

## Chapter 26: Innovative financing mechanisms to accelerate the introduction of HPV vaccines in developing countries

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Received 3 April 2006; accepted 15 May 2006

### Abstract

The costs of developing and producing new-generation vaccines have increased compared to many of the older, “traditional” vaccines because of new technologies and regulatory requirements. While the public sector often supports basic research costs, private manufacturers are usually responsible for the investments in product development and production scale-up. When considering investments, firms evaluate the probability of a market. Unfortunately, the developing country vaccine market is small (in revenue terms) and often unpredictable, particularly given inaccurate forecasting in the past. Low-income developing countries expect low prices. Demand (actual decisions to pay for and introduce the vaccine) is almost always lower than need (estimates of requirements to achieve optimal public health outcomes), a distinction that may be even more significant for HPV vaccines given the number of new vaccines against priority diseases that will become available over the coming 5 years.

One new mechanism under consideration to address some of these challenges is Advanced Market Commitments (AMCs). By providing an assured price subsidy for developing country purchase of a future vaccine meeting predefined standards, an AMC would provide industry with greater assurances of earning a reasonable return on their investment to serve the poorest developing countries. The AMC mechanism could provide critical motivation for increased industry (private) investment that would otherwise not occur. HPV vaccines are one of six vaccines being considered for a possible AMC pilot.

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*Keywords:* HPV vaccine; Innovative financing mechanisms; Advanced market commitments

### 1. Introduction

Almost 500,000 new cases of cervical cancer and 270,000 deaths among women are reported each year. Eighty-five percent of these deaths occur in developing countries. Because screening and treatment programs are not widely available, cervical cancer affects mainly poor women with limited

access to health services. There are currently two HPV vaccines in late-stage development that have the potential to prevent 65–75% of all cervical cancers [1]. However, ensuring these HPV vaccines are available, affordable and accessible to women will be challenging.

In this chapter we discuss issues related to the accelerated introduction of HPV vaccines in developing countries. First, we analyze the reasons for the under-investment in research and development (R&D) and/or manufacturing capacity for developing countries. Second, we take a closer look at trends in the vaccine market. Third, we discuss in more detail the Global Alliance for Vaccines and Immunization

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(GAVI) and Advanced Market Commitments (AMCs) as innovative approaches to address some of the market failures in developing countries.

## 2. Understanding investment decisions by manufacturers

Vaccine firms must allocate their limited human and financial resources to different vaccine projects, with investment in products to serve developing country markets that are competing against products targeting more reliable and lucrative markets.

There are a number of factors influencing a firm's view of the developing country market. First, the potential vaccine revenue from the poorest developing countries is limited. The developing country vaccine market is characterized by a strong price-to-volume bias. The traditional six vaccines of the Expanded Programme on Immunization (EPI), namely measles, diphtheria, pertussis, tetanus, oral polio, and BCG, are mature off-patent products that are used in almost every national immunization program and can be purchased at prices of less than \$0.15 per dose. A study by Mercer Management has found that these basic EPI vaccines account for over 80% of internationally procured doses of vaccine but less than 15% of revenues in the global market. This is compared to new vaccines such as pneumococcal conjugate, meningococcal conjugate, and varicella which account for only 1% of volume but 32% of total vaccine revenues [2]. Second, forecasts for new vaccines' uptake in developing countries have been quite inaccurate historically, with actual uptake being much slower than predicted [3]. Some of the inaccuracy may be due to forecasts being based on estimates of public health need rather than actual ability to purchase the product. By increasing the perceived unpredictability of the market, inaccurate forecasts undermine demand-supply discussions for future priority vaccines: a firm that sized its production facility to meet forecasted demand that never materialized, for example, will be very careful in the future to avoid making the same mistake. Unfortunately, there are several examples of inaccurate forecasts, particularly with the more recently introduced products containing hepatitis B and/or *Hemophilus influenzae* type b (Hib). Introduced in industrialized countries in the 1980s, hepatitis B vaccines had been introduced into less than 15% of sub-Saharan African countries by 2000, despite relatively low tiered prices [4]. In 2001, tender awards to purchase almost 100 million doses of hepatitis B vaccine were issued, although actual uptake (use of vaccines in countries) was less than 20 million doses [2].

