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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<sup>114–116</sup> 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.<sup>117–119</sup>
- ❖ Human papillomavirus (HPV) is sexually transmitted and is the primary cause of cervical cancer.<sup>114,120</sup> Persistent infection by oncogenic HPV is a prerequisite for developing cervical cancer, and at least 13 viral genotypes are known to be carcinogenic.<sup>121</sup> 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.<sup>121</sup>
- ❖ 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.<sup>121</sup>
- ❖ 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  $\geq 2$  or adenocarcinoma in situ) when administered before virus exposure.<sup>121</sup> 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.<sup>122</sup> The quadrivalent vaccine has been shown to substantially reduce disease incidence of genital warts in countries with high coverage rates.<sup>123</sup>
- ❖ 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.<sup>117</sup>
- ❖ In late 2013, the bivalent HPV vaccine received European Commission approval<sup>125</sup> for a reduced two-dose schedule (at 0 and 6 months) for girls aged 9–14 years.<sup>115,126,127</sup> In 2014 the quadrivalent product received European Commission approval<sup>128,129</sup> 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,<sup>130</sup> 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.<sup>115,128,129,131,132</sup>

Vaccine <sup>124</sup>	Age at 1 <sup>st</sup> dose	Doses in primary series (interval between doses)	Booster
Quadrivalent HPV	9–13 years	2 doses for girls <15 years (minimum 6 months between 1 <sup>st</sup> and 2 <sup>nd</sup> dose)	Not recommended
Bivalent HPV		If the interval between the two doses is <6 months, then a 3 <sup>rd</sup> dose should be given at least 6 months after the 1 <sup>st</sup> dose	
Quadrivalent or bivalent HPV: delayed start*	Applicable for girls $\geq 15$ years	3 doses (minimum 1–2 months between 1 <sup>st</sup> and 2 <sup>nd</sup> dose; minimum 4 months between 2 <sup>nd</sup> and 3 <sup>rd</sup> 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)
<b>Cervarix</b> 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 <sup>3</sup> Box, 10 vials: 11.5 cm <sup>3</sup> Box, 100 vials: 4.8 cm <sup>3</sup>
<b>Gardasil/Silgard</b> 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 <sup>3</sup> Box, 10 vials: 15 cm <sup>3</sup>

## PIPELINE PRODUCTS

- Merck has the nine-valent vaccine V503 in Phase III of development.<sup>133,134</sup> 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.<sup>135,136</sup>
- Other companies, including ISA Pharmaceuticals, Genexine and Transgene, have vaccines that use a mono-therapy approach to target HPV 16 in Phase II.<sup>137-139</sup>

## 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,<sup>115</sup> and this is particularly the case in middle- and low-income countries with regard to HPV vaccination.<sup>120</sup> 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.<sup>140</sup>
- 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.<sup>114,141,142</sup>
- 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).<sup>127</sup> 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.<sup>143</sup> 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'.<sup>58</sup>

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.<sup>59,61,144</sup> Taking into account the 111 million doses of Gardasil sold worldwide as of May 2013<sup>145</sup>, 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%)<sup>146</sup> and mortality rate in the world. In South Africa, cervical cancer is the second most common cancer among women (prevalence of 21%).<sup>147</sup> 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.<sup>148</sup> 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.<sup>149</sup>

