

Giving developing countries the best shot: An overview of vaccine access and R&D



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Executive summary

Vaccines have made possible some of the greatest public health successes of the past century. Immunisation helps avert an estimated 2.5 million child deaths each year, as well as millions more bouts of illness and disability.¹ Poor countries as well as rich have benefited, although developing countries almost always benefit only after long delays. Basic childhood immunisation is one of the few health interventions to which most of the world's poor have access, free of charge and through the public sector. In fact, immunisation is one of the most equitable health interventions, protecting girls and boys alike, and reaching the poor within countries at higher rates relative to the wealthy than other services.²

Despite their impact, vaccines have generally received less attention than drugs. But the vaccine landscape is shifting, and new opportunities, challenges, and debates have pushed vaccines to the centre of global health discussions. The issues are complex and the experience gained in the struggle for access to HIV medications is an imperfect guide. The basic principles—equitable access and research and development (R&D) based on needs—are the same, but vaccines differ from drugs in important ways.

There are multiple factors that make delivering vaccines to children in developing countries difficult. These include – among others – high prices of newer vaccines, the lack of R&D for better-adapted and needed vaccines, as well as weak health systems with corresponding health worker shortages. This paper will focus on the first two points, outlining some of the major issues and exploring possible solutions.

Two fundamental challenges surround vaccine access and R&D: First, the newest vaccines are often prohibitively expensive, in part because of a lack of adequate competition in the market, hindering their use in developing countries. Second, because there is little incentive for pharmaceutical companies to conduct R&D for diseases that affect populations with limited purchasing power, some diseases continue to be unaddressed by vaccines altogether, while many vaccines are not well-adapted for people in developing countries.

Challenges in expanding access to newer vaccines

Basic immunisation coverage has improved substantially in recent decades. According to WHO/UNICEF estimates, coverage of the third dose of the DTP (diphtheria-tetanus-pertussis) combination vaccine, a standard measure of immunisation coverage, reached about 80% in 2007 – a remarkable increase from only 20% in 1980.³ Nonetheless, 26 million children – roughly one in five born each year – remained unimmunised globally.⁴ Wider use of available vaccines could help avert a further two million deaths annually in children under five years.⁵

The Global Alliance for Vaccines and Immunization (GAVI) was founded in 2000 to expand the scope and accelerate the delivery of newer vaccines to children in the poorest countries. Initially, GAVI focused on adding two newer vaccines to the basic package: Hib (*Haemophilus influenzae* type b) and hepatitis B – vaccines that were already in routine use in wealthy countries by the early to mid 1990s.⁶ By the end of 2008, global coverage of the Hib vaccine was 28%, while Hep B was 69%.⁷ While this demonstrates important progress, it also illustrates the lag in vaccine delivery between developed and developing countries.

GAVI is currently focusing on adding two newer vaccines that have been introduced in wealthy countries over the last several years: vaccines to prevent the severe diarrhea caused by rotavirus and vaccines to prevent pneumococcal disease, which together account for 1.3 million child deaths per year.⁸ It is also looking to provide a new meningitis vaccine, the human papillomavirus (HPV) vaccine that helps prevent cervical cancer, and several others. The goal is to shorten dramatically the delivery time lag between rich and poor countries.

Yet since these newer vaccines remain relatively expensive, and since GAVI is facing serious funding shortfalls, ambitious introduction plans may be jeopardized. GAVI's ability to provide broad access to newer vaccines will depend on bringing prices down dramatically, as well as on filling the multi-billion dollar funding gap. Of the U.S.\$7 billion it will need for the five-year period until 2015, GAVI has secured only 40%, leaving a \$4.3 billion funding shortfall.⁹

Although an increasing number of developing country 'emerging' producers (from whom 53% of vaccines funded by GAVI are purchased)¹⁰ have entered the global vaccine market, the new and most expensive vaccines continue to be produced by a handful of multinational pharmaceutical companies whose oligopoly status allows them to charge high prices.

There has been considerable consolidation in the vaccine industry, with global vaccine revenue largely in the hands of just five companies: GSK, Merck, Novartis, Sanofi-Pasteur and Wyeth/Pfizer. The limited number of innovative firms – along with patent protection and the large economies of scale for vaccines – result in markets for new kinds of vaccines typically being controlled by one or two companies for long periods of time.

These companies do employ ‘tiered pricing’, and have agreed to provide the new vaccines to GAVI at significant discounts for use in the poorest countries. However, these tiered prices are almost certainly higher than those that could be achieved through competition. And the problem for middle-income countries is even more acute, as they do not qualify for GAVI-negotiated prices. Although middle-income prices are lower than those charged in wealthy markets, they often exceed substantially the prices offered to other developing countries. Middle-income countries are thus faced with the difficult decision of introducing these new vaccines at the expense of other national health priorities, limiting introduction to only the highest-risk groups, or not introducing them at all.