The historical pattern of slow and uncertain uptake of new vaccines combined with expectations of extremely low prices makes large investments by firms to serve the developing country market less attractive. Evidence is needed to credibly demonstrate to vaccine firms both that countries and donor partners are willing to pay more for vaccines and that developing country forecasts are based on solid global and country

work plans that result in more accurate and realistic estimates of new vaccine demand.

## 3. Vaccine pricing

Differential pricing (also called tiered pricing) is a strategy adopted by vaccine firms in which they sell a vaccine at lower prices (at the extreme, vaccines can be provided as a donation) to the poorest developing countries and charge higher prices in middle-income and industrialized countries. If firms fear that industrialized or middle-income countries will use political pressure to force all prices down to the lowest tier – the pricing intended for the poorest countries – they are likely to abandon tiered pricing and charge the industrial country price globally. This is exactly what happened in the 1980s when a US firm was questioned about developing countries receiving lower prices than the US Government [5]. Providing lower prices to the poorest countries is not a strategy that ensures large profits but, when combined with other more profitable markets, it allows firms to benefit from production economies of scale and to ensure a larger portion of the world has access to life-saving vaccines. The importance of tiered pricing is evident when one notes that total health expenditures per capita are roughly \$29 in low-income countries [6], well below the expected price of a single dose of HPV vaccine (and most other vaccines) in the industrialized world.

Pooled procurement has greatly improved vaccine access and, in some cases, has helped to facilitate differential pricing. UNICEF and the Pan-American Health Organization (PAHO) both purchase large quantities of vaccines; UNICEF purchases on behalf of developing countries around the world, and PAHO on behalf of countries in Latin America. Pooled procurement reduces the transaction costs of supplying developing countries and so lowers costs and thus can facilitate lower prices. These low prices have been critical in establishing national immunization programs for the basic paediatric vaccines. However, the success in driving down prices for mature vaccines has come at a cost as some firms have stopped production of certain vaccines and have difficulty justifying large investments in serving the low-income developing country market. To keep manufacturers focused on the needs of developing countries, future prices must at least be adequate for manufacturers to justify incremental investments and cover costs [7].

## 4. Status of HPV vaccine supply

The world's vaccine market is surprisingly small in revenue terms, representing less than 2% of the pharmaceutical market in 2002 (\$6.8 billion global vaccine sales compared to \$447.9 billion worldwide pharmaceutical sales) [8]. It is dominated by five multinational pharmaceutical companies, who share roughly 80% of the market (in revenues): Glaxo-Smith Kline (GSK), Sanofi Pasteur, Wyeth, Merck, and

