-eradication activities,[180] reducing the risk of re-emerging type-2 polio while also accelerating wild poliovirus eradication.[1,2,6,7,180] In 2013, Gavi decided to support the introduction of IPV in routine immunisation programmes.[179]

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

- Before 2010, there was only one WHO prequalified IPV product (Sanofi Pasteur's Imovax Polio). In 2010, Statens Serum Institute, GSK and Bilthoven obtained WHO prequalification status for their IPV vaccines. In July 2012, Serum Institute of India purchased Bilthoven Biologicals, and in 2013, the newly created Intravacc (the Dutch Institute for Translational Vaccinology) and Bilthoven Biologicals started their collaboration to improve the IPV production process, with the aim of a more affordable vaccine.[175,183]
- PAHO has benefited from the entry of these new manufacturers into the market. In 2013, the price of IPV was reduced as a result of Bilthoven's participation in the Revolving Fund. PAHO purchased IPV at US$4.14 from GSK in 2013, but purchased the Bilthoven vaccine the same year at US$2.90 and then at US$2.80 in 2014, a 30% price drop [Graph 9, overleaf].
- In February 2014, price announcements were made following UNICEF's IPV tender. Sanofi Pasteur and Serum Institute of India/Bilthoven Biologicals responded to the tender and offered their IPV vaccines at a reduced price. Sanofi Pasteur offered different prices based on groups of countries, while Serum Institute of India offered one price for all countries.
- However, the price announcement raised some concerns as it was the first time that a manufacturer responded to a UNICEF tender with a clear tiered-pricing offer. Sanofi's price offer classified countries in four tiers: three groups of countries that pay three distinct prices, and the Gavi-supported group comprising the lowest tier. According to the UNICEF website, tiers were determined on the basis of "GNI per capita, and by considering each country's overall level of development by adjusting the GNI per capita to account for inequities in wealth distribution within each country".[11]
- Sanofi's announcement to sell IPV to UNICEF at a lower price was supported by the Bill & Melinda Gates Foundation and is heralded as critical in light of the Global Polio Endgame Strategy.[171] But despite efforts to reduce prices, the lowest price for IPV remains more than seven times as expensive as the lowest price for OPV: in 2014, the lowest price to UNICEF for OPV is US$0.12 per dose (Bio Farma, 20-dose presentation), while IPV is priced at US$1 (Sanofi Pasteur, Gavi countries only, 10-dose presentation).

Graph 9: Price evolution of Inactivated Poliovirus (IPV) vaccines for PAHO, UNICEF and Gavi



Sources:
PAHO Revolving Fund, UNICEF Supply Division

* Forecasted data. Prices remain the same between 2015 and 2018.

** Special terms apply except for a single-dose liquid presentation. MSF requested details from UNICEF on these special terms but the information was not provided.

*** Sanofi Pasteur and the Gates Foundation have designed a price mechanism with additional financial contributions to attain the Gavi IPV price. MSF requested details on these subsidies but the information was not provided.

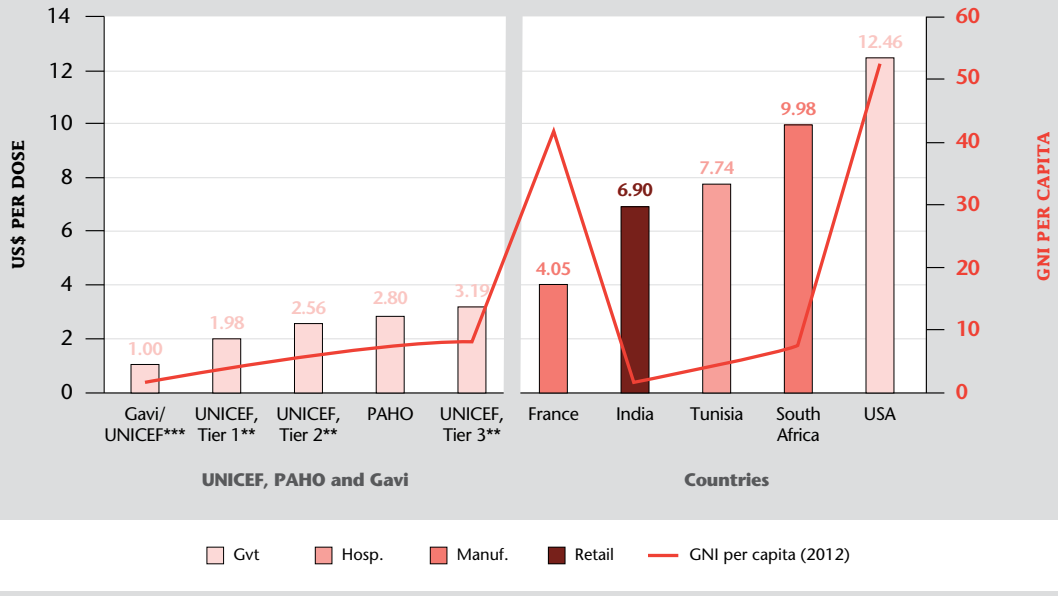
Notes and methodology:

- For PAHO, a weighted average price is used for 2006–2012, an average of the two available actual prices (from GSK and Bilthoven Biologicals) is used for 2013 and the actual price from Bilthoven Biologicals (sole supplier) is used in 2014.
- The rise in price for PAHO from 2006 to 2013 occurred because, prior to 2013, only one country had introduced IPV in its routine immunisation programme.
- Tiers for Sanofi Pasteur's vaccine are:[11]
  - Tier 1 countries: Cape Verde, Egypt, Morocco, Palestine, Philippines, Samoa, Swaziland, Vanuatu (GNI/capita: <US$4,000).
  - Tier 2 countries: Albania, Algeria, Fiji, Iran, Macedonia, Maldives, Namibia, Serbia, Thailand, Tonga, Tunisia, Turkmenistan (GNI/capita: US$4,000–6,000).
  - Tier 3 countries: Botswana, Gabon, Lebanon, Mauritius, Seychelles, Tuvalu (GNI/capita: >US$6,000).

PRICES IN COUNTRIES

- There are few data points from countries on IPV as several countries have introduced IPV through pentavalent or hexavalent combination vaccines that contain IPV. Therefore, prices of standalone IPV listed here might be higher in countries that have also introduced one of these combination vaccines (e.g. South Africa).
- The graph below [Graph 10] demonstrates that despite Sanofi Pasteur's tiered prices being aligned with country GNI per capita for countries who procure through UNICEF, the end result continues to be high and unaffordable prices for many countries. Comparing the PAHO price to the UNICEF price, the PAHO price appears pegged to the UNICEF price gradation despite UNICEF and PAHO procuring two different products. Regarding prices of IPV in countries that do not procure through UNICEF, the relationship between the price of the vaccine and the country's wealth is much less obvious, even when keeping in mind that there are different price categories represented in the graph.
- Prices of combination vaccines such as hexavalent DTaP-HepB-Hib-IPV vaccine or the DTaP-Hib-IPV vaccine have been explored in the pentavalent vaccines product card [see page 65].

Graph 10: Prices for Inactivated Poliovirus (IPV) vaccines by GNI/capita in several countries, 2013/2014*



Sources: PAHO Revolving Fund, UNICEF Supply Division, country price analysis (see Annex A for more information).

*Annex A, Section C

** Special terms apply except for a single-dose liquid presentation. MSF requested details from UNICEF on these special terms but was not given information.

*** Sanofi Pasteur and the Gates Foundation have designed a price mechanism with additional financial contributions to attain the Gavi IPV price. MSF requested details on these subsidies but was not given information.

Notes and methodology:

- All prices are for Sanofi Pasteur products (Ipol in the US, Imovax Polio in other countries), across presentations, except the PAHO price, which is for Bilthoven Biologicals vaccine.
- For the Sanofi Pasteur vaccine purchased through UNICEF, GNI per capita thresholds are: Tier 1: up to US$4,000; Tier 2: US$4,000–6,000; Tier 3: over US$6,000.[184]
- PAHO GNI per capita estimated at US$7,500.[184]

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Measles-containing Vaccines (Measles, MR, MMR)

WHO recommendations & general information

- Measles-containing vaccines include combination vaccines for measles and rubella (MR) and for measles, mumps and rubella (MMR) and monovalent measles vaccines.
- Measles is a highly infectious viral disease. Vaccination against measles has been recommended as part of the Expanded Programme on Immunization (EPI) since the programme's inception in 1974. Before that, 90% of individuals were infected with measles before the age of ten years.[185] There were 122,000 measles deaths in 2012, most of which were among children aged under five years.[185] Surveillance data show that there were 177,510 total reported measles cases globally for 2013, and 45,566 for the first five months of 2014.[186]
- The WHO recommends measles vaccination for all susceptible infants, young children and adults (in the absence of contraindications) as part of national immunisation programmes globally.[187] The first dose of measles vaccine, if administered at 11–12 months of age, provides a seroconversion rate of 99%. Of children who fail to respond to the first dose, 97% (median value) develop immunity after the second dose.[187] Mumps infection affects primarily the salivary glands and is most common among children aged between five and nine years. The disease is generally self limiting but serious complications can occur; these include meningitis, encephalitis, deafness and orchitis.[188]
- Mumps incidence has declined dramatically since the 1960s, when vaccines against it were first introduced. Currently, global mumps incidence is 100–1,000 cases per 100,000 population, with epidemic peaks every two to five years.[189]
- The WHO recommends routine mumps vaccination in countries where reduction of mumps is a public health priority, provided the country has a well-established childhood vaccination programme and the capacity to maintain coverage for routine measles and rubella vaccination at >80%. All mumps vaccine strains (except the Rubini strain) confer short-term protective efficacy rates above 90% with administration of one dose.[188]
- Rubella is an acute, contagious and generally mild viral disease, usually affecting susceptible children and young adults. Rubella infections occurring before conception or in early pregnancy are of greatest concern because rubella can be teratogenic, potentially leading to miscarriage, fetal death, or congenital malformations as part of congenital rubella syndrome (CRS). CRS can cause ophthalmic, auditory, cardiac and brain anomalies[190] and worldwide an estimated 110,000 children are born every year with CRS.[191] Large scale rubella vaccinations over the past decade have substantially reduced rubella and CRS in many countries but more needs to be done to reach the measles and rubella elimination targets set out in the Global Measles and Rubella Strategic Plan.[191–193]

- The WHO recommends that all countries yet to introduce combined rubella vaccines (as part of MMR) should immediately consider adding them to national immunisation programmes. WHO also recommends reviewing national-level epidemiological factors, CRS burden and specific population profiles when determining the immunisation strategy for targeting rubella. To keep CRS in check and work towards rubella control and elimination, vaccination coverage needs to be sustained at or above 80% in an attempt to avoid shifting of rubella infection from childhood to fertile age groups.[190] All licensed rubella vaccines (including those that are a component of MMR) induce seroconversion at a rate of 95% or higher after a single dose, with vaccine efficacy of 90–100%.[190]
- Nine months is the preferred age for the first dose for countries with ongoing measles transmission and high risk of measles mortality. In countries with low rates of measles infection among infants, 12 months is the preferred age for the first dose to achieve a seroconversion rate of >90%. Giving the second dose at 15–18 months ensures early protection of the individual and slows accumulation of susceptible young children, thereby reducing the risk of an outbreak.[124,185]
- The choice of age for rubella vaccination depends entirely on when the first dose of measles vaccine is given. Vaccination in pregnant women should be avoided because of the theoretical risk of congenital rubella.[124,190]
- Mumps vaccination is recommended as part of the combined measles, mumps and rubella vaccine.[124,188]

Vaccine	Age at 1st dose	Doses in primary series (interval between doses)	Booster
Measles	9 or 12 months (not <6 months)*	2 doses (minimum 4 weeks)	No booster
Mumps	12–18 months with measles-containing vaccine	2 doses (2nd dose at least 1 month before school entry)	No booster
Rubella	9 or 12 months with measles-containing vaccine	1 dose	No booster

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation*	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
Measles vaccine	Bio Farma	Apr 1997 (10-dose) Sep 2006 (20-dose)	Lyophilised, 10- or 20-dose vials + water diluent	0.219 (10 doses)	VVM 14 Carton, 50 vials (active) + carton, 50 ampoules of diluent = 26.11 cm^3 (1-dose vials), 13.1 cm^3 (2-dose vials), 5.22 cm^3 (5-dose vials), 2.611 cm^3 (10-dose vials)
Measles vaccine	GPO–Merieux	Sep 2010	Lyophilised, 10-dose vial + water (5 ml) diluent	N/A	VVM Type 14 Box, 10x10-dose vials + box, 10 vials of 5 ml diluent = 2.13 cm^3
Rouvax Measles vaccine	Sanofi Pasteur	May 2002	Lyophilised, 10-dose vial + water for injection (5 ml) diluent	0.450	VVM 14 Box, 10x10-dose vials + box, 10 vials of 5 ml diluent = 2.46 cm^3
Measles vaccine (live, attenuated)	Serum Institute of India	Feb 1993	Lyophilised, 1-, 2-, 5- and 10-dose vials + ampoule water diluent	0.252 (10 doses) 0.770 (1 dose; 2003 price)	VVM 14 Carton, 50 vials (active) + carton, 50 ampoules of diluent = 26.11 cm^3 (1-dose vials), 13.1 cm^3 (2-dose vials), 5.22 cm^3 (5-dose vials), 2.611 cm^3 (10-dose vials)
Measles and rubella vaccine (live, attenuated)	Serum Institute of India	Jul 2000	Lyophilised, 1-, 2-, 5- and 10-dose vials + ampoule water diluent	N/A	VVM 14 Carton, 50 vials + 50 ampoules = 25.11 cm^3 (1-dose vials), 13.1 cm^3 (2-dose vials), 5.22 cm^3 (5-dose vials), 2.611 cm^3 (10-dose vials)
Priorix Measles, mumps and rubella vaccine	GSK	Mar 2001 (1-dose) Dec 2011 (2-dose)	Lyophilised, 1- and 2-dose vials + ampoule water for injection diluent	3.250 (2 dose)	VVM 7 Vaccine vial = 9.6 cm^3 + diluent ampoule = 25.6 cm^3 Carton, 100 vials of vaccine and 100 ampoules diluent = 4.8 cm^3 (vaccine vial) + 12.8 cm^3 (diluent ampoule)
M-M-R II Measles, mumps and rubella vaccine	Merck Sharp & Dohme	Jan 2009	Lyophilised, 1-dose vial	N/A	VVM 7 Carton, 10 vials = 15 cm^3
Trimovax Merieux Measles, mumps and rubella vaccine	Sanofi Pasteur	Apr 2002	Lyophilised, 1-dose vial + 1-dose ampoule (diluent); and 10-dose vial + 5 ml vial diluent	3.100 (1 dose, 2012) 1.890 (10 doses, 2014)	No VVM (1 dose); VVM 14 (10 dose) 10 vials of 1 dose vaccine + 10 of 0.5 ml water in ampoules = 12.66 cm^3 10 vials of 10 dose vaccine + 10 of 5 ml water diluent = 2.46 cm^3
Measles, mumps and rubella vaccine (live, attenuated)	Serum Institute of India	Aug 2003	Lyophilised, 1-, 2-, 5- and 10-dose vials (+ ampoule diluent	2.150 (1 dose) 1.040 (5 doses) 1.025 (10 doses)	VVM Type 14 Carton, 50 vials + carton, 50 ampoules diluent = 26.11 cm^3 (1-dose vials), 13.1 cm^3 (2-dose vials), 5.22 cm^3 (5-dose vials), 2.611 cm^3 (10-dose vials)

*All reconstituted multidose vials must be discarded no more than six hours after opening (WHO multi-dose open-vial policy).[172]

PIPELINE PRODUCTS

- A live, attenuated MMR vaccine from GSK is in Phase III of development.[194]
- Bio-Manguinhos, in association with the Bill & Melinda Gates Foundation, is developing an MR vaccine.[195,196]

CHALLENGES

- Outbreaks of both mumps and measles have surged in developed countries in recent years. This is largely because public misconceptions about vaccine safety are causing parents to choose not to vaccinate their children,[193] in spite of conclusive independent evidence disproving the alleged causal link between MMR and autism, among other safety concerns, claimed by anti-vaccine advocates.[197,198]
- The Global Measles and Rubella Strategic Plan lists several challenges to the elimination of these diseases. These include establishing and guaranteeing sustained and predictable financing for immunisation efforts; improving data and reporting of vaccination coverage; and addressing concerns on the capacities of health systems. The plan also calls for working with governments to reach areas of high population density, areas with highly mobile populations and countries facing complex humanitarian emergency situations, where measles case fatality rates can be as high as 25%.[193]
- Alternative vaccine delivery methods, such as by the nasal route, are in development after research indicating they can provide a viable pathway for delivery, with improved vaccine seroconversion rates.[199]
- The measles monovalent vaccine supply is fragile because a single manufacturer (Serum Institute of India) produces 80% of the supply and is also the sole manufacturer of the only WHO prequalified MR vaccine.[200]

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Prices and affordability

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

MEASLES VACCINE

- The price of the measles vaccine is relatively low, but has followed an upward trend in the past decade [Graph 11]. This likely reflects reduced demand for the monovalent product, as countries progressively switch to combination vaccines such as MR and MMR (for instance, PAHO ceased orders for measles vaccines in 2006), and a decreasing number of manufacturers.
- The number of different products procured by UNICEF has declined from seven in 2002 to only three, two of which are produced by emerging manufacturers. Mono-dose measles vaccines were purchased by UNICEF for the last time in 2003; since then the much less expensive multi-dose vial presentation has been preferred.