The key to bringing prices down significantly – and thereby enabling wider coverage of newer vaccines – will be the competition generated by emerging suppliers entering the market. However, emerging suppliers face multiple barriers to swifter market entry: the increasing complexity of newer vaccines; increased regulatory stringency; lack of technological capacity; and intellectual property barriers. Unlike with medicines, though, building capacity among emerging vaccine suppliers requires intensive technology, or know-how, transfer, as it is not possible to simply reverse-engineer a vaccine. There is, in essence, no such thing as a ‘generic vaccine’, as it is impossible to certify that vaccines produced by different manufacturers are identical. Therefore, as with biologic drugs, vaccines cannot be licensed based on ‘bioequivalence’ to already-licensed products.

One way to address the know-how challenge is with the ‘hub’ model, whereby a public or non-profit institution provides a training platform for emerging suppliers, as opposed to relying on bilateral technology transfer relationships between individual producers.

Weak national regulatory authorities in emerging suppliers’ countries also constitute a barrier to their market entry, as approval by a domestic regulatory body is a prerequisite to applying for quality assurance by the World Health Organization (prequalification). WHO prequalification, in turn, is required for vaccines to be procured by GAVI/UNICEF.

Challenges in vaccine research and development

As with drugs, vaccine R&D is dominated by the paradigm of multinational pharmaceutical/vaccine companies charging high prices for products tailored to wealthy markets. Companies argue that high prices are needed to recoup R&D costs. This model distorts R&D priorities such that companies are not necessarily developing products to tackle the greatest global medical needs and are not producing products that are adapted to the particular needs of developing countries. In addition, companies are not necessarily producing products in a manner that ensures the lowest cost, focusing instead primarily on bringing vaccines to market as quickly as possible, as even a few months of advance over competitors can bring big commercial gains.

Most of the basic research upon which vaccine development depends continues to be carried out by universities and public laboratories, with multinationals assuming the later stages of vaccine development and marketing. With their large revenues, experience and expertise, companies have been able to bring new vaccines through the expensive and time-consuming development process. However, the public sector has historically played an important role in vaccine R&D in the U.S. and Europe. For example, the U.S. Army led the development of several vaccines after World War II. Re-engaging the public sector in vaccine R&D could help close the R&D gap.

Because the pharmaceutical industry for the most part does not conduct R&D targeted to developing country health needs, alternative mechanisms to stimulate needs-based R&D must be employed. There are several models that aim to either ‘push’ R&D via upfront funding (e.g. product development partnerships – PDPs), or to ‘pull’ R&D via incentives that entice industry to invest in developing needed products (such as advance market commitments, prize funds and GAVI itself).

An example of a successful ‘push’ mechanism is the Meningitis Vaccine Project, a PDP established in 2001 by PATH and WHO that has developed a needed vaccine to address a specific strain common in Africa’s ‘meningitis belt.’ Technology was licensed through the U.S. National Institutes of Health to the Serum Institute of India, which agreed to provide the vaccine at an affordable price in exchange for transfer of know-how support for clinical trials in Africa and India, and the prospect of a GAVI-supported market. The total project cost amounted to just \$60 million, excluding plant costs, and the vaccine is expected to be available for use in Africa toward the end of 2010. While this project

represents a success story, and shows how emerging suppliers can play an increasing role in vaccine R&D, the model will mainly be useful for adaptations of existing vaccines with known technologies, rather than for the development of entirely new and more complex vaccines, such as those for TB, malaria and AIDS.

An example of a successful ‘pull’ mechanism is GAVI itself, which through its long-term purchase commitments sends a signal to industry that developing countries are a viable and long-term market. However, GAVI’s pull has not been strong enough to stimulate the development of new and sophisticated vaccines.

The advance market commitment (AMC) model is a pull mechanism that ideally promotes needed vaccine R&D by guaranteeing a subsidized market for the resulting product if it meets certain specifications and is purchased by countries/donors. But the AMC launched by donors in 2009 to accelerate delivery of pneumococcal vaccines was aimed at two vaccines that were already in final stages of development and close to gaining marketing approval, thus rendering it more a procurement mechanism than an R&D incentive. It is possible that these vaccines could have been purchased as – or more – cheaply through conventional UNICEF tender procedures than with an AMC. Whether or not the pneumococcal AMC accomplishes its goals, the question will remain whether this is an appropriate mechanism to stimulate the development of new

vaccines, as originally hoped. While well-designed AMCs could play a role in mid-stage development or for less complex vaccines – as a complement to public sector research funding, PDPs, and other push mechanisms – they are unlikely to be a practical way to drive R&D for challenging early-stage vaccines that face substantial scientific obstacles.

Prize funds are another innovative pull mechanism to stimulate health-needs-driven R&D while securing access to a product at an affordable price upfront. The prize awarded to a successful product developer would be linked to the product’s public health impact, and producers may be asked to agree in advance to sell the product at an affordable price. Several prize fund proposals are on the table, but none has yet been established for vaccine development.