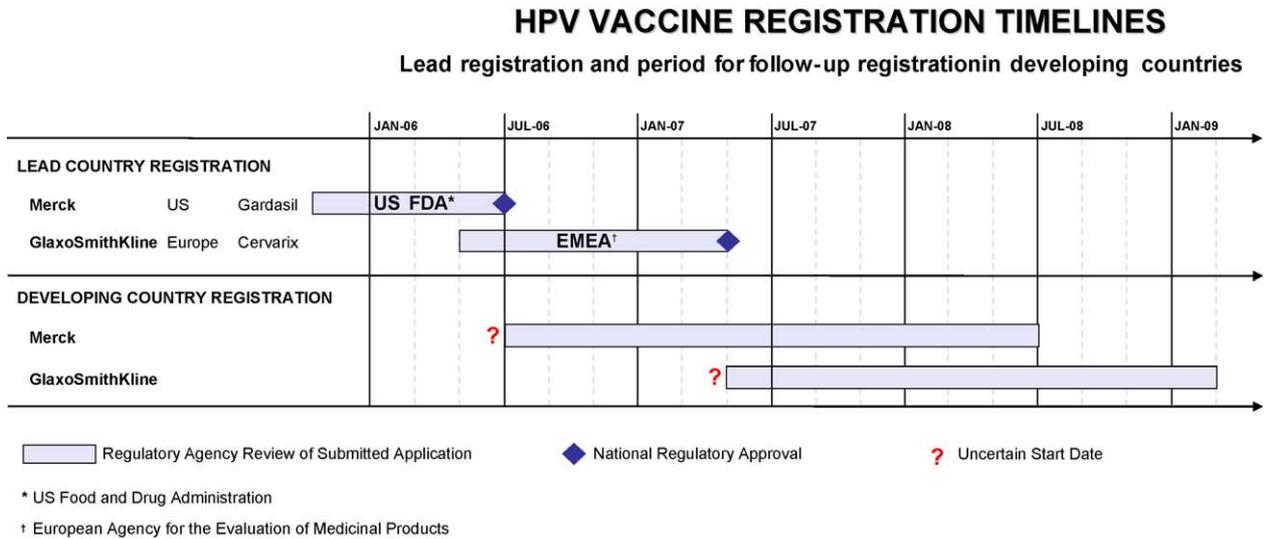


Fig. 1. The expected timeline for national regulatory approval of the Merck and GlaxoSmithKline HPV vaccines in the USA, Europe, and developing countries.

Chiron. The remaining 20% is shared by emerging companies in Asia (e.g. in India, Korea, or Indonesia) and small public- or private-sector manufacturers in industrialized and developing countries [9]. In the short and medium term, the global pharmaceutical firms are likely to remain the primary source for R&D of new vaccines, while the emerging suppliers will play an increasing role in supply of the more mature vaccines through efficient production of high volumes sold to developing countries.

Two highly effective HPV vaccines are in late-stage development, with licensure expected in mid-2006 or early 2007 (Fig. 1). The Merck vaccine (Gardasil®) protects against HPV types 16 and 18 and also against types 6 and 11, which cause genital warts. The GSK vaccine (Cervarix®) only protects against HPV types 16 and 18. Registration in a limited number of middle-income developing countries is expected to begin immediately following licensure in the producing country.

Initial production capacities for the two products were determined 2–4 years before licensure to minimize time to market. While they are unknown, it is likely that the capacity was set primarily to meet forecasted demand from industrial countries. Both firms are prioritising the introduction and promotion of their HPV vaccine in the more predictable and profitable industrialized country markets where significant opportunities exist to recoup their financial investments. Large emerging economies such as Brazil, Mexico and Thailand are considered important second-tier markets for introduction.

Both GSK and Merck have stated their commitment to tiered pricing for their HPV vaccine. However, as neither has indicated the likely price level for the vaccine, affordability is still uncertain.

The entry of other HPV vaccine producers is likely to have a significant impact on available capacity and potentially on pricing. A number of emerging vaccine suppliers from countries such as Brazil and India are exploring the possibility of

producing HPV vaccines. Given the complexity of intellectual property rights for the current technology, the emerging producers may only begin to impact the HPV vaccine market after 2015 or so.

### 5. Need versus demand: estimates for HPV vaccines

The potential market for HPV vaccines in developing countries in terms of need is large; however, demand is much less certain and is expected to ramp-up over a decade or more. While middle-income countries may be able to introduce and scale-up access to a new vaccine such as HPV more quickly than the lower income GAVI countries, Fig. 2 shows the estimated optimistic demand for HPV vaccines in GAVI-eligible countries (demand estimates for HPV vaccines were created by PATH (Program for Appropriate Technology in Health); GAVI-eligible countries have a gross national income of less than \$1000 per capita). The forecast assumes: (1) vaccination of adolescent girls only (11–15 years); (2) catch-up campaigns are not included; (3) an admittedly optimistic peak coverage rate of 80%; (3) a 6-year period from first launch to

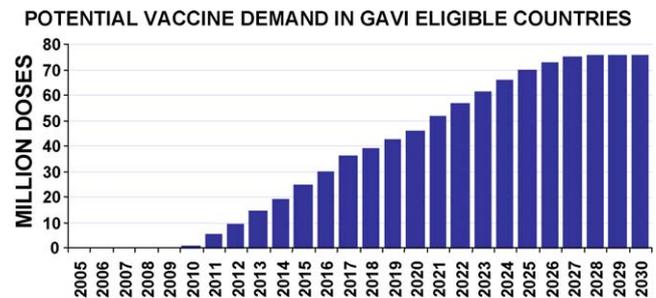


Fig. 2. An optimistic forecast for potential HPV vaccine demand in GAVI eligible countries assuming eventual coverage of 80% of adolescent girls in almost all countries.

peak coverage; (4) demand in GAVI-eligible countries beginning only after developing country impact is demonstrated.