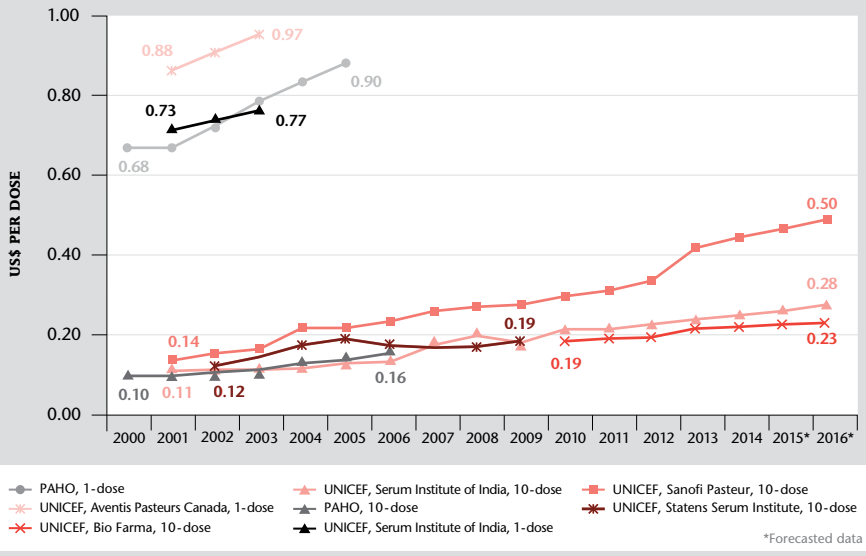
MR VACCINE

- Recent recommendations by WHO (2011)[190] to include rubella in routine immunisation have increased demand for MR and MMR vaccines.
- However, the number of manufacturers of the MR vaccine has always been limited to two, and following Crucell's exit from the market in 2012, Serum Institute of India was left as the sole manufacturer of a WHO prequalified MR vaccine.[113]
- Increasing demand from UNICEF and a diminishing number of manufacturers have driven up prices of the MR vaccine [Graph 12, overleaf].
- In 2013, Gavi announced its support of large-scale catch up campaigns with the MR vaccine, provided that countries self-finance the introduction of the vaccine into their routine immunisation programmes.[201]

MMR VACCINE

- MMR vaccines are more expensive than MR or measles vaccines. For instance, the lowest price per dose offered to UNICEF for the MMR vaccine (10-dose presentation by Serum Institute of India at US$1.025) is almost twice that of the MR vaccine offered in the same presentation by the same manufacturer (at US$0.55) [Graph 13, overleaf].
- There are large price differences between the products containing different strains of mumps. For instance, the PAHO price in 2014 for the single-dose MMR Jeryl Lynn strain vaccine (manufactured by GSK and Merck) was about 2.4 times more expensive than the single-dose MMR Urabe strain vaccine (manufactured by Sanofi Pasteur), and five times more expensive than the lowest-priced presentation of the MMR Zagreb strain vaccine (manufactured by Serum Institute of India).

Graph 11: Price evolution of measles vaccines for PAHO and UNICEF

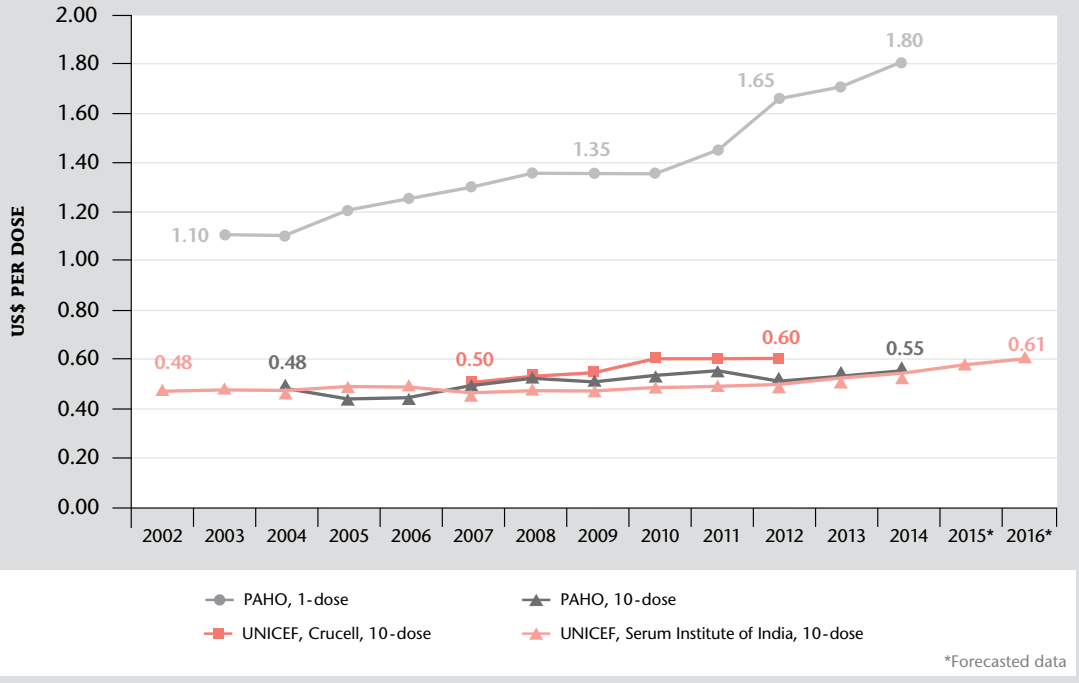


Sources:
PAHO Revolving Fund,
UNICEF Supply Division

Notes:

- Products omitted from graph because of data discontinuity. A 10-dose presentation was sold to UNICEF by Tanabe Seiyaku from 2002 to 2003; and Eisai Co from 2001 to 2003.
- Sanofi Pasteur product was sold under Aventis Pasteur Canada from 2001 to 2003.
- Novartis supplied measles vaccines to UNICEF in 2005 but has not agreed to the publication of prices.

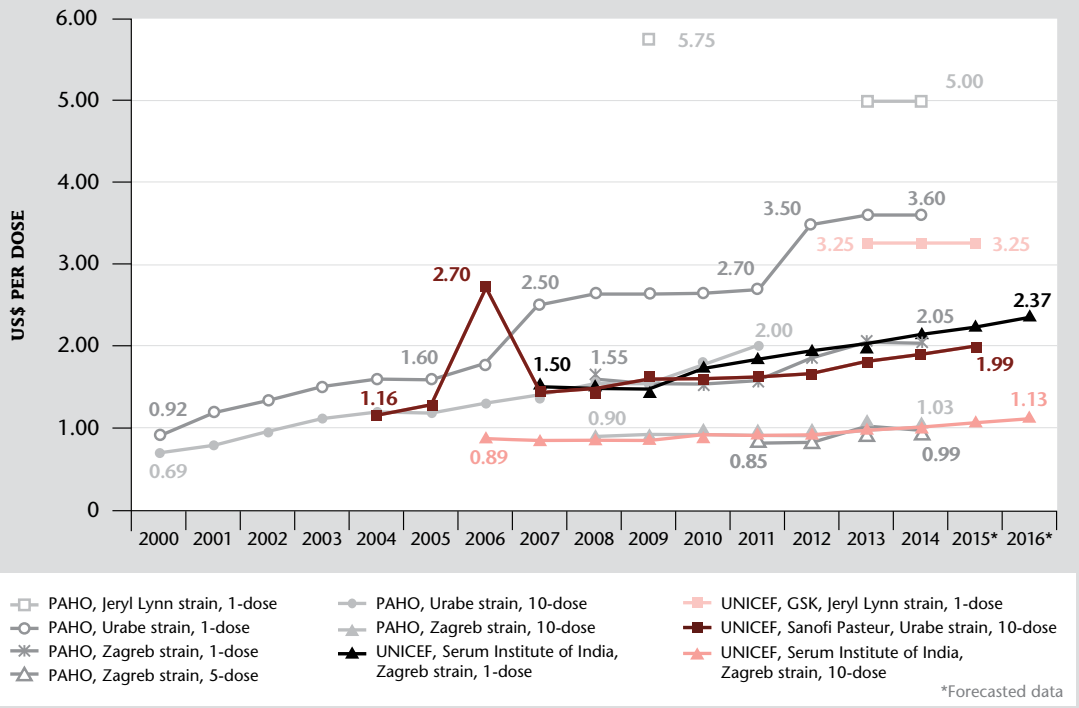
Graph 12: Price evolution of Measles-Rubella (MR) vaccines for PAHO and UNICEF



Sources: PAHO Revolving Fund, UNICEF Supply Division

Note:
Products omitted from graph because of data discontinuity: PAHO purchased a two-dose presentation of the vaccine from 2003–2005.

Graph 13: Price evolution of Measles-Mumps-Rubella (MMR) vaccines for PAHO and UNICEF



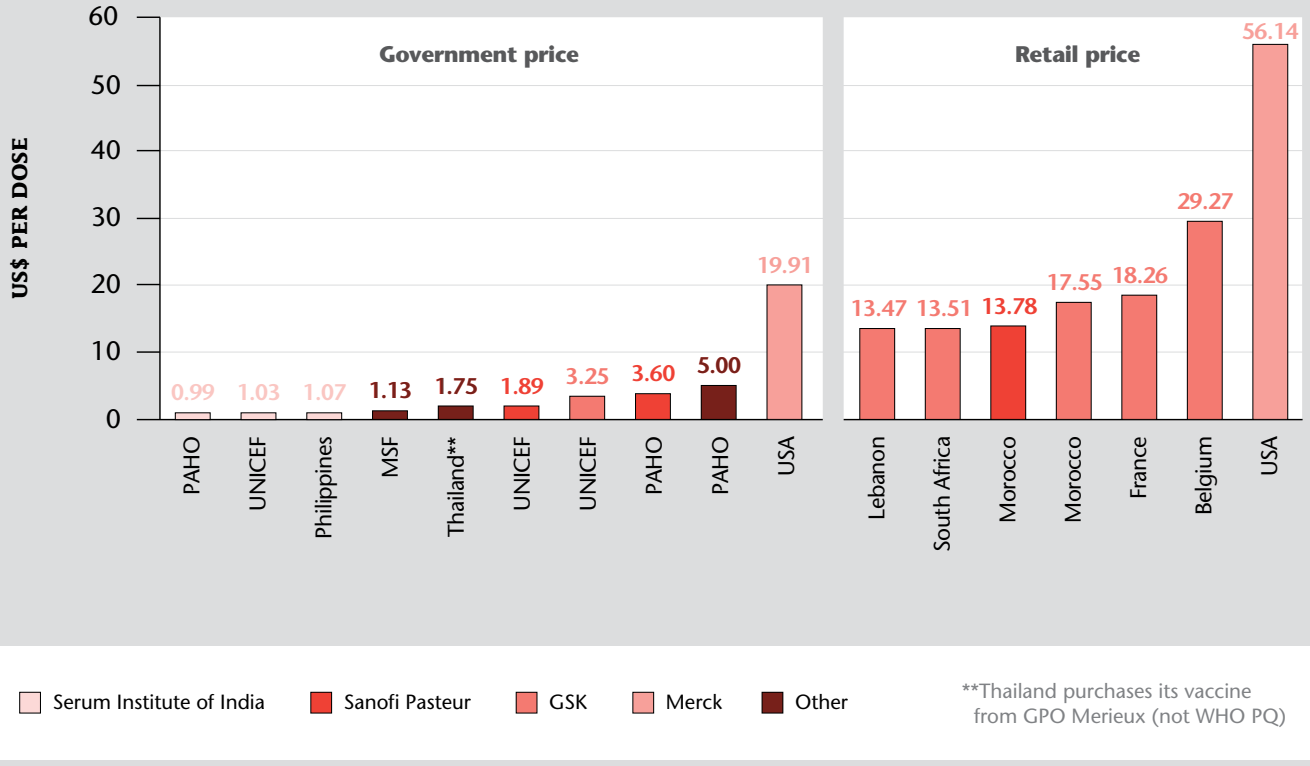
Sources: PAHO Revolving Fund, UNICEF Supply Division

Notes:
- Products omitted from graph because of data discontinuity: UNICEF purchased a 10-dose MMR Jeryl Lynn strain from GSK in 2002, and a Sanofi Pasteur Urabe-strain MMR vaccine in 2010 and 2012. Serum Institute of India also offers a two-dose MMR vaccine since 2010, priced similarly to its 10-dose presentation.
- Novartis has supplied MMR to UNICEF but has not agreed to the publication of prices.

PRICES IN COUNTRIES: FOCUS ON MMR

- Vaccines made with the Jeryl Lynn mumps strain are more expensive; countries opting for a measles or MR vaccine instead of an MMR product will unfortunately lose a disease-control opportunity to vaccinate against mumps.[197]
- In countries where only measles is included in the Expanded Programme on Immunization (EPI), MMR is available only through the private sector, often at very high prices. In South Africa, for instance, the price of the measles vaccine from the government is US$0.59, while a dose of MMR through the private sector will cost US$13.51 [Graph 14].
- The price of the MMR vaccine in the retail market in the US (MMRII, by Merck, at US$56.14) is extremely high compared to that in other countries; it is double the price paid in Belgium, the next high-income country included in our analysis (for Priorix, by GSK, at US$29.27), and triple the price paid in France.
- Combined measles, mumps, rubella and varicella (MMRV) vaccines are not yet WHO prequalified, but countries might decide to use MMRV instead of MMR. In the countries we analysed, only the USA and South Africa had pricing data available for MMRV. The vaccine is markedly more expensive than MMR, retailing in the private sector at US$36.42 per dose in South Africa (Priorix Tetra, by GSK) and at US$157.64 in the USA (ProQuad, by Merck).

Graph 14: Prices for MMR vaccines in several countries, by manufacturer and price type, 2013/2014*



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

Notes:

- Prices for UNICEF, MSF, PAHO, Thailand and the Philippines are for multidose vials; those for the other countries are for single-dose vials.
- MSF price is Incoterm Carriage Paid To (named destination) (see Annex C).
- When a country or organisation purchases several presentations of a same vaccine, only the lowest price is presented in the graph.

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Meningococcal Vaccines

WHO recommendations & general information

- Meningococcal meningitis is a life-threatening form of bacterial meningitis, and the *Neisseria meningitidis* bacterium causes one of the most virulent and severe forms of the disease. Six serogroups – A, B, C, X, W135 and Y – are responsible for almost all outbreaks of meningitis, with most outbreaks caused by serogroup A.[202–204]
- An area stretching from Senegal to Ethiopia in sub-Saharan Africa, known as the African meningitis belt, experiences the largest and most frequent outbreaks. Meningococcal disease incidence peaks annually in the dry season (December to June), during which time disease rates can reach 1,000 cases per 100,000.[202–204]
- In 2010, there were an estimated 422,851 deaths from meningitis.[205] The WHO recommends that countries with high (more than ten cases per 100,000 population) or intermediate (two to ten cases per 100,000) endemic rates, as well as countries with frequent epidemics, should introduce meningococcal vaccination programmes.[202] In countries with low endemicity (fewer than two cases per 100,000), vaccination is recommended for high-risk groups such as children, young adults living in closed communities, and for immunosuppressed individuals (e.g those with asplenia or advanced HIV).[202]
- Delivery strategy (routine immunisation, supplementary immunisation activities or private services) and the choice of which specific vaccine* to use is dependent on the country-specific epidemiological profile, locally prevalent serogroups, and overall socioeconomic capability.[202]

Vaccine	Age at 1st dose	Doses in primary series (interval between doses)	Booster
MenA Conjugate	1–29 years	1 dose	Need for booster yet to be established
MenC Conjugate	≥12 months (including teenagers and adults)	1 dose	No booster
	2–11 months	2 doses (2 months)	Booster 1 year after 2nd dose
Quadrivalent Conjugate Vaccine ACYW-135	9–23 months	2 doses (1st dose at 9 months with 3-month interval between 1st and 2nd doses)	No booster
	≥2 years	1 dose	No booster

*Polysaccharide vaccines can be used for children aged more than two years in outbreak settings or when there are conjugate vaccine supply constraints. Conjugate vaccines are preferred for their superior immunogenicity and potential to induce herd immunity. They are recommended for all children and adolescents aged nine months to 18 years, with other groups included on the basis of surveillance data.[202]

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
MenAfriVac Meningococcal A conjugate vaccine	Serum Institute of India	Jun 2010	Lyophilised, 10-dose vial + 10-dose ampoule (diluent)	0.52–0.58	VVM 30* Carton, 50 vials (active) + 50 ampoules (diluent) = 2.6 cm^3
Polysaccharide meningococcal A+C vaccine	Bio-Manguinhos	Dec 2007	Lyophilised, 10-dose vial + buffered saline solution diluents**	0.80 (2012)	VVM 14 10 vials = 2.96 cm^3
Polysaccharide meningococcal A+C vaccine	Sanofi Pasteur	Jul 1997	Lyophilised, 10-dose vial + specific meningococcal diluents in vial (5 ml)**	1.22	No VVM 10 vials of 10 doses (vaccine) + 10 vials 5 ml (diluents) in separate box = 2.46 cm^3
Menactra Meningococcal ACYW-135 conjugate vaccine	Sanofi Pasteur	Mar 2014	Liquid, 1-dose vial	N/A	VVM 7 Carton, 5 vials = 20.50 cm^3 Carton, 1 vial = 54.88 cm^3
Menomune Meningococcal ACYW-135 polysaccharide vaccine	Sanofi Pasteur	May 2013	2-vial set: lyophilised 10-dose vial + diluent vial†	4.00	VVM 30 Carton, 1 vial active + 1 vial diluent = 11.13 cm^3
Menveo Meningococcal ACYW-135 conjugate vaccine	Novartis	††	1-dose lyophilised + conjugate component**	N/A	VVM: N/A Box, 10 doses

*Stable under controlled temperature chain settings, i.e. at up to 40°C for four days, after which unopened vials should be discarded if not used.[206]
**All reconstituted multidose vials must be discarded no more than six hours after opening (WHO multidose open-vial policy).[172]
†As it is preservative free, opened vials can be kept for subsequent use (up to a maximum of 28 days) within stipulations of the WHO Policy Statement on use of opened multidose vials in subsequent immunisation sessions.[172]
††At time of research and publication, the link on the WHO PQ page did not work (www.who.int/immunisation_standards/vaccine_quality/PQ_vaccine_list_en/en/).