Because several new vaccines with vital implications for developing countries have come to market recently, every effort must be undertaken to ensure that children in these countries gain access to them. This will depend both on raising additional funds and bringing prices for newer vaccines down by accelerating the entry of emerging suppliers into these markets. Technology and know-how transfer will be crucial, and will also help emerging suppliers to assume a larger role in vaccine R&D. And innovative models to stimulate R&D will be critical to meeting still-unaddressed vaccine needs.

Background

Overview of vaccines and immunisation

In all countries, the basic package of vaccines comprises at least the six vaccines that were included in the original WHO Expanded Programme on Immunization (EPI): BCG (against tuberculosis), polio, measles, diphtheria, tetanus, and pertussis (the last three make up the DTP combination). With the help of funding from the Global Alliance for Vaccines and Immunization (GAVI), most countries also provide or are about to introduce vaccines against Hepatitis B (Hep B) and Haemophilus influenza type b (Hib). Vaccines against rubella, mumps, and yellow fever are also widely used in developing countries.

Three new vaccines important to developing countries have been developed in the last decade: the pneumococcal conjugate, rotavirus, and HPV vaccines. Pneumococcal disease causes over 800,000 under-five deaths in developing countries and between one and four million episodes of pneumococcal pneumonia in Africa alone.¹¹ Rotavirus causes over 500,000 deaths every year.¹² Thus, the new pneumo and rotavaccines could have a major impact on child mortality. Human papillomavirus (HPV) is the cause of cervical cancer, which kills more than 260,000 women each year, more than 90% of them in developing countries. The new HPV vaccines could theoretically prevent about 70% of these deaths. These vaccines command large markets in the developed world, but they are far more expensive than older vaccines and are not yet widely available in low- and middle-income countries. Much of the policy debate over vaccines in the last few years has focused on how to make these important vaccines available to poor countries.

Furthermore, several important new vaccines are in development, including the first vaccines against malaria and dengue fever as well as improved or cheaper versions of vaccines against meningococcal disease, Japanese encephalitis, cholera, typhoid and tuberculosis. Vaccines against other infectious diseases and even against some non-communicable diseases, including cancer, are being pursued. HIV vaccines would have an enormous impact, but are many years away.

Finally, the 2009 influenza scare – and the controversy over allocation of a limited supply of vaccines – brought about a belated recognition that developing countries are at least as vulnerable to pandemic flu and other unpredictable global epidemics and need fair access to protective vaccines.

Vaccine markets

Vaccines make up a small (about 3%) but rapidly growing segment of the global pharmaceutical market. Total sales are expected to grow from about \$20.5 billion in 2008¹³ to \$34 billion by 2012¹⁴. Sales in low- and middle-income countries were estimated at about \$1.6 billion in 2008¹⁵, or less than 10% of the total. UNICEF, which buys most vaccines for low-income countries and many for middle-income countries, procures 40% of global vaccine doses, which, however, account for only 5% of global market value.¹⁶ But low- and middle-income country markets are expected to contribute substantially to future growth.

This is a remarkable turnaround for an industry that was widely perceived to be in decline just a few years ago.¹⁷ Reports of firms abandoning vaccines¹⁸ have been replaced with giddy celebrations of blockbuster sales. Much of the new enthusiasm of industry and investors for vaccines derives from the unprecedented commercial success of two products, Wyeth's pneumococcal vaccine Prevnar and Merck's HPV vaccine Gardasil, each of which brought in more than \$2.8 billion in sales in 2008. These huge revenues were made possible by very high prices (over \$300 for a three-dose course of Gardasil), which have shattered the notion of vaccines as low-margin commodities.¹⁹

Vaccine suppliers and business models

Vaccine manufacturers are conventionally divided into two groups: the established multinational firms based in the U.S. and Europe, and the “emerging suppliers” based in developing countries. Mergers and the departure of many firms from the vaccine business in recent decades have left the first segment of the vaccine industry extraordinarily concentrated:²⁰ the five top multinational firms (GSK, Merck, Sanofi-Pasteur, Wyeth - now part of Pfizer -, and Novartis) accounted for about 85% of global sales in 2008.²¹ Their share of the market is much lower in volume terms, however, as the emerging suppliers produce large volumes of cheaper vaccines.

Traditionally, multinational vaccine companies, building on publicly funded basic research, have been responsible for most vaccine innovation, drawing on their greater revenues, experience, and expertise to bring new vaccines through the expensive and time-consuming development process. Their business model depends on charging high prices for new vaccines in order to recover R&D costs and return large profits to their investors. Bringing vaccines to market as quickly as possible is typically more important to them than achieving the greatest efficiencies in production.