This optimistic forecast should be tempered by the barriers to introduction that exist for HPV vaccines. First, a delivery system to reach adolescents or adolescent females must be adapted or built; in most African countries, vaccination of school-age children is rare except for one-off campaigns for accelerated measles control. Second, social barriers may arise if the vaccine is narrowly targeted at adolescent females. While targeting adolescent girls is the most cost-effective strategy, a focus on girls may elicit fears or generate social barriers to acceptance. As has been seen with tetanus toxoid vaccine, which is targeted at women of child-bearing age, misunderstanding can grow into conspiracy theories that these targeted vaccines are designed to secretly achieve some other purpose, such as preventing pregnancy. Alternatively, if the vaccine is promoted to prevent a sexually transmitted disease, there may be concern that it will increase promiscuity. Third, awareness of policy makers and the general population about the value of the vaccine is unclear. While there is growing awareness about cervical cancer in developing countries at the international level as a result of the work of the Alliance for Cervical Cancer Prevention and others [10], awareness in low-income developing countries remains low. Finally, health ministries face very limited budgets and limited human resources. The relative value of using scarce resources to introduce an HPV vaccine will be compared by each government against the value of using those resources to support a cervical cancer program (e.g. screening and treatment) as well as against investments in immunization and control of other diseases, such as malaria or acute respiratory infections.

## 6. Solutions to accelerate the introduction of an HPV vaccine in developing countries

Incentives to accelerate the development and introduction of priority vaccines in developing countries are broadly classified as push and pull mechanisms. “Push” mechanisms are direct investments in basic research, product development or production capacity; the public sector invests substantially in basic research and some early product development. “Pull” mechanisms provide greater confidence in future sales and their ability to generate a reasonable return on investment, for example by assuring sales volumes or prices. Efforts to assure future markets, such as GAVI’s multi-year commitments to purchase newer and underused vaccines for the poorest countries, is an example of a pull mechanism [11].

Vaccine candidates with high development costs, significant scientific risks and uncertain markets (e.g. no significant industrialized country market) may require both push and pull mechanisms to motivate rapid product development. In the case of HPV vaccines, the anticipated industrialized country market provided the pull to motivate investments in vaccine development. In addition to industrialized country

markets, firms are likely to target middle-income countries in Asia, Eastern Europe and Latin America. By increasing both the value and certainty of HPV markets in lower-income developing countries, the public sector may motivate private investment in the additional capacity needed to serve this population. Direct public investment in expanded production capacity may also be used to negotiate increased supply, lower costs and thus lower prices. However, the introduction of an HPV vaccine in low-income countries will depend not only on each government’s perception of the value of the vaccine and the relative demand for this product given other health options (e.g. rotavirus and/or pneumococcal vaccine or ACT (artemisinin-based combination therapies) drugs), but also the potential of external financing from bilateral donors or global mechanisms.

### 6.1. Public–private partnerships

Push and pull mechanisms are potential solutions to the economic challenges inhibiting rapid development and provision of priority vaccines (or drugs), particularly for poorer countries [11] where disease burden is high but the ability to pay is low. Partnership between the public and the private sectors allows entities to share the risks and the costs of developing, scaling-up, and introducing priority vaccines. Public–private partnerships (PPPs) are playing an increasingly important role in supporting and coordinating efforts to accelerate the investments and work programs necessary to ensure priority technologies reach populations in need [12–14].