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.<sup>150</sup>

### 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)

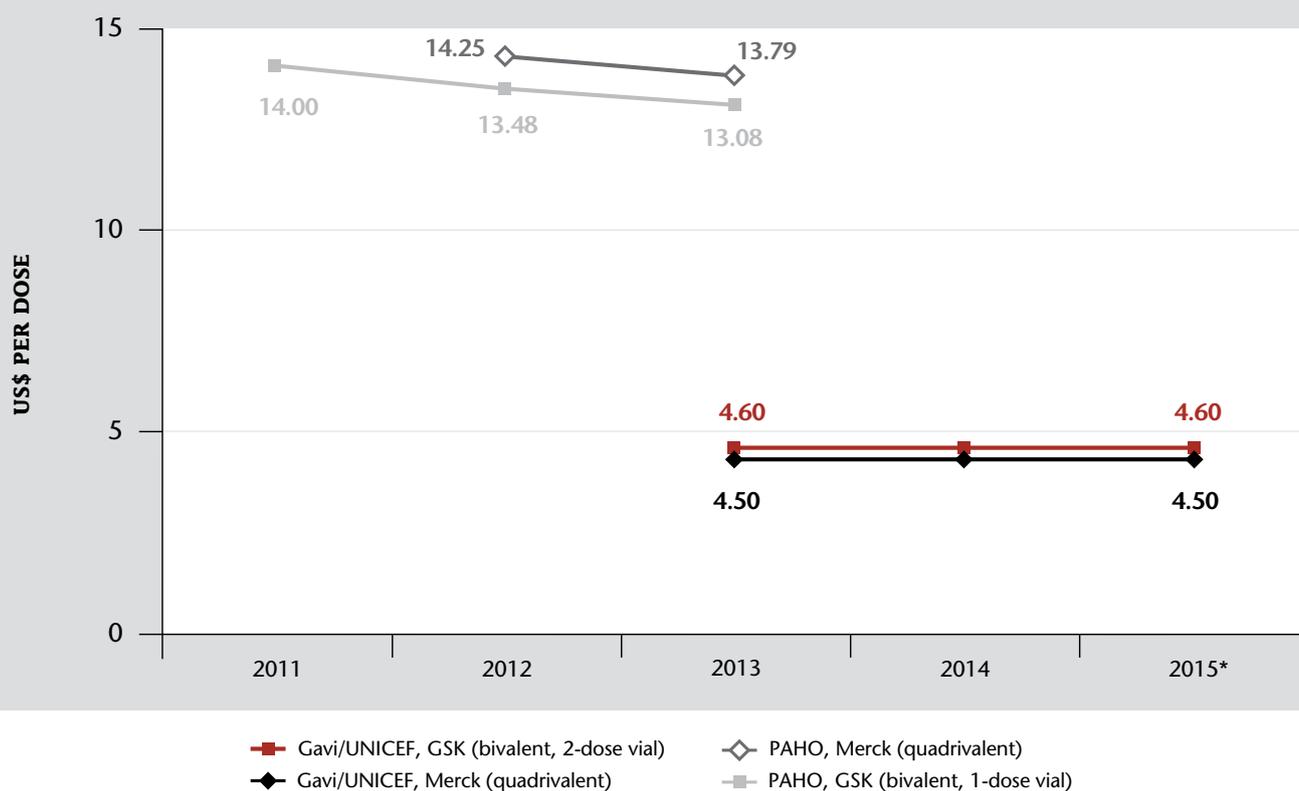
At US\$13.08–13.79 a dose, the Pan American Health Organization (PAHO) pays more than three times the price offered through UNICEF to Gavi-eligible countries [Graph 6].

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,<sup>96</sup> 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  $\leq$ US\$10 (approximately US\$2 per dose).<sup>151</sup> 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.<sup>152</sup> 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<sup>142</sup> 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.<sup>153</sup> 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).<sup>149</sup>