The multinational firms are primarily focused on high-price, relatively low-volume rich-world markets, which provide the great bulk of their revenues. But there are important differences among the firms. GSK and Sanofi have long experience in developing-country markets, public and private, and both sell in large volumes to UNICEF, together accounting for 52% of UNICEF's purchases in 2006. These manufacturers derive real if modest profits from sales in developing countries, which thus constitute an integral part of their business models. In contrast, Merck²² and Wyeth have only entered these markets recently and in many ways are still refining their approach. At least initially, they appeared to be motivated more by a sense of corporate responsibility (or by the fear of adverse publicity) than by a belief that low-income markets offer meaningful commercial opportunities. Both firms have explored donation strategies, but donation is not a sustainable business model and programmes are vulnerable to management turnover and changes in corporate strategy.

The emerging suppliers are a more diverse group that includes both traditional state-owned firms devoted to supplying national programmes with basic vaccines and privately owned manufacturers. Several of the private firms, particularly in India, have expanded rapidly and now supply a significant proportion of basic vaccines purchased by UNICEF. A few of the public manufacturers in developing countries have also begun to export their products and consider sales to other developing countries and public sector buyers such as PAHO and UNICEF. Among the more important and forward-looking public sector firms are Brazil's BioManguinhos and Butantan, China's Chengdu, and Indonesia's Biofarma; private firms with WHO-prequalified vaccines include India's Serum Institute, Panacea, Shanta, and Biological E. Both public and private sector emerging manufacturers are represented by the Developing Countries Vaccine Manufacturers' Network.²³

The emerging suppliers have traditionally sold older, less complex vaccines in high-volume, low-margin markets (emerging suppliers provide 86% of traditional vaccines globally²⁴). To thrive in these markets, they have focused on exploiting cost advantages rather than innovation. This is changing, however, and the more ambitious firms are increasing their investment in R&D and looking to develop more complex vaccines and, eventually, to enter high-income markets. Emerging manufacturers already produce Hepatitis B- and Hib-containing vaccines, included the pentavalent vaccines, and several firms are developing rotavirus, pneumococcal conjugate, and Japanese encephalitis vaccines, among others. Serum Institute's new Meningitis A conjugate vaccine has just been licensed (see below).

However, the emerging manufacturers are still well behind the multinational firms in technology, know-how, and regulatory expertise. Many are quite proficient at scaling up manufacturing processes for mass production but are still quite weak in earlier stages of R&D.

Building the innovative capacity of emerging suppliers will make markets more competitive and lessen, but not eliminate, dependence on the multinationals for new vaccines. For vaccines with both high-income and developing-country markets, tiered pricing is one way to facilitate access in low- and middle-income countries until competition can reduce prices for all, and generate vaccine versions tailored to developing-country needs. Yet many developing countries that do not qualify for the lowest price are dissatisfied with the current tiered pricing schemes and have resisted implementation of tiered prices for new vaccines. For vaccines with little prospect of rich-world sales, push funding, or perhaps large prizes, which de-link the price of a product from the cost of R&D, may be the best way to cover R&D costs while keeping prices low. These issues are discussed in more detail in the following sections.

Access to vaccines

A majority of the world's children now receive a set of basic childhood vaccines, but millions more remain unimmunised and several important newer vaccines have yet to reach children in most developing countries. The major barriers to access are high vaccine prices, inadequate financing for immunisation, and weakness of national immunisation systems. This paper will not address health system issues but will focus on price and financing. Since increasing the number of suppliers is a powerful way to reduce vaccine prices, this section will also discuss barriers to entry of new manufacturers.

The current situation

The struggle to bring vaccines to the world's poor has shifted dramatically in recent years. Several developments have brought real improvements for children in the poorest countries.

First, basic immunisation coverage has improved substantially, bringing, at the least, the six EPI vaccines to about 80% of the world's children, according to WHO/UNICEF estimates. These vaccines are very cheap, so weak health systems constitute the primary obstacle to expansion and maintenance of coverage.

Second, the creation of GAVI in 2000 has provided new resources for the purchase of more expensive vaccines on behalf of low-income and some lower-middle-income countries. (Eligible countries were defined at GAVI's inception as those with a GNI per capita below \$1,000; in 2011, the threshold will be increased to \$1,500 GNI per capita).²⁵ These funds have enabled most eligible countries to introduce Hep B and Hib vaccines, and should soon allow the introduction of rotavirus and pneumococcal conjugate vaccines as well, if GAVI's current financial challenges can be overcome.

Third, the major multinational vaccine firms have accepted in general the principle of providing their products to the poorest countries at discounted prices through UNICEF. At the same time, emerging suppliers have entered the UNICEF/GAVI market for all but the newest vaccines, increasing competition and contributing to significant price reductions for some vaccines, especially Hep B. Prices for other vaccines, notably the pentavalent combination vaccines (GAVI funds the pentavalent vaccine combining DTP, Hib and Hep B vaccines into one), have not yet fallen as rapidly as anticipated.