PIPELINE AND OTHER PRODUCTS

- GSK previously produced a meningococcal ACW-135 polysaccharide vaccine in a 50-dose presentation for outbreak response only. This particular presentation was procured by UNICEF at US$1.25 per dose in 2012,[207] after approval by the International Coordinating Group (ICG) for use in emergency settings, but GSK ceased its production in 2012.[208]
- GSK also produces a meningococcal C and Y conjugate vaccine with Hib for the USA and a European Commission-approved meningococcal ACYW-135 conjugate vaccine (Nimenrix), but neither is WHO prequalified.[194,209–211]
- Serum Institute of India has a meningitis ACYW-135 quadrivalent vaccine in development and Novartis has a meningitis ABCW-135 Y product in Phase II.[212,213]
- Pfizer has a meningococcal B (bivalent rLP2086) product in Phase III.[214,215]

CHALLENGES

- Inadequate global surveillance data make it difficult to predict more accurately the global burden of disease specifically attributable to meningococcal meningitis.[202]
- Absence of a licensed vaccine for serogroup X will hinder countries' abilities to provide an adequate public health response to recent localised epidemics and seasonal hyperendemicity observed between 2006 and 2010.[216]
- MenAfriVac has paved the way as the first vaccine approved by WHO for use in a controlled temperature chain (CTC) and has prompted a push to evaluate other vaccines for use in CTC. Encouraging manufacturers to develop CTC vaccines and to relabel vaccines for CTC use is a continuous challenge.[110]

Prices and affordability

THE MENINGITIS VACCINE PROJECT

The Meningitis Vaccine Project (MVP) was established in 2001 by the Program for Appropriate Technology in Health (PATH) and WHO, with funding (US$70 million) from the Bill & Melinda Gates Foundation. The aim of the MVP was to develop meningococcal conjugate vaccines appropriate for Africa. Serum Institute of India joined the partnership, received technology transfers, and committed to develop a vaccine priced at US$0.50 a dose or less.[217] A major aim of the MVP was to develop a vaccine that could provide an effective and affordable solution to combat epidemic meningitis while also addressing cold chain-related logistical challenges.[217]

With the cooperation of Synco Bio Partners in the Netherlands, and the Center for Biologics Evaluation and Research of the US Food and Drug Administration (FDA), Serum Institute of India began development of a meningococcal conjugate A vaccine, called MenAfriVac, in 2003. MenAfriVac was WHO prequalified in June 2010. Serum Institute of India is the sole supplier of the vaccine, selling it at US$0.528 a dose in 2013.[11] The total project cost was just US$60 million, excluding the cost of the manufacturing plant.[218] In 2013, the Bill & Melinda Gates Foundation awarded the project an extension grant of US$17 million over 2.5 years 'to support clinical research related to the use of the newly developed vaccine in infants'.[219]

More than 100 million people have been vaccinated and MenAfriVac has successfully halted outbreaks in countries such as Chad and Nigeria, with the number of cases in the Meningitis Belt at their lowest for a decade.[220] The low cost of the vaccine makes the project sustainable, as countries can finance and purchase vaccines themselves.[221]

In 2012, MenAfriVac was approved for use in a controlled temperature chain (CTC) for up to 40°C for up to four days. Other broader benefits of using a CTC include increased acceptance among healthcare workers because of reduced logistical burdens, and cost savings of up to 50% of the vaccine price.[108] Modelling studies show that making individual vaccines more thermostable not only increases their availability, but also the availability of other vaccines they are administered with, in addition to alleviating supply chain bottlenecks and lowering costs.[222]

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

- The development of MenAfriVac is one of the best examples of a vaccine research and development process that set affordability and adaptability targets from the outset. The MVP has been an extremely successful initiative that succeeded in producing a conjugate meningococcal vaccine at a low price, allowing UNICEF to purchase MenAfriVac at US$0.53 per dose in 2013.
- The price for conjugate meningitis C vaccines for the PAHO Revolving Fund has never decreased below US$14 per dose, and has even increased in recent years to reach US$19.50 per dose, making it the most expensive vaccine purchased by the Revolving Fund.
- Both meningitis A vaccine for UNICEF and meningitis C vaccine for PAHO have increased in price in 2013, by 23% for UNICEF (from US$0.43 to US$0.53) and 39% for PAHO (from US$14 to US$19.50).

PRICES IN COUNTRIES

- MSF purchases the meningitis A vaccine via the International Coordinating Group (ICG) mechanism at US$0.53 per dose (Incoterm CPT). Other than the MVP price for the meningitis A vaccine, the price of other conjugate meningococcal vaccines is very high.
- Prices for meningitis C vaccines in our analysis were only found in high-income countries and Hungary for the private sector. Outside of PAHO, retail prices per dose of meningitis C vaccines range from US$29.11 in Hungary for Menjugate by Novartis to US$50.62 in the Czech Republic for the same product.
- A few countries also provided prices for the tetravalent meningitis ACYW-135 vaccine, which is priced higher. For instance, meningitis ACYW-135 vaccines are available in Lebanon at the retail price of US$85.67–87.27 per dose (for Menveo by Novartis and Menactra by Sanofi Pasteur, respectively).

Pentavalent Vaccines (DTP-HepB-Hib)

WHO recommendations & general information

- The pentavalent vaccine combines diphtheria, tetanus, whole-cell pertussis, hepatitis B and *Haemophilus influenzae* type b (DTwP-HepB-Hib) vaccines to prevent all five diseases. Annually across the world, diphtheria accounts for an average of 2,500 deaths,[223] pertussis for 89,000 deaths[224] and tetanus for 72,600 deaths among children aged under five years.[225]
- Hepatitis B (HepB) alone accounts for between 500,000 and 700,000 deaths per year,[226] with most cases occurring in developing countries. Most cases of liver cancer across the world (60–80%) are also attributable to infection with the HepB virus.[226]
- *Haemophilus influenzae* type b (Hib) accounts for 200,000 annual deaths, with a disease incidence of two to three million cases; the most serious cases occur in children aged six to 12 months.[227,228]
- Historically, the trivalent diphtheria-tetanus-pertussis (DTP) vaccine was considered the cornerstone of the Expanded Programme on Immunization (EPI) that was started in 1974. HepB vaccines were first WHO prequalified in 1987, followed by Hib vaccines in 1998.[12] DTP vaccines were first used in 1948,[229] and then integrated with HepB and Hib to form a pentavalent vaccine. The first pentavalent vaccine was introduced in the late 1990s.[12] Vaccine efficacy for the components of the pentavalent vaccine is 85–95% for Hib,[228,230,231] 95% for HepB,[232] 95.5% for diphtheria,[233] 61–89% for pertussis,[234] and 80–100% for tetanus.[235] Studies evaluating the combined efficacy of the diphtheria-tetanus-whole-cell-pertussis (DTwP) vaccine found efficacy ranged from 46% to 92%.[234]
- More than 170 countries worldwide,[236] including all 73 Gavi-eligible countries,[237] have introduced the pentavalent vaccine, including India, which independently is forecast to account for 20% of the global demand for pentavalent vaccine (28,000,000 doses) in 2014.[238]
- Perinatal infections account for 21% of the overall global HepB disease burden,[239] the highest proportion of deaths from which occur in Asia and Africa. At present only 18 out of 56 Gavi-eligible countries offer the WHO-recommended HepB birth dose,[240] and even among them coverage is poor. However, with support, there is evidence to suggest that coverage rates can reach ≥90%. This was exemplified by the partnership between Gavi and the Chinese government, whereby provision of a HepB birth dose free of charge to the public (through co-financing between Gavi and the government of China) catalysed a dramatic scale-up in coverage rates from around 40% in poorer counties to >90% in most parts of the country, with <1% of children overall being infected with HepB.[241,242]
- The WHO recommends that all infants receive their first dose of monovalent HepB vaccine[124,229] within 24 hours of birth; such administration is 90% effective in halting vertical disease transmission.[243]

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

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
Quinavaxem DTwP-HepB-Hib vaccine	Berna Biotech (Crucell)	Sep 2006	Liquid, 1-dose vial	2.40–2.60	VVM 14
					2 ml vial = 10.28 cm^3
					3 ml vial (Green Cross)* = 12.85 cm^3
					3 ml vial (Berna) = 13.14 cm^3
DTwP-HepB-Hib vaccine	Biological E	Aug 2011	Liquid (DTP-HepB) + lyophilised (Hib), 1- and 10-dose vials	1.80 (10-dose vial)	VVM 14
					Box, 24 vials of 1-dose DTwP-HepB and 24 vials of 1-dose Hib = 29.36 cm^3
					Box, 15 vials of 10-dose DTwP-HepB and 15 vials of 10-dose Hib = 7.8 cm^3
					Additional 1-dose mono carton packaging presentation with one set of 2 vials DTwP-HepB-Hib = 34.7 cm^3
DTwP-HepB-Hib vaccine	Biological E	May 2012	Fully liquid, 1- and 10-dose vials	1.19 (10-dose vial) 2.35 (1-dose vial)	VVM 7
					Box, 24 vials of 10-dose = 2.9 cm^3
					Box, 48 vials of 1-dose =14.6 cm^3
Euforva/Hib Inj DTwP-HepB-Hib vaccine	LG Life Sciences	Aug 2012	Liquid (DTP-HepB) + lyophilised (Hib), 1- and 2-dose vials	1.96 (2-dose vial)	VVM 14
					Box, 1 vial Hib +1 vial DTwP-HepB = 41.33 cm^3 (2-dose vials)
					Box, 5 vials DTwP-HepB + 5 vials Hib = 14.15 cm^3 (2-dose vials)
Tritanrix HB+Hib DTwP-HepB-Hib vaccine	GSK	May 2006	Liquid (DTP-HepB) + lyophilised (Hib), 1- and 2-dose vials	2.95 (2 dose)	VVM 14
					Packaging: N/A
Easyfive – TT DTwP-HepB-Hib vaccine	Panacea Biotec	Oct 2013	Fully liquid, 1- and 10-dose vials	2.96 (1 dose) 1.94 (10 dose)	VVM 14
					Carton, 800 vials =18.05 cm^3 (1-dose vials)
					Carton, 24x25 = 600 vials = 4.30 cm^3 (10-dose vials)
DTwP-HepB-Hib vaccine	Serum Institute of India	Sep 2010	Fully liquid, 2-dose vial	N/A	VVM 14
					Carton, 24x25 = 600 vials = 4.30 cm^3

*Green Cross is a contracted manufacturer of Berna Biotech, responsible for filling the WHO prequalified Quinavaxem in vials of 3 ml occupying a cold chain volume of 12.85 cm^3

DTwP-HepB-Hib vaccine	Serum Institute of India	May 2010	Liquid, 1- and 2-dose ampoule (DTPw-HepB) + lyophilised 1- and 2-dose vials (Hib)	2.25 (2011 price)	VVM 14 Carton, 4x50 = 200 vials Hib + 4x50 = 200 ampoules DTwP-HepB = 39.2 cm^3 (1-dose vial) Carton, 4x50 = 200 vials of Hib + 4x50 = 200 ampoules of DTwP-HepB =19.6 cm^3 (2-dose vial)
DTwP-HepB-Hib vaccine	Serum Institute of India	Sep 2010	Fully liquid, 1- and 10-dose vials	2.70 (1 dose) 1.95–2.10 (10 dose)	VVM 14 Carton, 50 vials = 26.1 cm^3 (1-dose vials) Carton, 50 vials = 2.6 cm^3 (10-dose vials)

Notes:

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

PIPELINE PRODUCTS

Gavi anticipates the entry of one to four new manufacturers within the next three years.[246] One of these is the Indonesian manufacturer Bio Farma; the prequalification process for their PentaBio vaccine is ongoing, with WHO evaluation expected to take place in late 2014.[247]

Several companies are developing hexavalent vaccines; building on the success of pentavalent products, these new vaccines will additionally include the inactivated polio vaccine (IPV). Merck and Sanofi Pasteur have a collaborative product in Phase III[134,164,248] clinical trials and Sanofi Pasteur have a product nearing the end of Phase III.[164,249] In 2013, Biological E and GSK also announced that they were jointly developing a whole-cell pertussis fully liquid hexavalent vaccine.[250]

CHALLENGES

Some countries continue to use vaccines containing acellular pertussis (aP). However, recent guidelines from WHO's Strategic Advisory Group of Experts (SAGE) underline the need for countries using whole-cell pertussis (wP) to continue doing so; wP provides a higher initial efficacy and slower waning of immunity, and has a greater impact on disease transmission compared to aP vaccines.[251]

Adapting existing vaccines to more thermostable variants, which could be used in a controlled temperature chain, could result in major cost savings. Modeling studies have shown that changing pentavalent vaccines to a thermostable variant could result in improved availability of other EPI vaccines by up to 93% and improved availability of pentavalent vaccines by up to 97%.[222]

As countries have moved to pentavalent vaccine, demand for standalone DTP has declined significantly. In 2012, demand for DTP through UNICEF represented 17% of DTP-containing vaccine orders. In 2013, there was only one supplier (Bio Farma) for DTP vaccines through UNICEF.[238]

More than 70% of Gavi and UNICEF's pentavalent vaccine supply is from Indian manufacturers who are subject to Indian national regulatory authorities. The WHO lists six critical control functions that all national regulatory authorities must exercise in a competent and independent manner in order to guarantee vaccine quality. Dependence on a single national authority is therefore considered potentially risky in the event of any adverse changes to even one of the control functions.[252]

Any decrease in the number of manufacturers producing pentavalent vaccines could adversely constrain vaccine supply. Gavi forecasts that, to meet demand, at least four critical suppliers must remain in the market for the next ten years.[246]

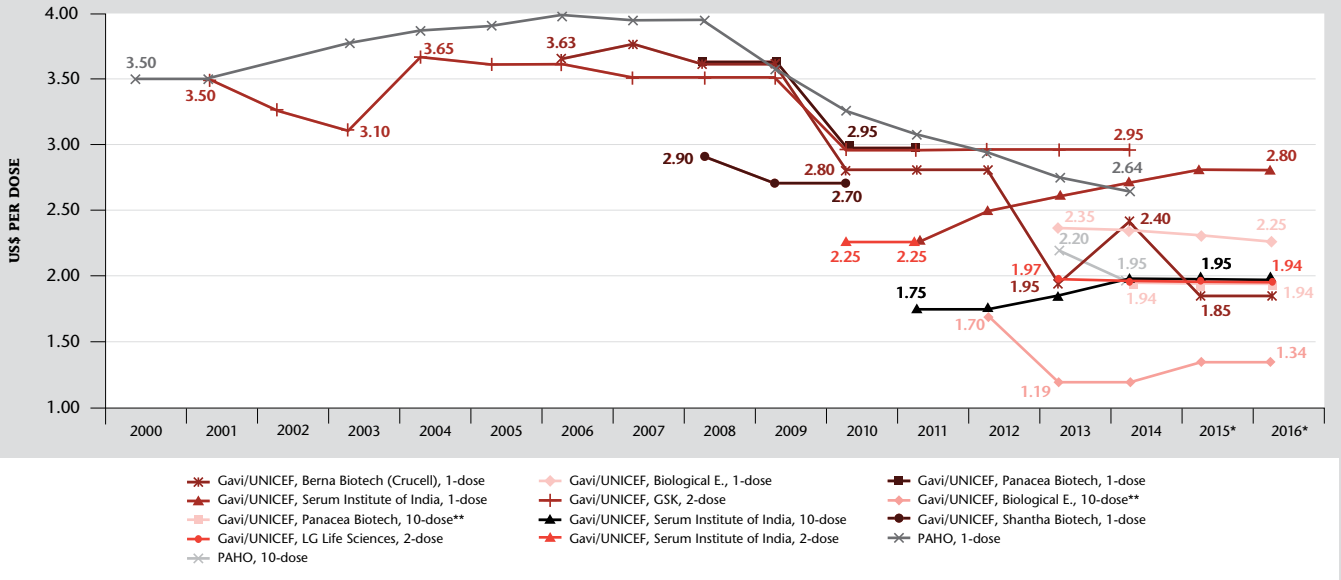
Prices and affordability

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

- The pentavalent vaccine market is the best example of a competitive market in which entry by emerging manufacturers has greatly contributed to lowering prices [see Graph 2, page 1]. The price of pentavalent vaccines started to decline in 2008 [Graph 15] with the entrance of Shantha Biotech, offering its US$2.90 single-dose vaccine to UNICEF at a 17% reduced priced compared to the previous lowest existing price of US$3.50 per dose (GSK, two-dose presentation).
- The introduction of vaccines in 10-dose vials in 2011 and 2012 and the decision of emerging manufacturers to decrease their prices[99] further lowered the price: the lowest price available decreased by 56%, from US$2.70 per dose in 2010 (Shantha Biotech, single-dose presentation) to US$1.19 per dose in 2013 (Biological E, 10-dose presentation).
- Prices of all presentations have decreased, an indication of strong competition in this market and a sustained demand over time for significant volumes. However, UNICEF prices seem to have stabilised, which means that the price for this vaccine might have reached its floor.

Graph 15: Price evolution of pentavalent vaccines for PAHO and Gavi/UNICEF



Sources: PAHO Revolving Fund, UNICEF Supply Division

* Forecasted data

** Special terms apply that are not publicly available

Notes:

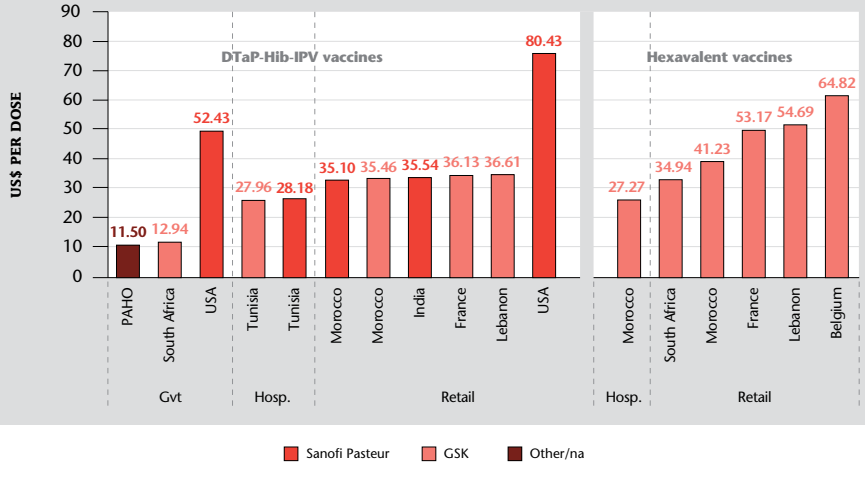
- All single-dose and 10-dose vaccines are liquid; all two-dose vaccines are lyophilised.
- Biological E also offered a 10-dose lyophilised vaccine in 2012, not represented on this graph.