### 6.2. GAVI and the GAVI fund (formerly vaccine fund)

Launched in 2000 to improve the access of developing countries to immunization and vaccines, GAVI is a global health partnership comprised of governments from industrialized and developing countries, UNICEF, WHO, the World Bank, the Bill and Melinda Gates Foundation, non-governmental organizations, vaccine manufacturers from industrialized and developing countries, and public health and research institutions. To achieve its mission of saving children’s lives and protecting people’s health through the widespread use of vaccines, GAVI established six strategic objectives for the period 2001–2005 [15,16]:

- improve access to sustainable immunization services;
- expand the use of all existing, safe, and cost-effective vaccines where they address public health problems;
- accelerate the development and introduction of new vaccines and technologies;
- accelerate R&D efforts for vaccines needed primarily in developing countries;
- make immunization coverage a centrepiece in international development efforts;
- support national and international disease-control targets for vaccine-preventable diseases.

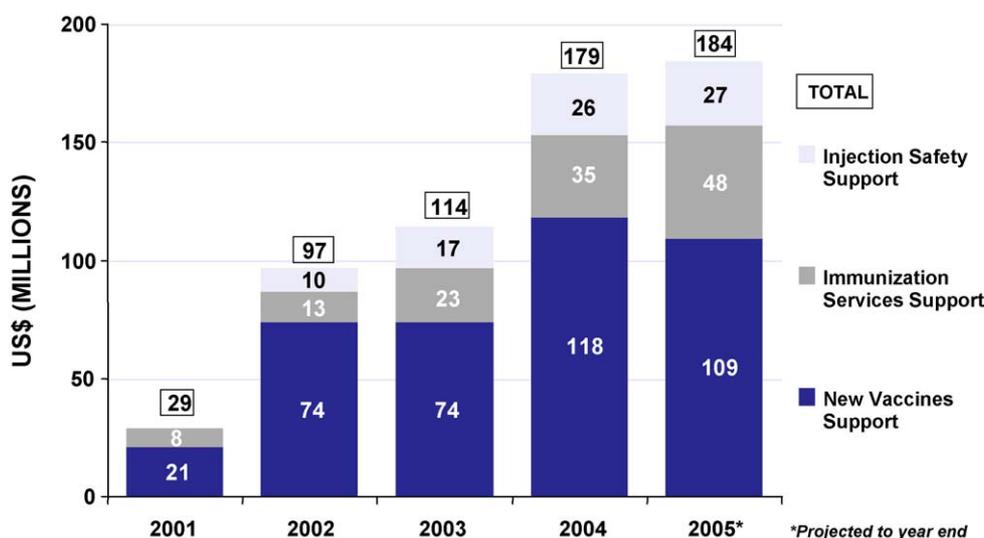


Fig. 3. GAVI support received by countries (overall and by type of support) in the period 2001–2005. Source: The GAVI Alliance ([www.gavialliance.org](http://www.gavialliance.org)) – March 2006 – Presentation by Mercy Ahun on GAVI Phase 2 and IFFIm at the 13th Task Force on Immunization, Brazzaville, Congo.

In its first 5 years (2001–2005), GAVI and its Vaccine Fund (now known as the GAVI Fund) have committed over \$1.2 billion to countries for three activities: (1) the introduction of new and underused vaccines (vaccines against hepatitis B, Hib, and yellow fever) into national immunization programs; (2) support for introduction of safe injection equipment (e.g. auto-disable syringes), which, if properly handled, eliminates the transmission of blood-borne pathogens through injections; (3) performance-based immunization services support aimed at strengthening the “routine” immunization system to increase coverage. Performance, as measured by DTP3 coverage, was verified by an independent data quality audit (DQA). Fig. 3 shows how GAVI funding was disbursed to countries in the period 2001–2005 [17].

Importantly, the financial credibility of GAVI’s financing of hepatitis B and Hib combination vaccines (e.g., DTP-HepB or DTP-HepB-Hib) has resulted in investment in new capacity by firms. A recent study by Boston Consulting Group [18] estimated that five pre-qualified DTP-HepB-Hib vaccines will be available by the end of 2007; three of these are expected from emerging suppliers.

In addition, GAVI has provided support to accelerate the development and introduction of priority new vaccines. Through its Task Force in R&D, GAVI has identified three vaccines that are of high interest: meningococcal group A, rotavirus and pneumococcal vaccines. GAVI has provided funding to accelerate activities in rotavirus and pneumococcal vaccine through the creation of PPPs called “Accelerated Development and Introduction Plans” (ADIPs). Work on meningococcal A vaccine is supported through a separate WHO-PATH partnership that works closely with GAVI.