These developments have improved access to vaccines in GAVI-eligible countries. But GAVI's own finances are now under severe strain. The organisation will be challenged to honor existing commitments and is unlikely to finance the large-scale purchase of additional vaccines for some time. The Bill and Melinda Gates Foundation in January 2010 announced that it will commit \$10 billion to research, development and delivery of vaccines over the next decade.²⁶ To date, however, it remains unclear if any of these funds will be allocated specifically to GAVI.

Moreover, the situation in middle-income countries, which receive very little donor support for immunisation, is increasingly contentious. The pharmaceutical industry sees these countries, especially the rapidly growing "emerging economies" such as Brazil, China, and India, as potentially lucrative markets, and is not willing to provide new vaccines to these countries at the same low prices it offers to UNICEF/GAVI. There is growing concern that these countries, in particular those with incomes only slightly above the GAVI threshold, may not be able to afford new vaccines or may be forced to divert funds from other health programmes to do so. As a result, middle-income countries, especially those that procure vaccines through PAHO, have become the new battleground over vaccine prices.

International financing for vaccine purchase

GAVI

Even the poorest countries are generally able to purchase the six basic EPI vaccines from their own health budgets, but many would not be able to afford the newer vaccines without external assistance. GAVI was created in 2000 to accelerate the adoption of new and underused vaccines in poor countries; it spent about \$600 million in 2008, mostly to purchase vaccines through UNICEF for 72 eligible low- and lower-middle-income countries. GAVI has helped most of these countries introduce Hep B and Hib vaccines, and it is poised to finance the introduction of rotavirus and pneumococcal vaccines.

There is no doubt that GAVI has done a great deal to facilitate access to vaccines among the poorest countries. But it is currently facing a serious financial crisis: spending on pentavalent, rotavirus, and pneumococcal vaccines is expected to push total expenditures to \$1.6 billion in 2013 while expected resources fall from a peak of \$1.0 billion or so in 2010 (see Figure 1). (The expected fall in resources comes in large part from a big decline in income from the International Finance Facility for Immunisation after 2010. The IFFIm was designed to “frontload” resources for immunisation by issuing bonds in capital markets that are to be subsequently paid off through donor pledges of future support). Unless donor pledges increase dramatically or a new source of funding is found, GAVI will have to make difficult choices in the

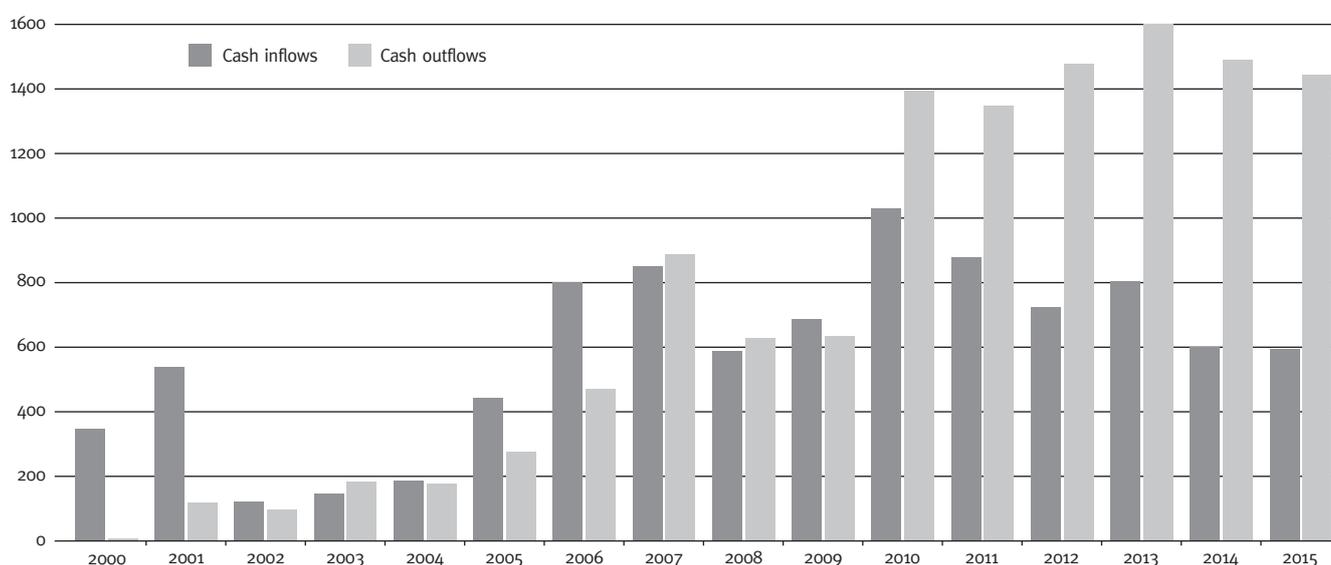
next few years. It may have to delay support for some vaccines, prioritise approved applications from eligible countries, or dramatically increase the share of vaccine costs borne by countries (“co-financing” rates).