PRICES IN COUNTRIES

PENTAVALENT AND OTHER COMBINATION VACCINES

- For certain countries, the pentavalent vaccine remains unaffordable. For example, Egypt only introduced pentavalent vaccine to its EPI in 2014, after entering into a ten-year agreement to procure 80 million doses of Biological E's product through the UNICEF Supply Division for US$200 million.[253,254]
- Among the countries we analysed, few had pentavalent vaccines in their drug lists, as several other presentations are available, such as the hexavalent (DTaP-HepB-Hib-IPV) vaccine or the DTaP-Hib-IPV vaccine (e.g. South Africa). The price of these presentations is usually much higher than prices for DTwP-HepB-Hib pentavalent vaccines, and there are no WHO prequalified products yet.[113] For example, in the Indian private sector, a pentavalent vaccine (Serum Institute of India) costs US$8.60 and IPV (Sanofi Pasteur) costs US$6.90 [see IPV Product Card, page 46], while a DTaP-Hib-IPV (by Sanofi Pasteur) costs US$35.54, which is more than twice the price of the two other vaccines combined. Countries introducing different combination vaccines might also scatter the demand across products, negatively impacting prices.
- Looking at current prices [Graph 16], DTaP-Hib-IPV vaccines are available at similar prices across all the countries we analysed (with the exception of the US, where the vaccine retails at more than twice the price available in any other country), which may show that manufacturers are not targeting developing countries and have not developed strategies to expand affordability and access.
- The hexavalent vaccine is considered a good combination vaccine to increase coverage of Hib and HepB in developing countries while integrating IPV in EPI. But the higher cost of hexavalent vaccines is likely to result in slow uptake in low- and middle-income countries, particularly until there is a broader manufacturer base to help lower costs. Currently, the cost of a hexavalent vaccine remains higher than IPV and pentavalent together.[164,255]
- Hexavalent vaccines are also not perfectly suited to respond to needs of developing countries. Acellular pertussis is much more expensive to manufacture than whole cell, while manufacturers will have to overcome several technical difficulties before a whole-cell pertussis hexavalent vaccine is available on the global market [see page 68].[164,255]

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



Notes:

- All prices are for 2014, except for the DTaP-Hib-IPV in India that is from 2008.

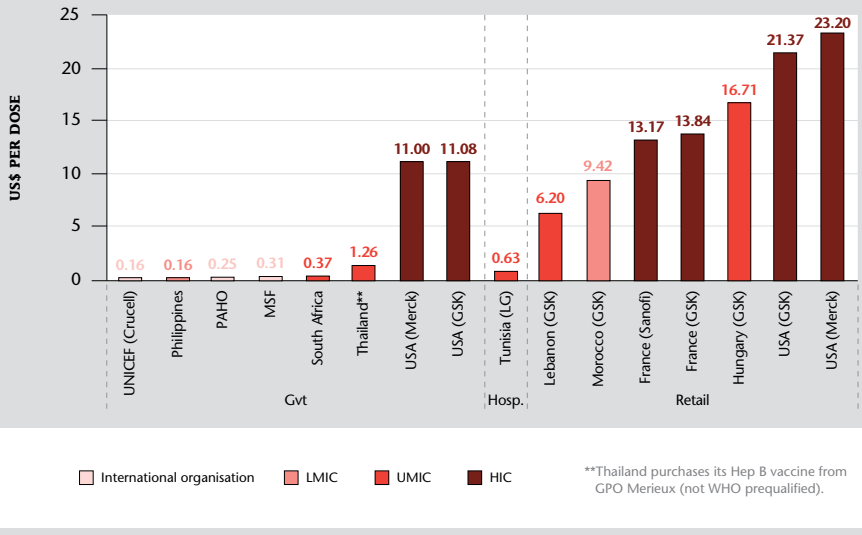
Sources: PAHO Revolving Fund, UNICEF Supply Division, country price analysis.

*Annex A, Section C

HEPATITIS B

- Early recombinant vaccines against HepB by GSK and Merck were first sold in high-income markets for US$40 a dose. Progress toward lower-cost vaccines was hindered by originator company patents. In the case of recombinant HepB vaccines, originators held dozens of process patents on development technology, delaying the efforts of lower-cost producers to create similar, lower-cost vaccines.[256]
- Now the HepB market has matured, and the entry of several emerging manufacturers has enabled a drop in price that allows international organisations and governments to access the vaccine at a rather low price (US$0.16–0.37 per dose for WHO prequalified vaccines in our analysis – see Graph 17).
- In the retail market, the vaccine is much more expensive. The lowest retail price included in our analysis ($6.20 per dose, Lebanon) is more than 15 times higher than the middle-income country government price included in our analysis (US$0.37 per dose, South Africa) for a WHO prequalified vaccine.
- Outside of government purchases, affordable prices are only available from emerging manufacturers. The HepB vaccine in hospitals in Tunisia, for instance, is a LG Life Sciences Ltd product, and is available at a price almost comparable to government prices in other countries (US$0.63 per dose).

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



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

Notes:

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

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Pneumococcal Conjugate Vaccines (PCV)

WHO recommendations & general information

- Every year, 2.58 million episodes of severe pneumonia caused by *Streptococcus pneumoniae* occur globally in children aged under five years, accounting for 18% of all episodes of severe pneumonia and 33% of all pneumonia-related deaths.[257] Most of this burden is disproportionately borne by low- and middle-income countries.[257,258]
- Children with HIV are eight times more likely to develop invasive pneumococcal disease than are their HIV-negative peers.[259]
- In 2007, WHO recommended pneumococcal conjugate vaccine (PCV) for inclusion in national immunisation programmes.[260]
- PCV is considered safe for administration in all target groups, including immunocompromised individuals. Vaccine efficacy against invasive pneumococcal disease caused by serotypes contained in PCV vaccine was found to be 71% when following the schedule in Option 2 (see table below).[124,260]
- WHO's recommendation was updated in 2012 to include and focus on the available 10-valent and 13-valent conjugate vaccines.[260]
- In 2012, 88 countries had introduced PCV into their routine immunisation schedules, including 23 countries with Gavi support. As of October 2013 that number increased to 32 Gavi-eligible countries, with a further 19 approved for introduction with Gavi support beyond 2013.[262,263]
- If the primary series is interrupted, resume without repeating the previous dose.[261]

Recommended schedules[124]	Age at 1st dose	Doses in primary series (interval between doses)	Booster
Option 1	6 weeks (minimum)	3 doses with DTP (4 weeks between doses 1, 2 and 3)	No booster with 3-dose schedule except for HIV+ and preterm neonates in their 2nd year if 3 primary doses were completed within the 1st year
Option 2	6 weeks (minimum)	2 doses before 6 months (8 weeks)	Booster dose at 9–15 months
Delayed start	If <1 year: 2- or 3-dose schedule	8-week interval between doses for both groups	Booster at 9–15 months if following 2-dose schedule. Second booster if HIV+ or preterm neonate
	If aged 1–2 years or 2–5 years + high risk: 2 doses		

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
Prevnar 7 PCV7* vaccine	Wyeth-Pfizer	Dec 2009	Liquid, single-dose vial*	N/A	VVM 30 Box, 5 vials = 21 cm^3
Prevnar 13 PCV13 vaccine	Wyeth-Pfizer	Aug 2010	Liquid, single-dose vial**	3.30[264]	VVM 30 Box, 50 vials = 12 cm^3 Box, 25 vials = 15.7 cm^3
Synflorix PCV10 vaccine	GSK	Single-dose vial: Oct 2009 2-dose vial: Mar 2010	Liquid, available in 1- or 2-dose preservative-free vial†	3.40–3.50[264]	VVM 30 Carton, single 1-dose vial = 58 cm^3 Carton, single 2-dose vial = 4.8 cm^3

PIPELINE PRODUCTS

- No new PCV vaccines are expected to achieve WHO prequalification or meet the Gavi Advance Market Commitment Target Product Profile (TPP) before 2018.[263]
- PATH has two products in the pipeline. One is a protein plus conjugate vaccine developed in partnership with GSK, the Medical Research Council Unit in The Gambia and the London School of Hygiene & Tropical Medicine, about to enter Phase III trials after evaluation of data from Phase II. The second is a PCV10 vaccine focused on serotypes prevalent in developing countries, under development by Serum Institute of India.[213,266,267]
- Merck has a pneumoconjugate vaccine candidate provisionally named V114 in Phase II.[134,268]
- Sanofi Pasteur is reportedly collaborating with Korean company SK Chemicals to develop, produce and market a pneumococcal conjugate vaccine soon.[269]

CHALLENGES

- Supply of the WHO prequalified products has been constrained in developing countries, particularly as scale-up of introductions in Gavi-eligible countries continues.[263,270]
- For the two-dose presentation of GSK's preservative-free PCV10 vaccine, specific pre-introduction measures are required, including training. Post-introduction evaluations are also required.[258,265]

*Being replaced by PCV13 or PCV10.
**Also available in prefilled syringe but not WHO prequalified.
†Two-dose presentation requires specific training and management.[265]

Prices and affordability

The PCV vaccine market is a duopoly of manufacturers Pfizer and GSK. Together with the HPV and rotavirus vaccines, PCV vaccines are some of the newest and most expensive vaccines, and present affordability challenges that prevent access.

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

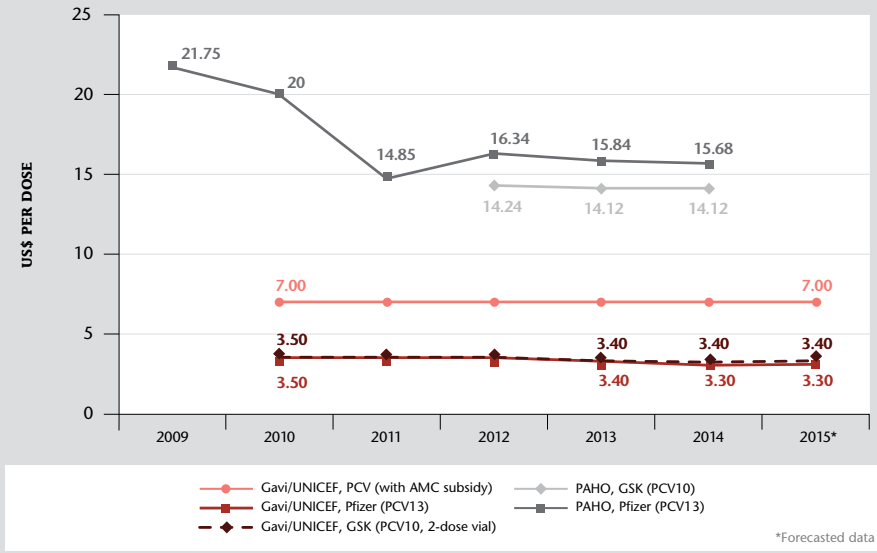
- PCV vaccine is significantly more expensive than the traditional vaccines. According to volumes and prices published on the UNICEF Supply Division (SD) website,[86] purchases of PCV accounted in value for 39.2% of all UNICEF SD vaccine purchases but only for 3% in terms of volume.
- Prices of PCV for PAHO have declined, but remain high, at US$14.12 and US$15.68 for PCV10 and PCV13, respectively [Graph 18, overleaf], at more than four times the Gavi tail price [see box below] offered to UNICEF.

THE PNEUMOCOCCAL ADVANCE MARKET COMMITMENT (AMC) FOR GAVI

The pneumococcal Advance Market Commitment (AMC) is a mechanism to incentivise companies to scale-up manufacturing capacity to meet the needs of Gavi-eligible countries. The AMC sets a maximum price of US$3.50 ('tail price') per dose for Gavi and Gavi-eligible countries through the UNICEF supply channel only. Manufacturers commit to not exceed this price for ten years, and in exchange they receive a part of the committed AMC subsidy (US$1.5 billion) in proportion to their contribution to the target demand (target demand at 200 million doses per year). Critiques of the AMC have been discussed earlier in this report.

- All Gavi-graduated and graduating countries that have not yet introduced a PCV vaccine are eligible to apply to introduce the vaccine under the AMC, which means that these countries can purchase the vaccine at the tail price, but have to finance it themselves. Some other conditions apply.[271]
- As of July 2013, 73% of the Gavi AMC subsidy had been awarded to Pfizer and GSK (corresponding to US$1,095 million).
- As of 2016, the annual supply of PCV to Gavi/UNICEF is projected to be 146 million doses, representing 73% of the 200 million doses per year targeted by the AMC.[263]
- In 2013, Pfizer reduced its tail price to US$3.40 per dose, with a subsequent decrease to US$3.30 per dose starting in 2014. Special conditions of the Pfizer price decrease include that the AMC donor funding for Pfizer contracts will be fully disbursed by 2015 at the latest, and that Gavi provides a financial guarantee for the tail price component of a total of 80% of the doses contracted in 2013–2015.[272] GSK also reduced its tail price to US$3.40 per dose for the 2014–2024 contract.

Graph 18: Price evolution of Pneumococcal Conjugate Vaccines (PCV) for PAHO and Gavi/UNICEF



Notes and methodology:

- All presentations are single-dose except PCV10 for UNICEF, which is a two-dose vial.
- See UNICEF SD web page[11] on PCV for full information on tenders and agreements for these prices.
- For UNICEF, where agreements include a range of prices during a calendar year period or for different countries or groups of countries, the lowest price in the range was kept.

Sources: PAHO Revolving Fund, UNICEF Supply Division.

PRICES IN COUNTRIES

The high price of PCV has hindered access in middle-income countries. While many Gavi-eligible countries have already introduced the vaccine, many middle-income countries have not [see Graph 3, page 14]. Cost effectiveness and especially the price of the vaccine have been cited by several countries as major barriers to introduction.[41] A study by Nakamura et al. in 2011 estimated that the vaccine could be cost effective in most low- to middle-income countries at US$10 per dose or lower.[273] But in 2014 Brazil was the only country outside of Gavi-eligible countries to have access to the vaccine at this price.

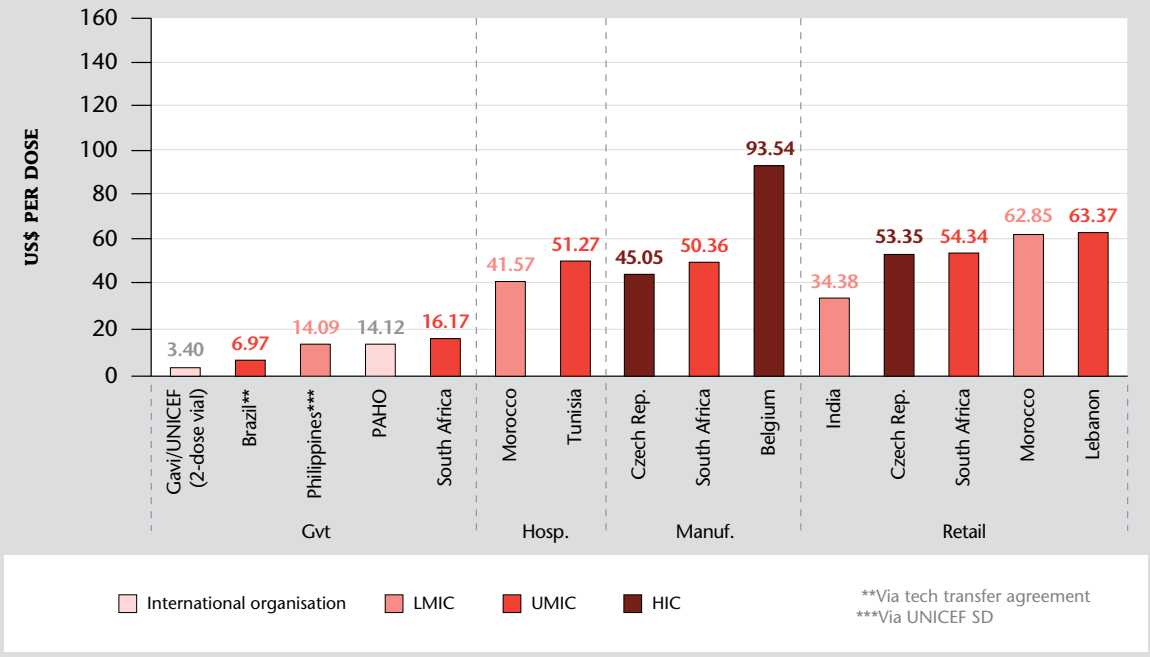
Brazil is an example of a country using technology transfer agreements to produce PCV domestically. The country entered a partnership with GSK in 2009 to vaccinate 13 million children (39 million doses) per year for at least eight years, until the country is ready to manufacture PCV on its own.[274] The price per dose* was EUR11.50/US$16.03 in the first years, then decreasing to EUR5.00/US$6.97.[170,275] However, the terms of the technology transfer arrangements are not publicly available and could limit the opportunity for Brazil to benefit from real competition when emerging manufacturers enter the market with cheaper products. The strategy could therefore not be advantageous for Brazil in the long term, for instance when Serum Institute of India enters the market with a PCV candidate in 2016/2017 at the expected lower price of US$2 per dose.[84]

As Pfizer's PCV vaccine, Prevnar 13 (PCV13), has an advantage over GSK's Synflorix (PCV10) because of its additional serotypes (PCV10 vs PCV13), GSK remains competitive by setting the price below that of Pfizer. The price difference is grounds for many middle-income countries to opt for the introduction of Synflorix over that of Prevnar 13.

Companies claim that they use differential pricing strategies like tiered pricing to maximise access, in effect maximising their revenues in middle-and low-income countries. In practice, prices in middle-income countries are extremely high and sometimes comparable to prices in high-income countries. Graphs 19 and 20, opposite, show that despite claims of differential pricing, the price of Pfizer's PCV13 remains high in many countries, and Graph 5 on page 26 of this report shows that the price countries pay for PCV13 is not entirely dependent on their wealth – despite relative wealth often being used by companies as a proxy to set prices for different markets.