At the end of its first 5 years, GAVI and the GAVI Fund have supported impressive achievements, with over 90 million additional children immunized against hepatitis B, 14

million against Hib, 14 million against yellow fever and more than 1 billion auto-disable injection devices distributed. It is estimated that GAVI has helped to prevent over 1.7 million deaths by end 2005.

GAVI is now moving into its second phase (2006–2015). To improve and streamline national planning processes for immunization, governments will be required to submit a comprehensive Multi-Year Plan (cMYP) [19] that includes a plan to assure the long-term sustainable financing of national immunization programs, including the introduction of new vaccines.

Additional funding will be raised by GAVI through the international finance facility for immunization (IFFIm). The IFFIm, conceived by the UK as a mechanism to front-load donor funding for development, is being piloted for immunization. It is receiving support from many donors, including the UK, France, Italy, Spain, Sweden, Brazil and Norway, and is expected to rise between \$3 and \$6 billion. The front-loaded resources are raised through the sale of bonds guaranteed by long-term donor commitments.

Funds leveraged through IFFIm will be channelled through the existing governance structures of GAVI and the GAVI Fund to facilitate integration with national plans and policies. IFFIm funds will support the purchase of vaccines, including continued support for hepatitis B and Hib vaccines and possibly new vaccines such as rotavirus, meningococcus A, pneumococcus, Japanese Encephalitis and HPV. IFFIm funds will help finance the higher introductory vaccine prices with co-financing from other countries. IFFIm will also fund: (a) a polio vaccine stockpile to secure supply in case of future outbreaks, (b) supplemental immunization activities (SIAs) such as measles and tetanus mass campaigns, and (c) capacity building in developing country health systems for the delivery of immunization services and maternal and child health programs [17]. The capacity building support

will be untied resources that each government can use as needed to address systemic bottlenecks and strengthen health and immunization systems. While this support is not likely to directly address HPV immunization, it will ultimately increase access to health services and improve the management of all health programs.

### 6.3. Advanced market commitments

An exciting innovative pull mechanism currently being explored is the advanced market commitment (AMC) [20,21]. AMCs have attracted the attention of the G8 Ministers of Finance, who, after review and analysis, have requested a vaccine pilot AMC proposal for launch in 2006. The objective of the pilot is to test this concept, not only for vaccines but for potential application to products in other sectors. An HPV vaccine is one of six candidates under consideration for the pilot, the others being rotavirus, pneumococcal, malaria, HIV/AIDS and tuberculosis.

An AMC is a financial commitment to subsidize the future purchase (up to a pre-agreed price) of a vaccine that is not yet available if the vaccine meets pre-defined standards and is demanded by developing countries. An AMC is not a purchase guarantee, as industry will only receive the subsidized price if countries demand the product after it has been developed.

The AMC establishes a larger and more credible developing country vaccine market at an earlier point in the product-development lifecycle. This will help stimulate manufacturers to make additional investments in the development and production of the desired vaccines and to accelerate their introduction in developing countries. The AMC is based on legally binding financing agreements from donors that ensure resources will be available to pay a subsidized price that is sufficient to justify investment to develop and introduce a successful new vaccine in low-income developing countries. The AMC price is likely to be significantly lower than industrial market prices but still adequate to provide a return on the incremental investments needed to ensure supply to the target countries.

Because AMCs are open to all firms, they can be designed not only to accelerate the development of new and effective vaccines but also to attract additional entrants to increase competition and spur product improvements. An AMC can also provide incentives for firms to invest in more efficient, larger-volume production facilities, thus lowering production costs—an efficiency that can be passed on to countries through lower prices in the long term.

#### 6.3.1. An AMC for HPV vaccines

As two effective HPV vaccines are already in licensure, the objective of an AMC for HPV would be to stimulate investment in additional production capacity to meet demand in the poorest developing countries. Pharmaceutical firms may not have sufficient incentive to invest rapidly in incremental capacity to serve the high volume/low price developing

country markets. There is unlikely to be competition for the HPV market in developing countries until the core intellectual property protection expires around 2015. Without an AMC or other mechanism to encourage the innovator firms to make additional investments to increase the global supply, HPV vaccines will likely have limited availability for at least a decade.