In this more difficult fiscal environment, GAVI’s goal of introducing new vaccines as soon as possible in developing countries will depend on accelerating a decline in prices, both by facilitating the entry of new suppliers and by placing greater emphasis on price in procurement. In vaccine procurement, however, price must be balanced against security of supply and the need to keep the GAVI/UNICEF market attractive to a range of firms.

The situation of middle-income countries

Even if GAVI can sustain its current model, it will not be able to expand its support to the bulk of middle-income countries for the foreseeable future. When the GAVI Board’s recent decision on eligibility policy takes effect in 2011, eligibility will be limited to countries with per capita GNI below \$1,500 (taking inflation into consideration, this is roughly equivalent to \$1,000 in 2000).²⁸ This change will reduce the number of eligible countries from the current 72 to about 58, although existing support for the graduating countries will continue at least through 2015. The Board also increased the minimum level of immunisation coverage that countries must achieve before they can introduce new vaccines with GAVI support; this provision will affect several large countries, including India.²⁹

Figure 1: GAVI’s projected resources and expenditures²⁷



Middle-income countries face a double challenge in affording new vaccines: they have almost no access to international assistance to buy vaccines, but at the same time they must pay significantly higher prices than GAVI countries for many vaccines as a result of industry's practice of tiered pricing (see below). As a result, many of these countries will have trouble introducing the new pneumococcal and HPV vaccines. Approaches to ensuring access to new vaccines in middle-income countries are discussed below in the section on tiered pricing.

The pneumococcal Advance Market Commitment

An advance market commitment (AMC) is an innovative financing model that subsidizes pharmaceutical companies for the development and production of new vaccines. The subsidy is meant to reduce the risk for pharmaceutical companies of investing in products for developing country markets with limited purchasing ability, and is only paid once a vaccine meeting certain specifications is purchased by eligible developing countries (or donors on their behalf) at a pre-set price. The subsidy covers an agreed volume of vaccines, after which a predetermined and lower long-term price (also called 'tail price') is offered to countries. This aims to ensure the vaccine's use is sustained beyond the duration of the subsidy.

GAVI and UNICEF will procure the new pneumococcal conjugate vaccines through an AMC. Although AMCs were originally proposed as a way to stimulate development of new vaccines for neglected diseases, the two leading pneumococcal vaccines were already in advanced development for high-income markets when the AMC was launched (GSK's 10-valent conjugate, marketed as Synflorix, and Wyeth/Pfizer's 13-valent conjugate, marketed as Prevnar 13). The AMC may accelerate development of a pneumococcal vaccine by one or more emerging suppliers, but it is serving primarily as a procurement mechanism rather than an R&D incentive. The pneumococcal AMC has been criticized as too expensive and too complicated, and as favoring the multinational firms over emerging suppliers.³⁰ It is possible that these vaccines could have been purchased as, or more, cheaply through conventional UNICEF tender procedures, and the use of this complicated new mechanism to buy almost-licensed vaccines has certainly confused the discussion. Moreover, the agreement includes no provisions to encourage technology transfer to developing country manufacturers. But if the pneumococcal AMC works as hoped, it will bring a new generation of pneumococcal vaccines to many of the world's poorest countries at almost the same time they are introduced in the rich world.

Pfizer and GSK signed on to the AMC in March 2010, committing to supply 30 million doses of vaccine each for ten years,³¹ but it remains to be seen whether developing country producers will be able to meet AMC requirements and tap into allocated funds before these are exhausted. In addition, the implications for the AMC of the new GAVI eligibility policies will have to be worked out, in particular the higher immunisation coverage requirement and the likely graduation of several countries in 2011. Whether or not the pneumococcal AMC accomplishes its goals, the question remains whether this is an appropriate mechanism for stimulating development of new vaccines, as originally hoped. This issue is addressed in the R&D section.

Vaccine prices

Vaccine prices, like those of other products, are shaped by the balance of supply and demand. But several unusual features of vaccine markets have a strong influence on prices in developing countries. First, markets for new kinds of vaccines tend to be controlled by one or at most two firms for extended periods, because of the very small number of innovative multinational firms, the large economies of scale in vaccine production, and patent protection. This lack of competition gives originating firms substantial freedom to set prices during the first phase of a vaccine's lifecycle, before additional suppliers enter the market. Second, this supplier market power is balanced in part by the market influence of public sector purchasers, in particular the 'pooled procurement' mechanisms operated by UNICEF and PAHO. Third, 'tiered pricing,' or market segmentation by national income, is increasingly standard (see below). Fourth, the large fixed costs and long lead times required to build new manufacturing plants mean that predictability of demand is very important to manufacturers, who will offer lower prices in return for long-term commitments.