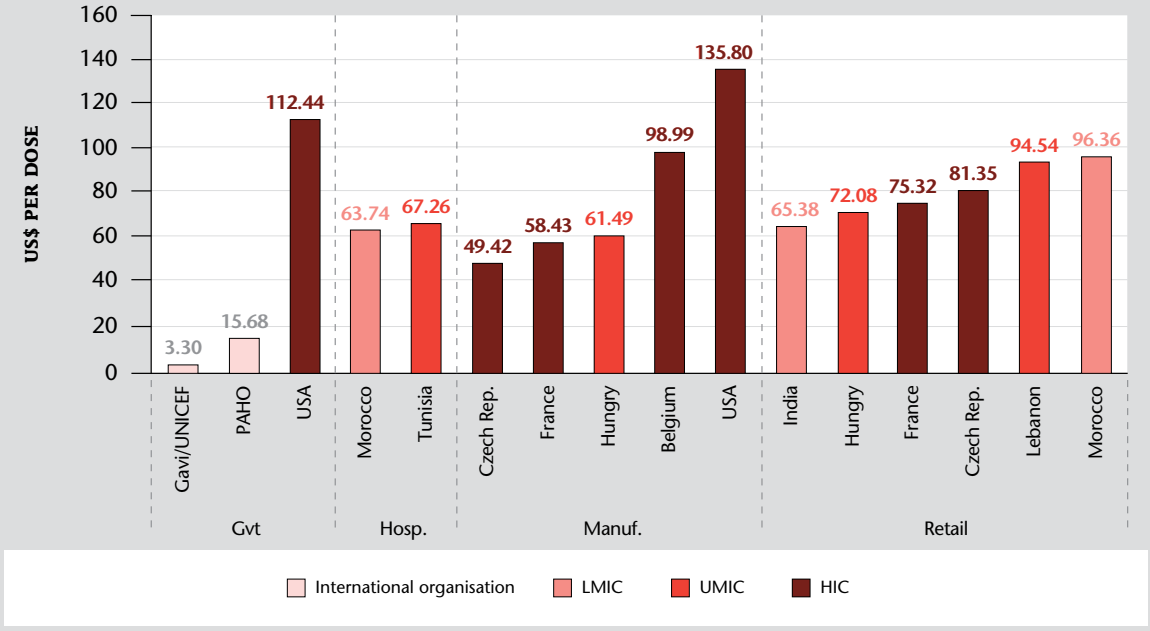
* Using OANDA average 2009 exchange rate euros to US dollars at 1.3937.

Graph 19: Prices for GSK's Pneumococcal Conjugate Vaccine (PCV10) in several countries, by income group and price type, 2013/2014*



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

Graph 20: Prices for Pfizer's Pneumococcal Conjugate Vaccine (PCV13) in several countries, by income group and price type, 2013/2014*



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

Andrea Bruce/Noor Images

Oral Cholera Vaccines (OCV)

WHO recommendations & general information

- Cholera is an acute diarrhoeal disease, caused primarily by the O1 and O139 toxigenic serogroups of the *Vibrio cholerae* bacterium. The spread of cholera is exacerbated by poor sanitation and a lack of clean drinking water; the disease most seriously affects young children living in disease-endemic settings.[276] WHO conservatively estimates there to be 2.8 million (uncertainty range: 1.2–4.3 million) cases of cholera globally per year resulting in 91,000 deaths (uncertainty range: 28,000–142,000). Morbidity and mortality estimates are probably under-reported because of a lack of consistent global surveillance.[277]
- Dukoral vaccine (Crucell) provides effective protection (100%) against cholera for children aged two to five years for up to six months after vaccination, but this efficacy drops to 47% at the end of two years. For children aged over five years, Dukoral has a protective efficacy at one and two years post-vaccination of 78% and 63%, respectively. After two doses, Shanchol vaccine (Shantha Biotechnics) offers a protective efficacy of 66% across all ages, and 50% overall, three to five years after vaccination.[276]
- WHO emphasises that cholera control should be a priority in disease-endemic regions and specific geographic areas susceptible to outbreaks. WHO recommends immunisation with existing vaccines, in conjunction with other preventive and control strategies, through periodic mass vaccination campaigns or the incorporation of cholera vaccination into routine immunisation efforts. High-risk populations, preschool and school-age children, HIV-infected individuals, pregnant mothers and the elderly are to be prioritised.[44,276] Pre-emptive or reactive vaccination, or both, can be considered depending on local infrastructure and an evaluation of the current and historical epidemiological situation for epidemic settings, but not to the exclusion of appropriate oral rehydration therapy and measures to improve water quality and sanitation.[276,278]
- There has been increasing evidence of the effectiveness of providing oral cholera vaccines in epidemic settings [see box, page 81],[279,280] and the creation of a global oral cholera vaccine stockpile in 2012 [see box, page 81][281] will in the future allow for a robust and early response to potential epidemic outbreaks.

Vaccine	Age at 1st dose	Doses in primary series (interval between doses)	Booster
Dukoral	2 years*	At 2–5 years of age: 3 doses (minimum 7 days and maximum 6 weeks between 1st and 2nd dose and 2nd and 3rd doses**) At ≥ 6 years: 2 doses (14 days between 1st and 2nd doses)	At 2–5 years of age: every 6 months At ≥ 6 years of age: every 2 years
Shanchol (and mORC-Vax)	1 year	2 doses (14 days between 1st and 2nd doses)	After 2 years

*Dukoral is not licensed for children aged under two years.
**Restart primary series if interval between first and second dose or second and third dose is more than six weeks or if interval between primary series and booster is more than six months.

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
Dukoral Inactivated, monovalent-O1, whole-cell oral cholera vaccine with toxin B cholera subunit	Crucell	Oct 2001	Liquid, 1-dose vial + buffer sachet	4.75[278,8,282]	No VVM 1-dose carton = 271 cm^3 2-dose carton = 136 cm^3 20-dose carton = 44 cm^3 170-dose carton = 24.4 cm^3
Shanchol Inactivated bivalent-O1/O139 oral cholera vaccine	Shantha Biotechnics	Sep 2011	Liquid, 1-dose vial	1.85[283]	VVM 14 Carton, 35 vials = 16.8 cm^3

PIPELINE PRODUCTS

- Paxvax has a single-dose, oral, live, attenuated cholera vaccine (PVXV0200) in Phase III of clinical trials that is expected to be approved shortly by the US FDA. The vaccine is anticipated to be used in epidemic outbreak settings and for individuals travelling to cholera-endemic regions.[284]
- Vietnam-based VABiotech produces a reformulated, buffer-free, killed whole-cell cholera vaccine, designed to be administered in a two-dose regimen. This product has been redeveloped into a bivalent (O1/O139), whole-cell vaccine (mORCVAX) and has been licensed for use in Vietnam since 2009. WHO prequalification is expected to take place by 2015.[285]
- Korean manufacturer Eubiologics has an oral cholera vaccine undergoing licensing in Korea; the vaccine is expected to be WHO prequalified in 2015.[286]
- Cuba's Finlay Instituto is developing a live and an inactivated oral cholera vaccine said to be in the "advanced stage" (probably Phase III) of clinical trials.[287,288]

CHALLENGES

- Manufacturing capacity is limited, but manufacturers have announced that they could scale up production if there is a committed demand. Shanchol's manufacturer, for example, has indicated the immediate availability of up to 600,000 doses and the capacity to scale up production to two to four million doses in 2013 and to ten to twenty million doses in 2014 if merited by the demand,[289] but managing irregular demand is thought to pose a challenge.[290]
- Questions remain regarding prioritisation and usage of the cholera vaccine stockpile when faced with multiple simultaneous epidemics or emergency situations combined with seasonal peaks in incidence in endemic countries.[290,291]
- There are as yet no guidelines for the use of cholera vaccine among children aged under one year.[291]
- Shanchol is stable for at least 5 days at up to 40°C, according to research by both Sanofi Pasteur[292] (Shantha Biotechnic's parent company) and independent scientists.[293] Relabelling Shancol for use under controlled temperature chain (CTC) settings has progressed with Indian drug regulatory authorities and could be a precursor for future WHO prequalification for use in CTC.

THE GROWING EVIDENCE THAT ORAL CHOLERA VACCINE SHOULD BE USED TO CONTROL CHOLERA OUTBREAKS

In Haiti, after the onset of the cholera epidemic in October 2010, a decision was made not to use oral cholera vaccine (OCV), in part because not enough doses of the vaccine were available. In early 2011, it was decided to consider cholera vaccination if sufficient volumes could be made. At the same time, both manufacturers announced that they could scale up production capacity, provided that firm orders and commitments were made.[294] In 2012, the PAHO Technical Advisory Group recommended introduction of OCV in Haiti's routine immunisation schedule while conducting Supplemental Immunisation Activities (SIA) in camps and rural areas.[289] In 2012, Partners in Health sponsored one pilot project and provided 45,000 doses of OCV in the Artibonite region of the country and reached very high coverage, showing that the vaccine could be used in the midst of an epidemic.[295]

In 2012, the Ministry of Health in Guinea and MSF organised Guinea's first mass vaccination campaign, with two doses of OCV (Shanchol) as an additional tool to control the epidemic in the country. Researchers found that the two doses of OCV provided 86% protective effectiveness against cholera.[279,280]

A study of the outbreak response campaign shows that cholera immunisation was well accepted and reached high coverage, validating the benefits of cholera immunisation as "an additional tool in the outbreak response strategies".[279]

THE ORAL CHOLERA VACCINE STOCKPILE

The use of oral cholera vaccine (OCV) in low-income countries was first mentioned in a World Heath Assembly resolution in 2011.[281] Following several rounds of technical consultations, a global OCV stockpile was created in 2013, with the aim that it would serve as an additional tool to control cholera epidemics and outbreaks, especially in low-income countries. The stockpile is managed by the International Coordinating Group (ICG), composed of four decision-making partners (IFRC, MSF, UNICEF and WHO),[296] and has received financial commitments from the Bill & Melinda Gates Foundation, the European Union and other donors.[281] The OCV stockpile was planned to initially comprise two million doses per year, stored and maintained by participating manufacturers.[281] Between July 2013 and June 2014, the stockpile made its first two million doses available.[296]

In November 2013, the Gavi Board decided to support the stockpile by gradually increasing its capacity to 20 million doses per year for the period 2014–2018, for use in epidemic and endemic settings. The total contribution from Gavi is estimated at US$115 million over the five-year period.[290,297] The stockpile was used for the first time in February 2014 in South Sudan, where MSF and MedAir delivered 132,925 doses of the vaccine for use in internally displaced populations.[298]

Prices and affordability

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

- Several cost-effectiveness studies have been conducted on the use of OCV in endemic situations and in refugee settings, but there is a lack of information relative to the synergistic impact of immunisation when coupled with traditional cholera interventions (e.g. sanitation and education).[276] The most recent cost-effectiveness study showed that immunisation was cost effective at US$1 per dose of the vaccine (with an additional cost of delivering the vaccine of US$0.50 in low-income countries and US$1 in middle-income countries), under specific conditions and taking into account the benefits of vaccination herd immunity.[299] This study shows that cost effectiveness is reachable, but with a low-priced vaccine.
- Dukoral was the only WHO prequalified OCV available prior to 2011 and it was quite expensive not only because of the manufacturer's monopoly, but also because of low and unpredictable demand. A background paper prepared by UNICEF for the 2009 WHO SAGE showed that the cost of immunisation mainly comprised the high cost of the vaccine. For instance, in a refugee setting in Sudan in 2004 the cost of protection against cholera was US$7.10 per fully immunised person, 90% of which was the vaccine price (US$6.40 for two doses).[300]
- The momentum for increased use of OCV has followed the entrance in 2011 of a new product – Shanchol by Shanta Biotech – offered at a much lower price than the pre-existing Dukoral vaccine. Shanchol costs about US$1.85 per dose, which is about one-third the price per dose of Dukoral (US$4.75).[278–283] If demand for Shanchol increases, the price could potentially decrease further.
- As shown in the table on page 80, Shanchol's form and presentation offer operational and programmatic advantages compared to Dukoral; in particular, it does not need to be reconstituted with a glass of water and presents a lower cold chain volume.

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Rotavirus Vaccines (RV)

WHO recommendations & general information

- Diarrhoea accounts for 11% of all deaths in children aged under five years.[301] It is transmitted directly via the faecal-oral route or indirectly through infected fomites.[302] Rotavirus is one of the most common aetiological organisms and is responsible for 40% of diarrhoea-related hospitalisations, according to sentinel site observations.[302] Nearly every child will be infected by rotavirus before the age of three to five years. The WHO estimates that 453,000 rotavirus gastroenteritis (RVGE)-associated deaths occur annually in children aged under five years.[302]
- As a result of genetic reassortment within the genome, rotavirus has at least 12 different G-type viral particle antigens and 15 P-type viral particle antigens.[302] The most common strain is G1P[8], but there is more diversity in the distribution of strains in Africa and Asia. There is mounting evidence for significant cross-protection among predominant strains of rotavirus for both the monovalent and pentavalent vaccines.[303,304]
- Rotavirus vaccination can reduce severe rotavirus infections by 74%[305], although lower vaccine efficacy against severe rotavirus diarrhoea has been seen in some low-income countries in Africa (Malawi 49.4%).[306]
- The WHO recommends rotavirus vaccination in all national immunisation programmes.[302] As of July 2014, rotavirus vaccination had been implemented in public health programmes in 67 countries, including 39 Gavi-supported countries.[307,308]
- The WHO estimates the incidence of rotavirus vaccine-induced intussusception to be one to two cases per 100,000 infants vaccinated;[302,309] however, recent studies indicate that the relative risk of intussusception for the GSK monovalent vaccine exceeds 8.1 while the Merck pentavalent vaccine has a non-significant relative risk of 1.1.[310] In a modelling exercise on non-restricted vaccination age (up to three years), an additional 47,200 lives in low- and middle-income countries could be saved compared to the restricted schedule. However, an additional 294 children would die of intussusception caused by older age at administration.[311] Continuous monitoring and evaluation of the risk of intussusception is required, including in countries newly introducing the vaccine.

Vaccine[124]	Age at 1st dose	Doses in primary series (interval between doses)	Booster
Rotavirus 1	6 weeks	2 doses, administered concurrently with DTP1 and DTP2 (4 weeks between doses)	Not recommended
Rotavirus 5	6 weeks	3 doses, administered concurrently with DTP1, DTP2 and DTP3 (4 weeks between doses)	Not recommended
RV1 or RV5: delayed start	Not applicable if aged >24 months	2 doses for RV1 or 3 doses for RV5 (4 weeks between doses)	Not recommended

Products & manufacturers

Product	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$)	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
Rotarix Monovalent rotavirus vaccine	GSK	Mar 2009	Monovalent: liquid, single-dose vial, tube or applicator	2.50	VVM 14
					Box, 1 dose (applicator) = 143 cm^3
					Box, 10 doses (applicator) = 85.3 cm^3
					Box, 1 dose (plastic tube) = 115.3 cm^3
					Box, 10 doses (plastic tube) = 43.3 cm^3
					Box, 50 doses (plastic tube) = 17.1 cm^3
					Box, 1 dose (vial) = 256 cm^3
					Box, 10 doses (vial) = 156 cm^3
RotaTeq Pentavalent rotavirus vaccine	Merck	Oct 2008	Pentavalent: liquid, single-dose tube	3.50	No VVM technology has been validated for use with RotaTeq
					Box, 10 doses = 75.3 cm^3
					Box, 25 doses = 46.3 cm^3

PIPELINE PRODUCTS

- Lanzhuo Institute Biological Products (China) has two oral lamb rotavirus vaccines: (LLR)[312] which was approved in China 2000[313] and Ovine LD9 + human G2, G3, G4 in Phase III.[314]
- The Center for Research & Production of Vaccines & Biologicals (Polyvac, Vietnam) obtained licensing for oral, single-dose rotavirus vaccine (three-dose regimen) in April 2012.[315]
- Bharat Biotech received commercial licensing in January 2014[316] for Rotavac (116E), an oral, single-dose and multidose presentation with a 3-dose regimen.[316] Cold chain storage includes 36 months at –20°C to –25°C and six months at 2–8°C.[316]
- Phase I studies supported progression to the currently underway Phase II safety and immunogenicity studies of the RV3-BB rotavirus vaccine programme (conducted by the Murdoch Children's Research Institute) for neonatal rotavirus vaccine.[317,318]
- International Medical Foundation has redeveloped Rotashield to be administered as a two-dose regimen, with one dose soon after birth and the second by two months of age. Phase IIb trials were completed in Ghana.[319–321]

Prices and affordability

The rotavirus vaccine market is a duopoly between Merck and GSK. Together with the PCV and HPV vaccines, rotavirus vaccines are some of the newest and most expensive vaccines, presenting affordability challenges that prevent access.

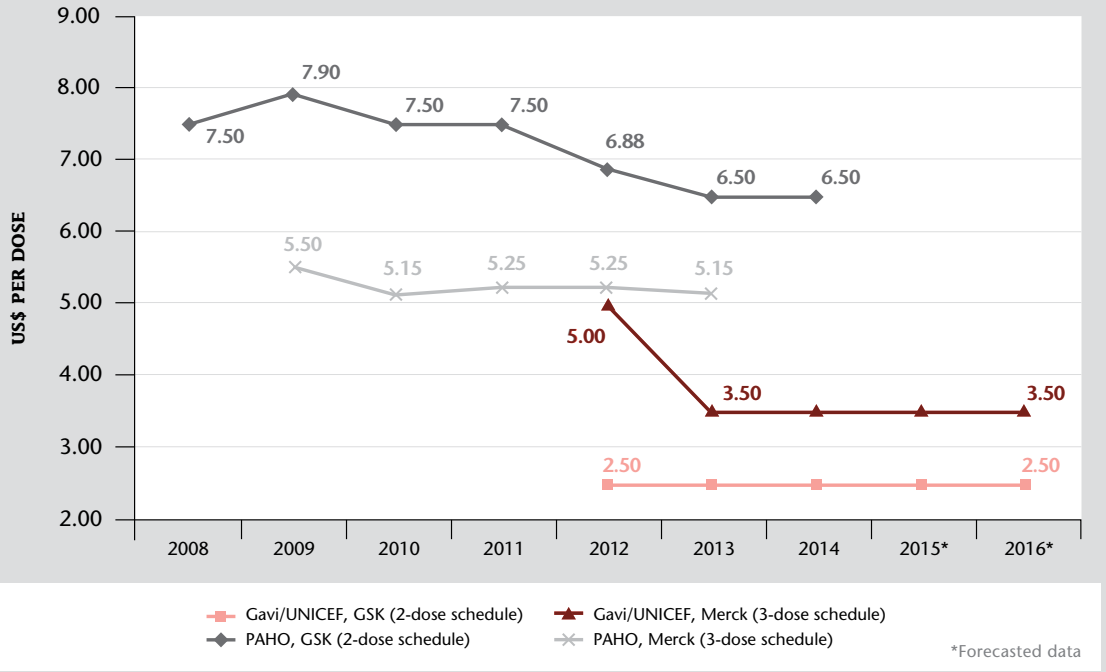
Rotarix by GSK has the advantage of following a two-dose schedule while three doses are necessary to complete the schedule for RotaTeq by Merck. Therefore, even when the price per dose of Rotarix is higher than of RotaTeq, the price per immunisation course for Rotarix may still be lower.