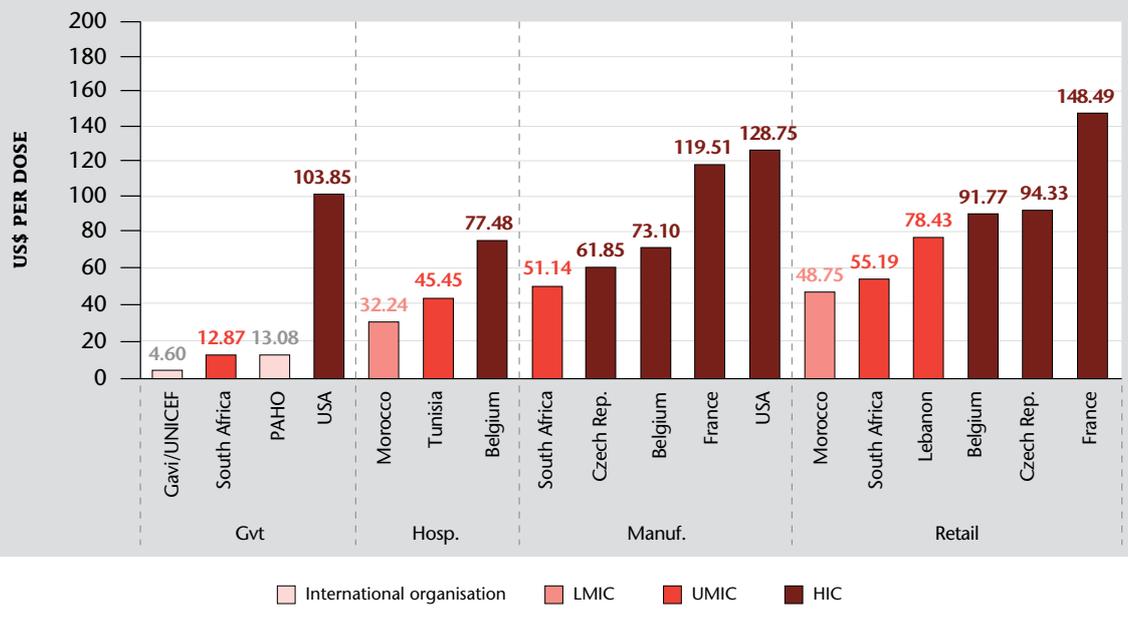
❖ In Brazil, HPV vaccine is supplied through a partnership between Merck and Instituto Butantan, via an investment of 1.1 million Brazilian reais (US\$462 million\*) to purchase 36 million doses over five years (15 million doses should be distributed the first year, starting in March 2014).<sup>154</sup> 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 reais 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)<sup>156</sup> 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.<sup>155</sup>

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

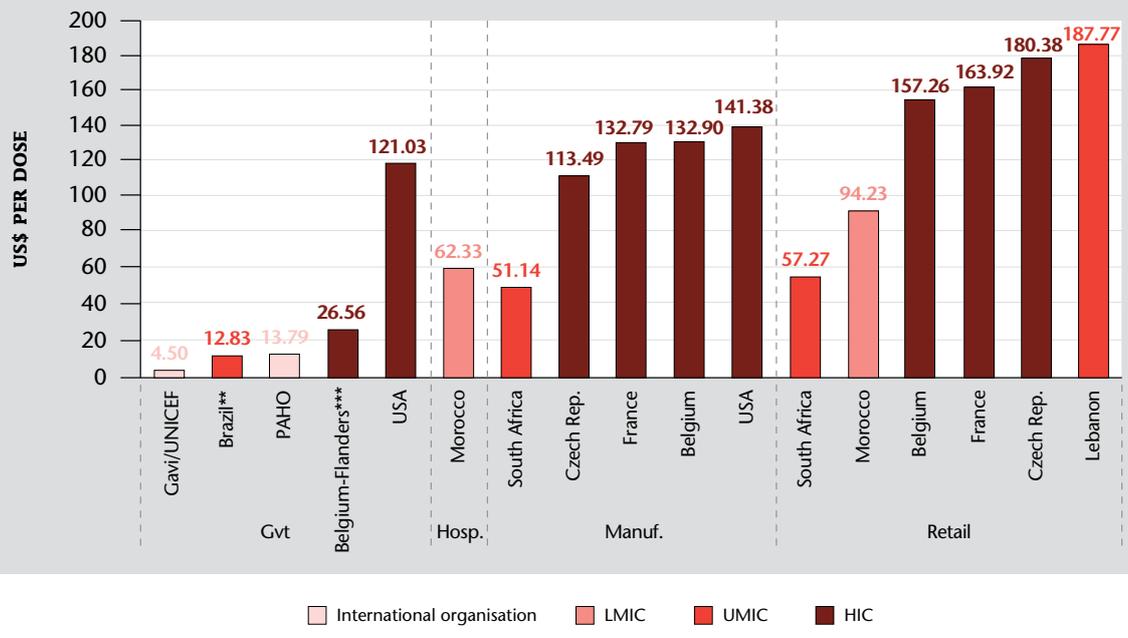


**Sources:**

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