Production costs are not in general an important component of the price of new vaccines in rich-world markets, where firms are able to charge well above cost. And while some margin is necessary to recover R&D costs, actual prices are not determined in a simple way by, or justified by, R&D costs. But marginal cost of production does set a floor for the bottom tier of new vaccine prices (prices charged in GAVI countries) and become an important determinant of price in mature, competitive markets. Production costs in turn vary considerably among classes of vaccines, by production volume, and by site of production: emerging suppliers have significant cost advantages in some but not all cases.

Thus, prices of vaccines in low- and middle-income countries for new vaccines tend to be determined initially by the pricing practices of the multinational originator firms. Marginal cost of production sets at least a theoretical minimum for the poorest countries. The speed at which new firms can enter the market is the key factor over the longer run, however, as prices can be expected to fall in all markets with increased competition and, in many cases, lower production costs for emerging suppliers. But vaccine technology can constrain how far prices can fall even with competition and production efficiencies.

Tiered pricing of vaccines and the PAHO controversy

The multinational vaccine firms all support – and practice, to the extent they are free to do so – tiered pricing: a policy of charging high prices in rich countries, low prices in GAVI countries, and intermediate prices in middle-income countries. Tiered pricing is less central to the business models of the emerging manufacturers, who typically sell older vaccines in more competitive markets.

For firms, tiered pricing is a profit-maximizing strategy: by charging different prices to classes of customers with different willingness and ability to pay, they are able to maximize profits in high-income countries while earning money in countries that cannot afford rich-country prices. Tiered pricing also helps firms prevent or defuse criticism over high prices. For developing countries as a whole, tiered pricing is clearly preferable to a situation in which all countries paid the same high price. With respect to vaccines, low-income countries benefit the most from tiered pricing, receiving the lowest prices, although the prices they pay under this system are not necessarily as low as they would pay in fully-competitive markets. The practice of charging higher prices in middle-income countries than in the poorest countries has been contentious, however. Firms argue that middle-income countries, especially better-off upper-middle-income countries such as Brazil, have substantially greater capacity to pay for vaccines than do GAVI countries. Middle-income countries argue that their populations include many poor people and that the prices they are asked to pay are in any case too high and very high in relation to what least-developed countries pay.

The controversy over tiered pricing came to a head in 2009 in a dispute between firms and the PAHO Revolving Fund, a pooled procurement mechanism used by most countries of the Latin American region. The Revolving Fund, which has helped member countries to strengthen immunisation systems and introduce new vaccines, has until recently been able to buy most vaccines at prices very similar to those paid by UNICEF on behalf of GAVI (see Table 1). But

the suppliers of the new pneumococcal conjugate and HPV vaccines insisted that PAHO must pay more than GAVI; PAHO, in turn, insisted on a so-called “most-favored nation” (MFN) clause in its contracts with suppliers that requires that PAHO receive the lowest prices available to any purchaser, including UNICEF.

PAHO’s decision not to procure the new GSK and Wyeth vaccines, at least in the short run, removed the obstacle that the dispute over the MFN clause posed to the launch of the AMC. However, this conflict may re-emerge later in 2010 when UNICEF begins to procure rotavirus vaccines on behalf of GAVI.

Since the current state of GAVI’s finances will delay purchase of HPV vaccines, the most immediate threat posed by the PAHO conflict has been to GAVI procurement of pneumococcal vaccines. PAHO is currently paying \$65 to vaccinate a child (\$21.75 per dose) for three doses of the Wyeth 7-valent vaccine, while the AMC will pay \$21 to vaccinate a child (\$7.00 per dose) (and eventually \$10.50 per child (\$3.50 per dose)) for three doses of the superior – and more expensive to produce – 10- and 13-valent vaccines.

It is difficult to know how much middle-income countries outside the PAHO region pay for vaccines, since these prices are not in general made public. Anecdotal evidence suggests that these prices vary a great deal, with some lower-middle-income countries that procure through UNICEF receiving prices close to those paid by GAVI, while others pay much more.

Tiered pricing can help developing countries (and GAVI) to afford new vaccines in the initial period before the entry of additional suppliers makes markets more competitive. But these prices must address the needs of all developing countries. While many middle-income countries have somewhat greater capacity to pay for vaccines than the poorest countries, higher prices mean fewer resources for other health priorities. PAHO should continue using its collective bargaining power to ensure that the mark-up charged by firms is modest. Other regions would probably benefit from creating similar pooled procurement mechanisms, which can strengthen countries’ bargaining power vis-à-vis firms.

The problem of vaccine affordability is particularly acute for lower-middle-income countries, as some of these countries will soon become ineligible for GAVI subsidies. One measure that would help is to allow these countries to continue to procure through UNICEF at GAVI prices. At the same time, PAHO and GAVI should avoid being played off one another by the firms and develop joint strategies that further their shared interests.