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

- The Gavi/UNICEF agreement with manufacturers for rotavirus vaccines is recent (2012) and prices have not changed much since.
- For PAHO, prices for rotavirus vaccines have remained high, decreasing only by 6% and 13% for the Merck and GSK products, respectively, between 2008 and 2014.

Graph 21: Price evolution of rotavirus vaccines (RV) for PAHO and Gavi/UNICEF



Sources: PAHO Revolving Fund, UNICEF Supply Division.

Notes and methodology:

- For UNICEF, the price offered by GSK is only available to the 73 countries eligible for Gavi support in 2009, provided the procurement is done through UNICEF. The price for Merck's vaccine "consists of 1) a number of doses to be procured at US$5 for a single country in 2013–2015, with doses free of charge to be made available in 2015–2016 based on achieving the required number of doses to be procured, and 2) contracted quantities for other countries at US$3.50".[11]
- When prices were expressed in euros (rotavirus vaccine from GSK), prices were converted into US dollars using the 2013 average annual exchange rate as provided by OANDA (euros to US dollars: 1.3279).[170]

PRICES IN COUNTRIES

- Prices for rotavirus vaccines remain high, limiting their introduction in middle-income countries. For instance in Lebanon, the retail price* of Rotarix (GSK) is 30 times the price for UNICEF and more than 2.7 times the retail price for South Africa [Graph 22]. The retail price of RotaTeq (Merck) in Lebanon is also on par with the price of the vaccine in Belgium [Graph 23], despite the five-fold difference in GNI/capita between these two countries. Variation of GNI/capita is normally the basis on which companies say they set tiered prices.

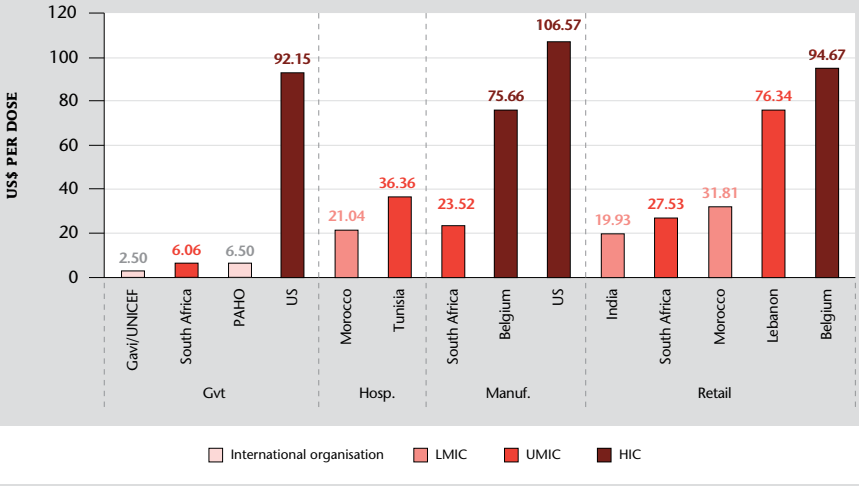
  ** Because the vaccine was not in the national schedule in Lebanon as of 2014,[31] the retail price corresponds to the price at which individuals can purchase the vaccine in the country.*

- Rotavirus vaccination is considered by several studies to be a very cost-effective intervention in developing countries, but most of the studies use vaccine prices much lower than the actual cost per dose paid by middle-income countries.[322,323] Even if price is not the only element for a country to consider when deciding to introduce the vaccine, 'vaccine price has a significant influence on the cost-effectiveness of vaccination',[324] and only a decrease in current prices could lower barriers to the introduction of rotavirus vaccination in several middle-income countries.

- Even in high-income countries, the high price of rotavirus vaccine has been cited as a barrier to its introduction (together with safety concerns). As a result, most Western European countries, including the UK, France and Germany,[325–326] have delayed introduction of the vaccine. For instance, the UK announced the introduction of the vaccine in its immunisation program in late 2012,[326] and France only in early 2014.[327,328]

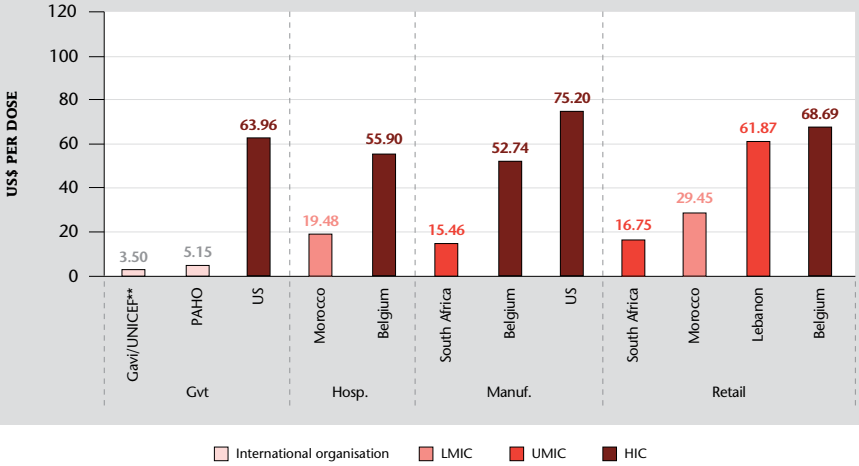
- Competition from emerging-country suppliers is expected to increase between 2015 and 2020 and should make rotavirus vaccine available at a lower price. Bharat Biotech announced it will sell its Rotavac vaccine for US$1 per dose for use in a three-dose schedule,[85] making the full schedule 40% cheaper than the lowest price currently available to UNICEF per schedule (US$3 vs US$5). In countries like India, the price per schedule could even be reduced 12- to 17-fold.

Graph 22: Prices for GSK's rotavirus vaccine in several countries, by income group and price type, 2013/2014*



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

Graph 23: Prices for Merck's rotavirus vaccine in several countries, by income group and price type, 2013/2014*



**The price for Rotavirus vaccine, pentavalent, consists of a.) a number of doses to be procured at US$5 for a single country in 2013–2015, with doses free of charge to be made available in 2015–2016 based on achieving the required number of doses to be procured, and b.) contracted quantities for other countries at US$3.50.

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

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Tetanus Toxoid Vaccines (TT)

WHO recommendations & general information

- Tetanus is a bacterial disease caused by the *Clostridium tetani* bacterium. Infection can result in case-fatality rates as high as 100%. Disease in humans results from production of the potent neurotoxin tetanospasmin, which manifests in symptoms such as muscle stiffness and spasms.[329] Most tetanus cases occur in developing countries among newborns or in mothers after unhygienic births or poor postnatal hygiene. The WHO estimates that in 2010, 58,000 newborns died as a result of neonatal tetanus, and in 2011, 72,600 children under the age of five died from tetanus.[225,329–331]
- Since 1999, the WHO has declared the goal of eliminating maternal and neonatal tetanus globally and achieving and sustaining high coverage of three doses of DTP to prevent tetanus in all age groups [see box, The Maternal and Neonatal Tetanus Elimination Initiative, page 91].
- In countries where the elimination target has not been reached, the WHO recommends using the 'high-risk approach', whereby all women of childbearing age are targeted through use of concerted campaigns and supplementary immunisation activities.[329]
- Vaccines against tetanus are available as: single tetanus toxoid (TT); combined with diphtheria and pertussis vaccines (DTwP, DTaP); alone with diphtheria (DT, dT; 'D' and 'd' vaccines contain, respectively, a higher and lower dose of diphtheria toxin); as a component of the pentavalent vaccine (DTwP-HepB-Hib).[329]
- In countries with a high prevalence of maternal and neonatal tetanus (MNT), all pregnant women are to be immunised with at least one dose of a TT-containing vaccine (usually dT); this is under the assumption that they have completed the childhood vaccination series. Pregnant women with unknown immunisation history are to receive two doses, the first as early as possible, and the second a minimum of four weeks later.[329,332]
- It is recommended that districts with limited access to routine vaccination services and areas where the elimination target (fewer than one case per 1,000 live births) has not been achieved adopt the 'high-risk approach'. Implementing this approach covers all women of child-bearing age with three doses of TT over a 12-month period, with an attempt to complete five doses overall if possible.[329,332]

Vaccine	Age at 1st dose	Doses in primary series (interval between doses)	Booster
DTP, primary course	<1 year (doses to be given at 6, 10, 14 weeks)	3 doses (4 weeks minimum between 1st and 2nd dose and between 2nd and 3rd dose)	1st DTP booster at 1–6 years of age If aged 4–7 years, 1st booster administered as DT 2nd at 12–15 years (TT) 3rd booster (6th dose of tetanus vaccine overall) for women at time of first pregnancy (TT)

Products & manufacturers

Product [113]	Manufacturer	WHO PQ date	Form and presentation	Lowest known price (UNICEF, US$) [333]	Vaccine vial monitor (VVM) type and cold chain volume (per dose)
Teatox TT Tetanus toxoid vaccine	BB-NCIPD	May 2006	Liquid, 10- and 20-dose vials*	N/A	VVM 14
					10-vial carton, 10-dose vials = 4.12 cm^3
					10 vial carton, 20-dose vials = 2.05 cm^3
TT vaccine Tetanus toxoid	Bio Farma	Mar 1999	Liquid, 10- and 20-dose vials*	10-dose: 0.095 (2013)	VVM 30
					10-vial box, 10-dose vials = 2.10 cm^3
					10- vial box, 20-dose vials = 0.75 cm^3
Tetanus toxoid vaccine (1 dose Uniject)	Bio Farma	Oct 2003	Liquid, 1-dose Uniject	N/A	VVM 30
					Secondary packaging of 100 = 12 cm^3
Tetanus toxoid vaccine (adsorbed)	Biological E	Dec 2009 (20-dose vial) Jul 2012 (1- and 10-dose vials)	Liquid, 1-, 10-* and 20-*dose vials	10-dose: 0.070 20-dose: 0.050	VVM 30
					48-vial box, 1-dose vials = 14.70 cm^3
					30-vial box, 10-dose vials = 3.90 cm^3
					20-vial carton, 20-dose vials = 2.90 cm^3
Tetavax Tetanus toxoid vaccine	Sanofi Pasteur	Jul 1997	Liquid; 10- and 20-dose vials*	N/A	No VVM
					10 vials of 10 doses = 2.46 cm^3
Tetanus toxoid vaccine (adsorbed)	Serum Institute of India	Apr 1995	Liquid, 1-dose ampoule Liquid, 10- and 20- dose vials*	10-dose: 0.077 20-dose: 0.053	VVM 30
					50-ampoule carton, 1-dose ampoules = 15.71 cm^3
					50-vial carton, 10-dose vials = 2.61 cm^3
					25-vial carton, 20-dose vials = 2.43 cm^3
Shan TT Tetanus toxoid vaccine	Shantha Biotechnics	Aug 2007	Liquid, 10- and 20-dose vials*	10-dose: 0.080	VVM 14
					30-vial carton, 10-dose vials = 4.36 cm^3
					30-vial carton, 20-dose vials = 2.57 cm^3

PIPELINE PRODUCTS

- The Chinese manufacturer Walvax has a TT vaccine in Phase III clinical trials.[334]

CHALLENGES

- Lack of adequate health infrastructure in countries with high MNT prevalence continues to be a challenge to improving routine immunisation and supplementary immunisation activities that address MNT.[332,335,336]
- Major funding gaps continue to exist for continuation of key immunisation activities targeting MNT, including strengthening of existing immunisation programmes, routine immunisation structures and supplementary immunisation activities.[332,337]

*Opened multidose vials can be kept for use in subsequent immunisation sessions for up to a maximum of 28 days, provided certain conditions are met (WHO policy on use of opened multidose vials).[172]

THE MATERNAL AND NEONATAL TETANUS ELIMINATION INITIATIVE

The first call to eliminate neonatal tetanus was made at the World Health Assembly in 1989; ten years later this was bolstered by the call to eliminate maternal tetanus (elimination is considered achieved when there is fewer than one case per 1,000 live births in every district of a country). However, both calls missed their initial target of eliminating neonatal tetanus by 1995 and maternal tetanus by 2005, and progress towards elimination has been slow. The Maternal and Neonatal Tetanus Elimination (MNTE) initiative was re-launched in 1999, and the current goal is to achieve global elimination by 2015.[329,332] Cumulatively, 54 countries initiated or expanded TT Supplementary Immunisation Activities (TT-SIAs) between 1999 and 2012.[330]

Strategies to achieve MNTE focus on promoting clean delivery practices, routine immunisation of pregnant women, TT-SIAs in high risk areas, and surveillance.[331] It is estimated that the cost of immunising women with three doses of TT through TT-SIAs is around US$1.80[335] per woman. As of December 2013, 34 countries (out of the 59 identified countries that had not eliminated MNT in 1999) had achieved MNT elimination, leaving 25 countries where the disease is yet to be eliminated.[331,330] The MNTE initiative is supported by the public and private sectors, with stakeholders including governments, civil societies, the Bill & Melinda Gates Foundation, Gavi, PATH, UNICEF, USAID, WHO, and others. Funding from Gavi has reached US$61.4 million, through funds received from the International Finance Facility for Immunization (IFFIm) since 2007 and allocated to 32 countries.[337] The association Kiwanis also partnered with UNICEF in 2010 through The Eliminate Project and has raised US$51 million to date (with a goal of reaching US$110 million before 2015).[335]

As more countries approach elimination, the current 2012–2015 strategic plan aims to achieve and maintain elimination. The estimated cost to achieve elimination, mainly through TT-SIAS, between 2012 and 2015, is US$227 million. One of the biggest challenges of the initiative is the availability of funds.[332] Funds are especially hard to secure, as the initiative is competing against other global health priorities such as measles and polio eradication.[336]

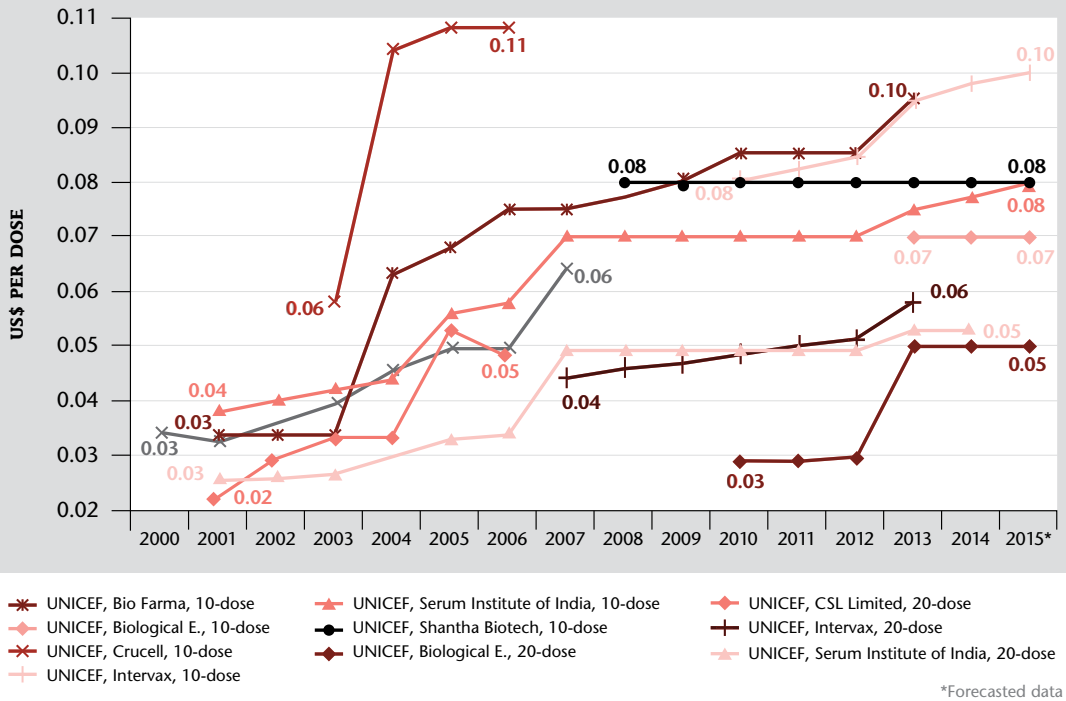
Prices and affordability

PRICE EVOLUTION: UNICEF AND PAHO

(See Annex A for more information on prices used in this section)

- As seen in Graph 24 below, the price of TT vaccines supplied to UNICEF is relatively low: between US$0.05–0.093 per dose in 2014.
- However, despite the large manufacturer base and a generally low price, the lowest price available to UNICEF has increased by 127% between 2001 and 2014 (the lowest prices being US$0.22/dose for a vaccine by CSL Limited in a 20-dose vial in 2001 and US$0.50/dose for a vaccine by Biological E in a ten-dose vial in 2014).
- A large supplier base and fierce competition on price can drive originator manufacturers out of the market. Crucell decided to leave the TT market after it could not compete with lower price offers to UNICEF from other suppliers.

Graph 24: Price evolution of Tetanus Toxoid (TT) vaccines for PAHO and UNICEF



Sources: PAHO Revolving Fund, UNICEF Supply Division.