#### 6.3.2. How an AMC works in practice

- Donors sign legally binding agreements to fund the AMC for the target vaccine if the vaccine meets certain agreed standards and if the vaccine is demanded by governments.
- At the outset of the AMC, the vaccine performance standards are established (target product profile—TPP) specifying, for example, the vaccine effectiveness and public health impact in the target countries. In addition, the AMC market size in terms of total financial resources available and the AMC subsidized price per dose are agreed.
- An Independent Assessment Committee (IAC) is established to determine if a new vaccine meets the TPP (performance) standards.
- When a vaccine meets the TPP standards (depending on the vaccine, this could be in 3 years or, in the case of early-stage vaccines, 15 years) and countries decide to introduce the vaccine and pay the low co-payment price, AMC funds are then used to pay the higher subsidized price.
- When the AMC fund is depleted, a manufacturer is obligated to continue to provide some agreed amount of vaccine at a relatively low, pre-agreed price (Fig. 4).

In the case of HPV, the predictable financing of an AMC and the increased predictability of prices once the AMC is depleted would help to create demand in developing countries and provide an incentive to the two firms licensing the vaccine to invest in larger production facilities. The AMC would not only ensure greater supply of HPV but would allow firms to take advantage of scale economies, thus lowering the costs

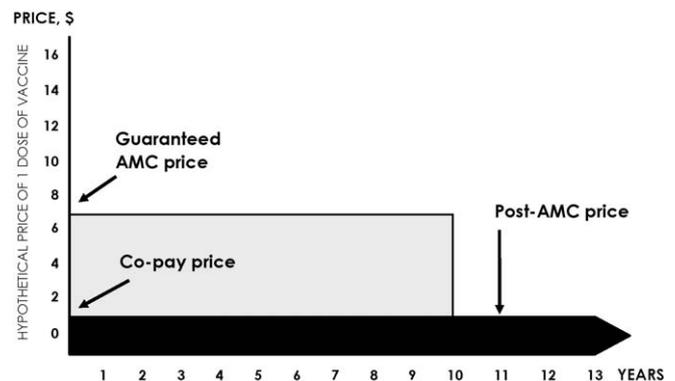


Fig. 4. Advanced Market Commitment (AMC) mechanism where manufacturers commit to supply a vaccine at a pre-guaranteed price. Developing countries pay a low co-payment price and AMC funds are used to pay the pre-agreed price. When AMC funds are depleted, manufacturers continue to provide the vaccine at a relatively lower price (which could be the same as the co-payment price).

of production. These lower costs would, ideally, be passed on to countries through lower prices once the AMC is depleted. More importantly, the AMC includes a mechanism for firms to set the long-term, post-AMC price so that developing country governments can be assured of predictable future prices when making introduction decisions.

AMCs reduce the risk that the global public health system will not have funds to purchase desired new vaccines and, because of the increased predictability, AMCs may help create demand. However, firms still face significant uptake risk given weak national health systems, poor forecasting and limited budgets to support related immunization delivery costs. To maximize the potential success of this mechanism, AMCs must be linked with efforts to provide governments with evidence needed for timely introduction decisions and to translate national decisions into realistic – and accurate – forecasts for new vaccines.

AMCs are a valuable complement to existing efforts to accelerate the development, production and introduction of priority new vaccines, although they are neither a panacea nor the sole option available. Direct push investment in vaccine development or, in the case of HPV, production capacity are also viable alternatives, and in some cases, critical complements to a pull mechanism like AMCs.

HPV vaccine introduction will depend not only on adequate global capacity and affordable prices but, more importantly, it will also depend on national and global efforts to strengthen health and immunization systems, improve surveillance and screening programs, and ensure governments have the evidence and capacity to prioritize resource allocations within the larger health sector plan.

### Disclosed potential conflicts of interest

Authors have disclosed no potential conflicts of interest.

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