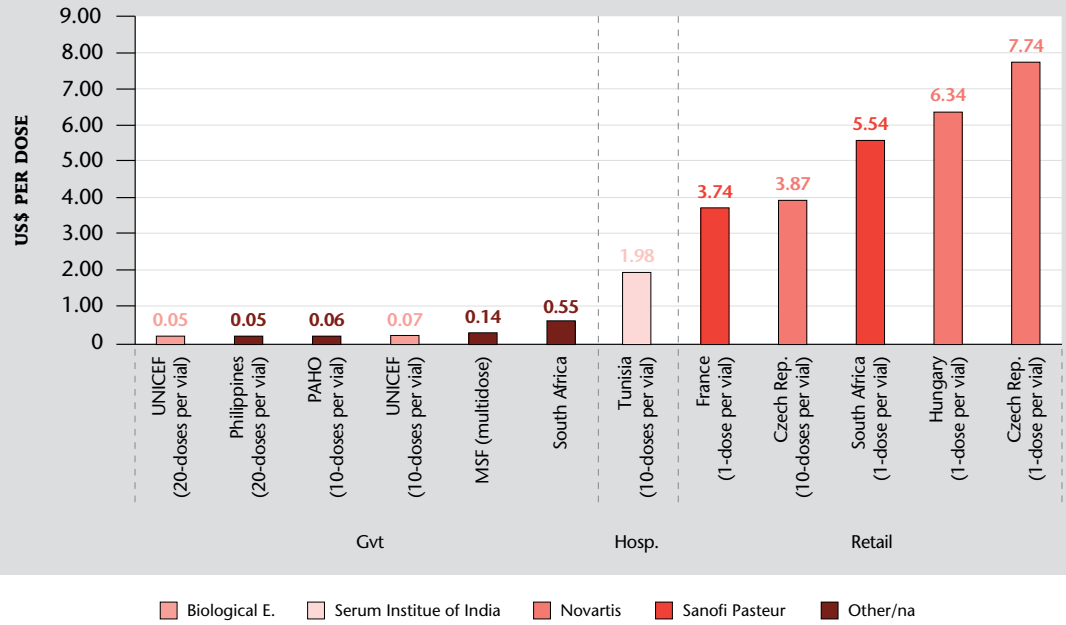
Notes:

- For UNICEF, where agreements include a range of prices during a calendar year period or for different countries or groups of countries, the lowest price of the range was kept.
- Not represented on the graph: Intervax offered 10-dose and 20-dose presentations to UNICEF at US$0.037–0.043 per dose and US$0.024–0.027 (respectively) in 2001–2003; Sanofi Pasteur offered 10-dose and 20-dose presentations to UNICEF at US$0.08 per dose in 2003.
- Novartis has supplied TT to UNICEF but has not agreed to the publication of prices.

PRICES IN COUNTRIES

- From Graph 25 below, it appears that the price of TT vaccines is low for international organisations, but goes up to US$7.74 in the private sector (Czech Republic).
- Outside of government purchases, low prices seem to be available from emerging manufacturers. For instance, in hospitals in Tunisia, a TT vaccine by Serum Institute of India is available for US$1.98 per dose.
- One study from Pakistan in 2004 showed that SIAs to prevent neonatal tetanus were cost-effective (at US$0.04 per dose of the vaccine, representing 11% of the total cost of immunisation, at US$0.40 per dose administered).[338] The vaccine is available for close to this price through international organisations such as UNICEF.

Graph 25: Prices for Tetanus Toxoid (TT) vaccines in several countries, by income group and price type, 2013/2014*



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

Notes:

- Numbers in parentheses are number of doses per vial, when known.
- MSF price is with CPT Incoterm (see Annex C).
- The Philippines procures through UNICEF.
- Only the lowest price available to PAHO, UNICEF and MSF is presented in the graph.

ANNEXES

ANNEX A: SOURCES AND METHODOLOGY FOR PRICE ANALYSIS

1. INTERNATIONAL ORGANISATIONS

UNICEF

Sources: UNICEF Supply Division;[86,11] WHO recommendations for routine immunisation: summary tables;[124] WHO list of prequalified vaccines.[113]

Extract date: 11 March 2014.

Definitions and comments:

- Data show the awarded price per dose per product per supplier per calendar year, based on multiyear supply agreements.
- Data show most prices with CPT ('Carriage paid to') Incoterms for 2001–2003; FCA ('Free carrier') Incoterms* for 2004–2006 onwards.
- Where agreements include a range of prices during a calendar year period or for different countries or groups of countries, the lowest price of the range was used.
- Data collected focused on paediatric vaccines.
- Graphs do not include manufacturers who refused to provide their prices to UNICEF (e.g. Novartis). Manufacturers that supplied a vaccine for only one year are also usually not represented.
- When prices were expressed in euros, prices were converted into US dollars using the 2013 average annual exchange rate as provided by ONDA[170] (euros to US dollars: 1.3279).

** Incoterms: Please see Annex C*

PAHO

Sources: PAHO Revolving Fund website;[67] PAHO Archives and Immunization Newletters;[339] WHO list of prequalified vaccines.[113]

Extract date: 11 March 2014.

Definitions and comments:

- Data show the price per dose per antigen per calendar year, based on annual contracts. Prices are weighed average price (WAP), except if a manufacturer's name is mentioned.
- Assumptions about the manufacturer were sometimes made based on the WHO prequalified vaccines list and the country of origin, when available.
- PAHO does not specify the Incoterm used in its vaccine procurement. Prices are assumed to be CPT ('Carriage paid to'), FOB ('Free on board') or FCA ('Free carrier') Incoterms.

MSF

Source: MSF Supply.

Extract date: 28 May 2014.

Definitions and comments:

- Raw quotations from each manufacturer. Incoterms vary by vaccine and manufacturer.
- Data collected focused on paediatric vaccines.
- When prices were expressed in euros, prices were converted into US dollars using the 2013 average annual exchange rate as provided by OANDA[170] (euros to US dollars: 1.3279).
- In the analysis, MSF is included in the 'international organisation' category.

2. COUNTRIES

A. DISCLAIMER

While constructing the price database for the publication, we aimed to be as precise and up-to-date as possible and took all reasonable precautions to verify the accuracy and reliability of the data used in the analysis. MSF is not held responsible for data and content coming from and available on third-party websites.

- As much as possible, the data are presented in a comparable way. However, because of the complexity of vaccine pricing and the lack of transparency regarding vaccine price components, not every price point is comparable. Comparisons are subject to specific situations and factors that can affect prices and that are particular to each country. See below for country-specific information, sources and definitions.
- The mention of specific products does not mean that MSF endorses or recommends specific company products.
- All price data are provided in US dollars (US$). Exchange rate volatility may be responsible for price differences. To mitigate exchange rate volatility, the rate used for all price points is the average exchange rate over a one-year period (average of 2013: 1 January to 31 December 2013) as provided by OANDA,[170] except if otherwise mentioned.
- The intended goal of this analysis is to show the purchase price differences that exist between countries and the absence of easily accessible and comparable vaccine price data. The lack of descriptive information enabling a precise contextualisation of the data prevents this analysis from being used as a stand-alone comparative tool for international vaccine pricing.

B. DATA DESCRIPTION

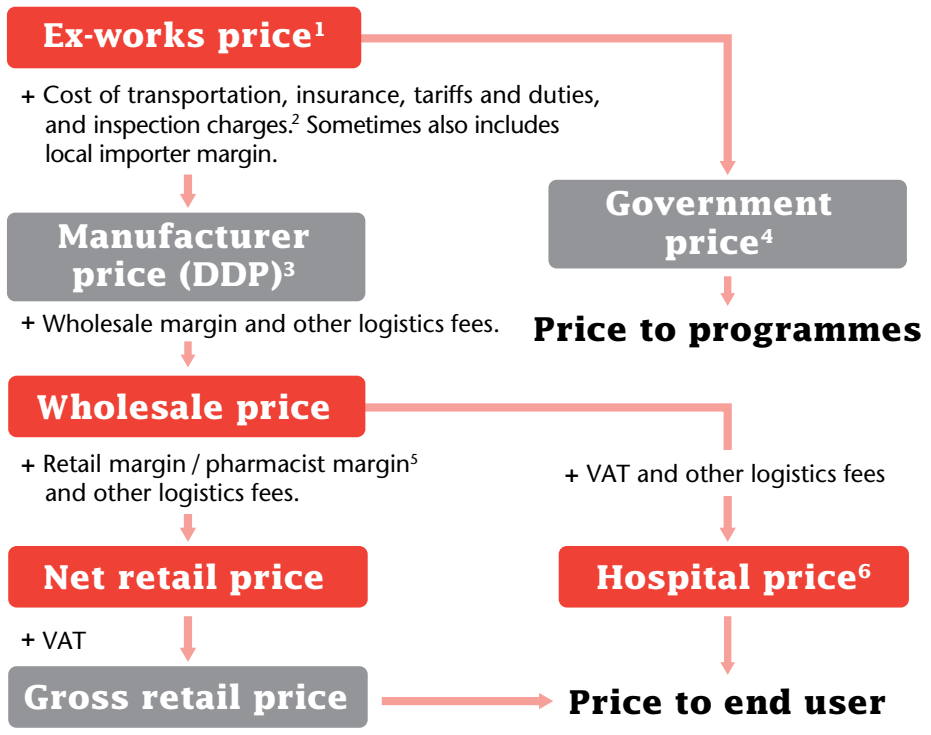
Methodology

- Sources used: country national registries, Ministry of Health websites, literature search, press search and personal communication.
- Data collected focused on paediatric vaccines and WHO prequalified products.
- The selection of countries included in the database is mainly based on data availability.
- Collection and formatting of prices from local registries was done between April and May 2014; 320 price points were collected from 13 countries.
- Searches in national medicine price registries were conducted using ATC codes (Anatomical Therapeutic Chemical (ATC) Classification System for the classification of drugs), product names, antigen names, manufacturer's names, depending on information provided in each database. Searches were conducted in local languages when needed.
- Where there was uncertainty about the reliability and accuracy of the data provided, it was not included in the analysis (e.g. errors on names of products, sometimes no clear identification of product or manufacturer, unrealistic product presentations, etc.)
- There was usually no mention of Incoterms associated with vaccine prices. In this analysis, except if otherwise mentioned, all prices are assumed to be Incoterm DDP (Delivered Duty Paid) .
- Difficulties encountered in data gathering that may have influenced the analysis include:
  - websites that were difficult to navigate, often providing information only in the local language;
  - pricing lists that were sometimes hard to read, with no consistency regarding names of antigens, products or manufacturers;
  - a lack of descriptive information; a lack of price components information (e.g. taxes, logistics fees, exchange rate, wholesale and retail margins, etc.) and little to no information regarding procurement systems and Incoterms used;
  - price targets sometimes ambiguous (price to the public, to hospitals, to specific programmes, etc.)

Price categories

- Prices of vaccines can be comprised of different components, depending on what is incorporated in the price, as described in the illustration below.
- For the purpose of our analysis, price data have been subdivided into four main price types:
  - **Government price (Gvt):** price paid by the government for national immunisation programs.
  - **Hospital price (Hosp/ Hospitals):** price paid in hospitals and public institutions.
  - **Manufacturer price (Manuf.):** price of the vaccine before it enters the wholesale and retail distribution network. Does not include wholesale or retail margins, but may include taxes and transportation fees.
  - **Retail price (Retail):** price as paid by the population, inclusive of taxes, transportation fees, and margins. Sometimes referred to as 'private sector' price.
- All prices except the 'government price' are official prices available outside of government immunisation programmes.
- In some countries, health insurance will cover the cost of the vaccine purchased in the private market, representing a burden for public health insurance schemes. In other countries, where the vaccine is not reimbursed by health insurance, the 'retail price' is a direct burden to personal budgets.

The components of vaccine price*



* This is an example of components of vaccine prices, but components and order of the components could change from one country to another.

COMMENTS

1. Initial price of the vaccine, at the manufacturer's production site.
2. Seller or buyer bears the costs, depending on the Incoterms used in contracts.
3. DDP (Delivered Duty Paid) price is when the goods are placed at the disposal of the buyer. In our country analysis we assumed that "manufacturer prices" were using DDP incoterm.
4. Government tenders do not include any additional mark ups or taxes. Sometimes "government price" is the ex-works price and does not include other costs.
5. Pharmacist margins are usually regulated by law.
6. Prices accessible in hospitals, excluding cost of administration.

COUNTRY SPECIFICATIONS

The 13 countries included in this analysis are classified as follows:

Country, currency	Exchange rate to US$, average year 2013	GNI per capita (US$ 2012)	Country classification	PCV3 coverage in 2013 (%)	DTP3 coverage in 2013 (%)	Birth cohort, in thousands
India, INR	0.0172	1,580	LMIC	N/A	76	25,595.2
Philippines, PHP	0.0235	2,500	LMIC	N/A	94	2,403.9
Morocco, MAD	0.1178	2,960	LMIC	82	99	749.9
Tunisia, TND	0.6135	4,150	UMIC	N/A	98	189.5
Thailand, THB	0.0325	5,210	UMIC	N/A	99	686.7
South Africa, ZAR	0.1038	7,610	UMIC	87	90	1,098.8
Lebanon, LBP	0.0007	9,190	UMIC	N/A	98	63.8
Brazil, BRL	0.4643	11,630	UMIC	93	95	2,994.6
Hungary, HUF	0.0045	12,380	UMIC	92	99	98.1
Czech Republic, CZK	0.0511	18,120	HIC	N/A	99	118.3
France, EUR	1.3279	41,750	HIC	89	99	791.9
Belgium, EUR	1.3279	44,660	HIC	93	99	129.3
United States, USD	1.0000	52,340	HIC	92	94	4,229.9
Sources	OANDA[170]	World Bank[45]	World Bank[97]	WHO immunisation coverage[31]	WHO immunisation coverage[31]	World Population Prospects[340]

N/A: Not Applicable.

Note on income groups: economies are divided according to 2012 GNI per capita, calculated using the World Bank Atlas method.[45,97] The groups are:

- low-income country (LIC), US$1,035 or less
- lower-middle-income country (LMIC), US$1,036–4,085
- upper-middle-income country (UMIC), US$4,086–12,615
- high-income country (HIC), US$12,616 or more

C. INDIVIDUAL COUNTRY SOURCES AND DEFINITIONS

Belgium

Sources:

- INAMI, http://www.inami.fgov.be/care/fr/hospitals/specific-information/forfaitarisation/index.htm.
- Other sources: Le Soir,[156] VaxInfo.org.[341]

Last update: 1 April 2014.

Extract date: 5 May 2014.

Price categories:

- Manufacturer price: price exclusive of transportation fees, margins and taxes.
- Hospital price: price paid in hospitals.
- Retail price: as purchased at the pharmacy, includes wholesale margin, pharmacist's margin, transportation fees and VAT.

Additional information:

- The special price of the Gardasil HPV vaccine at EUR20 per dose in Flanders was obtained through a public tender. The two manufacturers of HPV vaccine participated and the Flemish region gave the entire market to the company with the best offer (525,000 doses: 105,000 doses per year for five years). In Belgium, there is no public tender at the national level for drugs or vaccines.

Brazil

Sources:

- Portal da Transparencia, Federal Government: http://www.portaldatransparencia.gov.br/convenios/DetalhaConvenio.asp?CodConvenio=677932&TipoConsulta=0.
- Other sources: Agencia Brasil,[154] The Financial Times,[275] FirstWord-Pharma.[274]

Extract date: 5 May 2014.

Price categories:

- Government price: price obtained through agreements with companies.

Additional information:

- Brazil uses technology transfer agreements that allow the country to access vaccines (e.g. HPV vaccine and PCV) at lower prices; such partnerships could limit the longer-term opportunity for Brazil to benefit from real competition when emerging manufacturers enter the market with cheaper products.

Czech Republic

Source: SUKL, State Institute for Drug Control, http://www.sukl.eu/sukl/list-of-reimbursed-medicinal-products-valid-as-of-1-4-2014.

Last update: 1 April 2014.

Extract date: 25 April 2014.

Price categories:

- Manufacturer price: net manufacturer's price (ex-factory), excludes any wholesale and retail margins and excludes 15% VAT.
- Retail price: gross retail price, final price to consumer. Includes manufacturer price plus the maximum profit margin under the Ministry of Health's price regulation and VAT.

Additional information:

- Acting in compliance with Section 39n(1) of Act No. 48/1997 Coll., on Public Health Insurance, as amended ('Act'), the State Institute for Drug Control publishes the List of Prices and Reimbursements for Medicinal Products and Foods for Special Medicinal Purposes ('List').
- The List, published on the first day of the calendar month, includes a full list of medicinal products (MPs) and foods for special medicinal purposes (FSMPs) covered by the public health insurance scheme; these products are reimbursed by decision of the Institute, including the maximum or announced ex-factory prices, the amount and terms of reimbursement, including the maximum possible reimbursement for the end consumer.

France

Source: AMELI 'Base de données des médicaments et informations tarifaires': http://www.codage.ext.cnamts.fr/codif/bdm_it/index_presentation.php?p_site=.

Last update: 29 April 2014.

Extract date: 5 May 2014.

Price categories:

- Manufacturer price: price exclusive of transportation fees, margins and taxes.
- Retail price: as purchased at the pharmacy, includes wholesale margin, pharmacist's margin, transportation fees and VAT.

Additional information:

- Only reimbursed vaccines are included in the list.
- Data are updated every week.

Hungary

Source: National Health Insurance Fund Administration (OEP): http://www.oep.hu/portal/page?_pageid=35,56067708&_dad=portal&_schema=PORTAL.

Last update: 14 January 2014.

Extract date: 24 April 2014.

Price categories:

- Manufacturer price: excludes wholesale margin, retail margin and taxes.
- Retail price: includes wholesale and retail margins and taxes (5% taxes).

India

Sources:

- Communication with a private practice.
- R. Lodha and A. Bhargava 2010.[342]

Price categories:

- Retail price: official maximum retail price (MRP) inclusive of all taxes, as indicated on the vaccine box.

Additional information:

- Price data are from 2008 and 2014.

Lebanon

Source: Lebanon Drugs Public Price List: http://www.moph.gov.lb/Drugs/Pages/Drugs.aspx.

Last update: 1 April 2014.

Extract date: 18 April 2014.

Price categories:

- Manufacturer price: the pharmacist's margin has been subtracted from the retail price to obtain the price without the margin. This price is an estimate, representing the manufacturer price, with taxes and transportation fees.
- Retail price: price as listed on the website, inclusive of the pharmacist's margin (between 19.35% and 23.08%).

Additional information:

- Drugs Public Price List according to the resolution 51/1 and based on the exchange rate number 14/2/9990 issued on 10 April 2014.

Morocco

Source: Agence Nationale de l'Assurance Maladie (ANAM) - guide des médicaments remboursables: http://www.assurancemaladie.ma/anam.php?id_espace=6&id_srub=19.

Extract date: 21 April 2014.

Price categories:

- Hospital price: this is the price accessible to hospitals. Defined on the ANAM website as the 'Prix en Etablissement de soins'.
- Retail price: this is the price accessible to the public when purchased in pharmacies. Defined on the ANAM website as the 'Prix Officine (Pharmacie)'.

Additional information:

- All vaccines in this list are reimbursed, except HPV and rotavirus vaccines. All reimbursed vaccines are reimbursed at 100%.

The Philippines

Source: Communication with a country EPI contact.

Date: 10 March 2014.

Price categories:

- Government price: price of vaccines purchased by the EPI department of the Ministry of Health.

Additional information:

- Most of the vaccines in the Philippines are procured through UNICEF SD, thus prices for most vaccines are very similar to prices published by UNICEF.

South Africa

Sources:

- South African Medicine Price Registry: http://www.mpr.gov.za/.
- Communication with the South African Department of Health.

Last update: 12 March 2014.

Extract date: 4 April 2014.

Price categories:

- Government price: exclusive of VAT and transportation costs.
- Manufacturer price: excludes logistics fees and VAT.
- Retail price: SEP (single exit price), which is the maximum anyone should be charged for a product, including logistics fees, VAT, etc.

Additional information:

- Note that prices in the Medicine Price Registry are provided by product and by ml (price per dose needs to be calculated).
- In South Africa, EPI vaccines are purchased through BioVac, and contracts sometimes include techology transfer arrangements to BioVac so that South Africa can build up its national manufacturing capacity.
- The exchange rate South African rand/US$ rate is volatile; therefore part of price differences with other countries might be attributed to the fluctuating exchange rate.

Thailand

Source: Thailand National Health Security Office (NHSO).

Date: 1 May 2014.

Price categories:

- Government price: excludes overhead cost under the Government Pharmaceutical Organisation's Vendor Managed Inventory (VMI) System (5% for vaccines).

Additional information:

- For vaccines, the NHSO supply only two of the vaccines we analysed. The Department of Disease Control (DDC) is the chief supplier of vaccines to the public sector.
- The price listed here is the lowest price available for that product.

Tunisia

Source: Pharmacie Centrale de Tunisie: http://www.phct.com.tn/index.php?option=com_searchproduct&view=searchproduct&Itemid=48&lang=en&ctg=M.

Last update: 19 March 2014.

Extract date: 24 April 2014.

Price categories:

- Hospital price: this is the price accessible to hospitals; it does not include taxes.

United States

Source: Centers for Disease Control and Prevention (CDC) website: http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html.

Last update: 1 April 2014.

Extract date: 4 April 2014.

Price categories:

- Government price: for vaccines included in the CDC Vaccines for Children Program (VFC) list of paediatric vaccines. Price includes Federal Excise Tax and transportation fees. This would correspond to the Incoterm Delivery Duty Paid (DDP), named place of destination.
- Manufacturer price: private sector prices are those reported by vaccine manufacturers annually to CDC.

Additional information:

- 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 US territories). Prices quoted include Federal Excise Tax and transportation fees. Private providers and private citizens cannot directly purchase vaccines through CDC contracts.

ANNEX B: COMPANY CONTACTS

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ANNEX C: INCOTERMS

Incoterms (International Commercial Terms), "provide rules and guidance to importers, exporters, lawyers, transporters, insurers and students of international trade."[343]

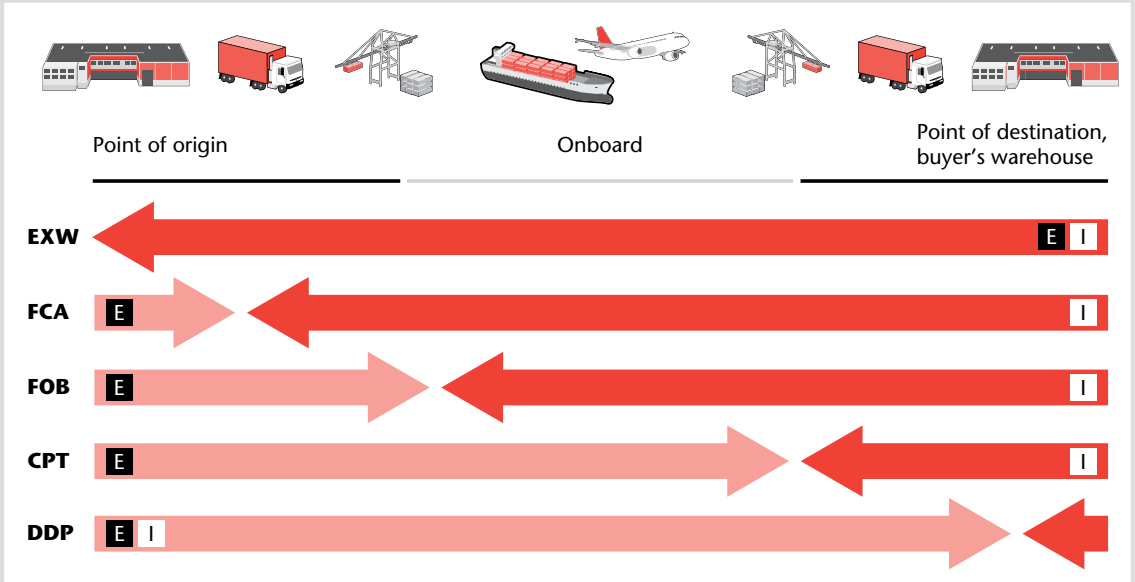
Incoterms are an important part of trade. They define when responsibility for goods is transferred from the seller to the buyer, and what part of the transportation, logistics and insurance costs is the responsibility of each of the parties. They will influence the price paid for vaccines, as for any other goods.

Incoterms mentioned in this report are:*

- **EXW Ex Works:** 'Ex Works' means that the seller delivers when it places the goods at the disposal of the buyer at the seller's premises or at another named place (i.e., works, factory, warehouse, etc.). The seller does not need to load the goods on any collecting vehicle, nor does it need to clear the goods for export, where such clearance is applicable.
- **FCA Free Carrier:** 'Free Carrier' means that the seller delivers the goods to the carrier or another person nominated by the buyer at the seller's premises or another named place. The parties are well advised to specify as clearly as possible the point of handover within the named place of delivery, as the risk passes to the buyer at that point.
- **CPT Carriage Paid To:** 'Carriage Paid To' means that the seller delivers the goods to the carrier or another person nominated by the seller at an agreed place (if any such place is agreed between parties) and that the seller must contract for and pay the costs of carriage necessary to bring the goods to the named place of destination.
- **FOB Free On Board (for transport by sea and inland waterway):** 'Free On Board' means that the seller delivers the goods on board the vessel nominated by the buyer at the named port of shipment or procures the goods already so delivered. The risk of loss of or damage to the goods passes when the goods are on board the vessel, and the buyer bears all costs from that moment onwards.
- **DDP Delivered Duty Paid:** 'Delivered Duty Paid' means that the seller delivers the goods when the goods are placed at the disposal of the buyer, cleared for import on the arriving means of transport ready for unloading at the named place of destination. The seller bears all the costs and risks involved in bringing the goods to the place of destination and has an obligation to clear the goods not only for export but also for import, to pay any duty for both export and import and to carry out all customs formalities.

**Definitions reproduced from 'The Incoterms Rules', International Chamber of Commerce website,[343] where more information is available.*

Annex C - Incoterms



ANNEX D: ABBREVIATIONS

AMC	Advance Market Commitment
ARV	Antiretroviral drug
BCG	Bacillus Calmette-Guérin vaccine (against tuberculosis)
CDC	United States Centers for Disease Control and Prevention
CTC	Controlled Temperature Chain
DCVM	Developing Country Vaccine Manufacturers
DCVMN	Developing Countries Vaccine Manufacturers Network
DFID	Department for International Development (UK)
DOV	Decade of Vaccines Collaboration
DTP	Diphtheria, Tetanus and Pertussis vaccine
DTwP	Diphtheria, Tetanus and whole-cell Pertussis vaccine
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration (US)
Gavi	The Gavi Alliance (formerly Global Alliance for Vaccines and Immunizations)
GNI	Gross National Income
GPRM	Global Price Reporting Mechanism
GSK	GlaxoSmithKline
GVAP	Global Vaccine Action Plan
Hep B	Hepatitis B
Hib	*Haemophilus influenzae* type b
HIC	High-income country
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus Vaccine
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IPV	Inactivated Polio Vaccine
LMIC	Lower-middle-income country
LPC	Lowest price clauses
MIC	Middle-income country
M&E	Monitoring & Evaluation
MFN clause	Most Favoured Nations Provision/Clause
MR	Measles-rubella vaccines
MMR	Combined Measles, Mumps and Rubella vaccine
MMRV	Combined Measles, Mumps, Rubella and Varicella vaccine
MSF	Médecins Sans Frontières
OANDA	Online foreign exchange broker
OCV	Oral Cholera Vaccine
OPV	Oral Polio Vaccine
Pentavalent	Combined diphtheria, tetanus, whole-cell pertussis, hepatitis B and *Haemophilus influenzae* type b (DTwP-HepB-Hib) vaccine
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal Conjugate Vaccine
Polio	Poliomyelitis
PVP	Pooled Vaccine Procurement initiative
PQ	Prequalification or Prequalified (WHO)

QSS	WHO Quality, Safety and Standards
R&D	Research and Development
SAGE	Strategic Advisory Group of Experts
SIA	Supplemental Immunisation Activities
SII	Serum Institute of India Ltd
TPP	Target Product Profile
Td	Tetanus-diphtheria vaccine
TT	Tetanus Toxoid
UMIC	Upper-middle-income country
UNICEF	United Nations Children's Fund (UNICEF SD: Supply Division)
V3P	Vaccine Product, Price and Procurement Project
VVM	Vaccine Vial Monitor
WHA	World Health Assembly
WHO	World Health Organization
WHO PQ	WHO Prequalification of Medicines Programme

ANNEX E: SUMMARY OF WHO POSITION PAPERS – RECOMMENDATIONS FOR ROUTINE IMMUNISATION

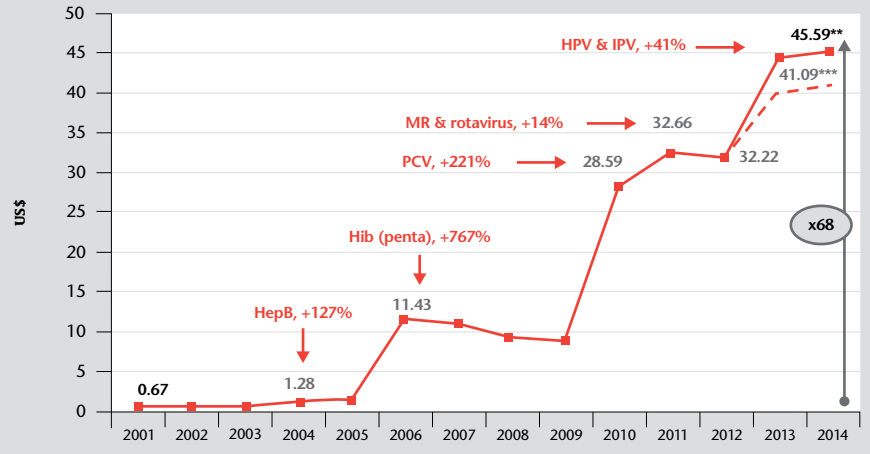
Last update: 30 May 2014

For more information, go to: http://www.who.int/immunization/policy/Immunization_routine_table1.pdf?ua=1

Antigen		Children	Adolescents	Adults	Considerations
BCG		1 dose			Exceptions HIV+
Hepatitis B		3–4 doses	3 doses (for high-risk groups if not previously immunised)		• Birth dose • Premature and low birth weight • Co-administration and combination vaccine • Definition high-risk
Poliomyelitis		3–4 doses (at least one dose of IPV) with DTP			• OPV birth dose • Type of vaccine • Transmission and importation risk criteria
DTP		3 doses Booster (DTP) 1–6 years of age	Booster (Td)	Booster (Td) in early adulthood or pregnancy	• Delayed/Interrupted schedule • Combination vaccine
Haemophilus influenzae type b	Option 1	3 doses, with DTP			• Single dose if ≥12 months of age • Not recommended for children >5 yrs old • Delayed/Interrupted schedule • Co-administration and combination vaccine
	Option 2	2 or 3 doses, with booster at least 6 months after last dose			
Pneumococcal (conjugate)	Option 1	3 doses with DTP			• Vaccine options • Start before 6 months of age • Co-administration • HIV+ and preterm neonates booster
	Option 2	2 doses before 6 months of age, plus booster dose at 9–15 months of age			
Rotavirus		Rotarix: 2 doses with DTP RotaTeq: 3 doses with DTP			• Vaccine options • Not recommended if >24 months old
Measles		2 doses			• Combination vaccine • HIV+ early vaccination • Pregnancy
Rubella		1 dose	1 dose (adolescent girls and/or women of child-bearing age if not previously vaccinated)		• Achieve and sustain 80% coverage • Co-administration and combination vaccine • Pregnancy
HPV			2 doses (girls)		• Target 9–13-year-old girls • Pregnancy • Older age groups (≥15 years) • HIV+ and immunocompromised

ANNEX F: NOTES AND METHODOLOGY FOR THE GRAPH ON THE PRICE OF VACCINES TO IMMUNISE A CHILD

Graph 1 (from page 7 of this report)



Notes:

- Baseline cost in 2001 based on the following schedule: 1 BCG + 2 measles + 3 DTP + 3 OPV. Cost in 2014 based on the following schedule: 1 BCG + 2 MR + 3 Penta + 3 OPV + 1 IPV + 3 PCV + 2 Rota + 3 HPV.
- Indicator used: lowest available UNICEF price per antigen per year since 2001 (across UNICEF's suppliers and across presentations) to complete all primary series in routine immunisation as recommended by WHO. The percentage presented in the graph is the difference from the previous year.
- The graph does not represent the full cost of immunisation, only the cost of vaccines. Many elements, such as human resources, transportation, cold chain, infrastructure, wastage, other immunisation supplies, waste management, etc., would need to be added to have a full picture.
- Most prices are with CPT Incoterms* from 2001 to 2003; FCA Incoterms* from 2004 to 2006 onwards.
- Only specific countries can access these low prices (mostly Gavi-eligible countries). Prices are based on multi-year supply agreements.
- The analysis does not include vaccines recommended for specific regions (e.g. yellow fever). It includes only doses in primary series, not booster dose recommendations.
- The analysis includes HPV as it is a primary series vaccine, even though WHO recommendations are for adolescents girls only.
- For PCV, the price per dose is composed of a tail price (US$3.50) and subsidies (US$3.50) achieved through the Advance Market Commitment (AMC). As US$7 dollars is often considered the 'reference price', we used this price in the analysis.
- For the rotavirus vaccines, we used the cheapest full course option, Rotarix (GSK), which has a schedule of two doses (versus three doses for Merck's RotaTeq).
- For the MR/MMR vaccine, the price has been calculated using the cheapest option, which is to use the MR vaccine. Also, WHO only recommends vaccination against mumps in specific settings.
- Exchange rate: when prices were expressed in euros, prices were converted into US dollars using the 2013 average annual exchange rate as provided by OANDA (euros to US dollars 2013 annual average exchange rate: 1.3279).

Timeline: WHO recommendations and Gavi decisions on vaccines funding

- **2001:** used as the baseline year, as it is the year the GAVI Alliance (the Global Alliance for Vaccines and Immunisation, now known simply as Gavi) was created. The baseline vaccine routine immunisation includes one BCG, three DTP, three OPV and two measles vaccines.
- **2004:** WHO reiterates 1992 recommendation for universal vaccination against hepatitis B.
- **2006:** WHO recommends universal vaccination against *Haemophilus influenzae* type b. DTP and HepB vaccine prices are used until 2006, even though the pentavalent vaccine already existed, on the basis that countries were ramping up pentavalent introduction and that Hib was not added to the WHO recommendations for routine immunisation before 2006. The pentavalent price is used as of 2006.
- **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, especially using rubella-containing vaccines such as MR or MMR vaccines.
- **2013:** Gavi offers support to access the measles-rubella vaccine by providing support for measles and rubella catch-up campaigns under the condition that countries self-finance the vaccines for their routine immunisation programme.
- **2013:** Gavi supports the introduction of HPV in Gavi-eligible countries; 21 countries were approved in 2013 and 2014 to receive Gavi support to introduce the HPV vaccine.
- **2014:** At the end of 2013 SAGE (WHO Strategic Advisory Group of Experts on Immunisation) published guidelines on the introduction of IPV in routine immunisation. As part of the polio end-game strategy, Gavi supports the introduction of IPV in Gavi countries, but also includes several policy exceptions in order to broaden the number of countries that can apply for its support. Prices from the UNICEF tenders are published in February 2014.

BCG: bacille Calmette-Guérin; DTP: diphtheria-tetanus-pertussis vaccine; OPV: oral poliovirus vaccine; MR: measles-rubella vaccine; Penta: DTP-HepB-Hib vaccine [HepB: hepatitis B, Hib: *Haemophilis influenzae type b*]; IPV: inactivated poliovirus vaccine; PCV: pneumococcal conjugate vaccine; Rota: rotavirus vaccine; HPV: human papilomavirus vaccine

*See Annex C.

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PURPOSE AND DISCLAIMER:

This report intends to present a landscape description and analysis of developments in the vaccine sector. The MSF Access Campaign aims to be as precise and up-to-date as possible in our analyses, and MSF took all reasonable measures to verify the accuracy and reliability of the data used. However, if you identify any errors or have complementary information or comments that would help to improve the accuracy of this publication, please share your comments on the webpage below. We welcome your feedback to advance the discussion on vaccine affordability.

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