Table 1: UNICEF, PAHO and U.S. public sector prices in 2010³²
(U.S.\$; 10 dose vials unless otherwise indicated)

Vaccine	UNICEF/ GAVI*	PAHO*	U.S. public sector	No. of doses as per WHO recommend- ations	Cost of vaccination UNICEF/GAVI/ per child	Cost of vaccination PAHO/ per child	Cost of vaccination U.S./ per child
BCG (PAHO 20 dose vial)	0.11	0.10	--	1	0.11	0.10	--
DTPw	0.18	0.15	--	3+1	0.72	0.60	--
MMR (Zagreb strain for UNICEF & PAHO)	0.93	0.92	18.64	2	1.86	1.84	37.28
Yellow Fever	0.90	0.65 Brazil Origin 1.15 France Origin	--	1	0.90	0.65-1.15	--
HepB (1 dose vial)	0.27****	0.28	10.25	3+1**	1.08	1.12	41.00
Hib (lyophilized)	3.40 (1 dose vial)	2.25 (1 dose vial)	8.66 (10 doses vial)	3+1**	13.60	9.00	34.64
DTP-HepB-Hib (pentaval- ent; 1 dose vial, liquid)	2.94	3.20	--	3+1	11.76	12.80	--
Rotavirus	***	5.15 Rotateq 7.50 Rotarix	59.18 Rotateq 83.75 Rotarix	3 Rotateq 2 Rotarix	***	15.45 Rotateq 15.00 Rotarix	177.54 Rotateq 167.50 Rotarix
Pneumococcal (7-valent for PAHO and U.S., 10- or 13-valent for GAVI)	7.00 (via AMC)	20.00	91.75	3	21	60.00	275.25

* Weighted average prices per dose.

Minimum calendar (plus booster) for children less than 5 years old.

Full vaccination package (including booster) included in cost of vaccination.

** The booster doses for Hep B and Hib are not officially recommended in the WHO guidelines, but they are listed as an option if given in combination vaccine. Prices are based on including the 4th dose (booster dose).

Booster not financed by GAVI (only for 1-11 month old children).

*** Not yet procured by UNICEF/GAVI.

**** Weighted average prices per dose from 2009.

Over the longer run, more efficient solutions should be explored that would cover the cost of developing new vaccines appropriate for developing country populations while allowing prices to fall closer to marginal cost (see R&D section). Middle-income countries can and should contribute to these solutions. In the absence of new models of funding R&D, measures that accelerate the entry of new suppliers would help to bring prices of new vaccines down more rapidly (see table 1).

Manufacturing costs

Manufacturing costs do not in general directly determine vaccine prices, which are set by profit-seeking firms in markets that are more or less competitive. But they do set a floor below which prices cannot fall even in tiered pricing or highly competitive situations. Vaccine production costs include variable costs associated with each dose of vaccine (“cost of goods”), which include

the cost of the vaccine components, vials, and so on; “semi-fixed” costs associated with each production batch, including quality tests; and the fixed costs of plant and equipment. Fixed and semi-fixed costs make up the bulk of total cost, typically contributing 60% and 25% respectively; this gives vaccine manufacture large economies of scale, since average costs fall with increasing volume over a large range.³³

The main factors that determine manufacturing cost are vaccine and production technology, presentation, and manufacturing scale. Location of production matters, as some costs are lower in developing countries. Design choices are also critical, and market incentives in rich countries may drive the development of more complex—and thus expensive—vaccines than are required for public health impact.

Technology: Vaccines of different types can have dramatically different costs of production (see Figure 2). At one end of the spectrum, simple live-attenuated vaccines such as oral polio or measles can be produced in very large batches from very inexpensive inputs, and cost no more than a few pennies per dose. At the other extreme, the new pneumococcal conjugate vaccines require the manufacture or purchase of purified bacterial polysaccharides, conjugation of these polysaccharides to a protein carrier, mixing and carefully balancing of component vaccines against as many as 13 bacterial strains or serotypes, and a very large number of quality control steps. These vaccines cost \$1-3 per dose to produce not counting the cost of the plant itself.

Production technology also determines batch size, which is itself an important determinant of cost, since some expenses are incurred on a per-batch basis.

Access to technology and superior know-how may give the multinational firms a cost advantage in some cases. On the other hand, emerging suppliers, for whom reducing cost is a greater concern, may be more motivated to realize efficiencies.

The cost of producing technologically sophisticated vaccines can be expected to come down over time as firms accumulate experience and as more efficient production technologies are developed. But the nature of some vaccines makes them intrinsically more costly to manufacture than others. For this reason, choices made during the earliest stages of vaccine development have critical consequences for later manufacturing cost. Once a technology has been chosen, producers are largely locked in. For example, it will probably be necessary to switch to an entirely different vaccine

concept to achieve a low-cost pneumococcal vaccine with broad serotype coverage.

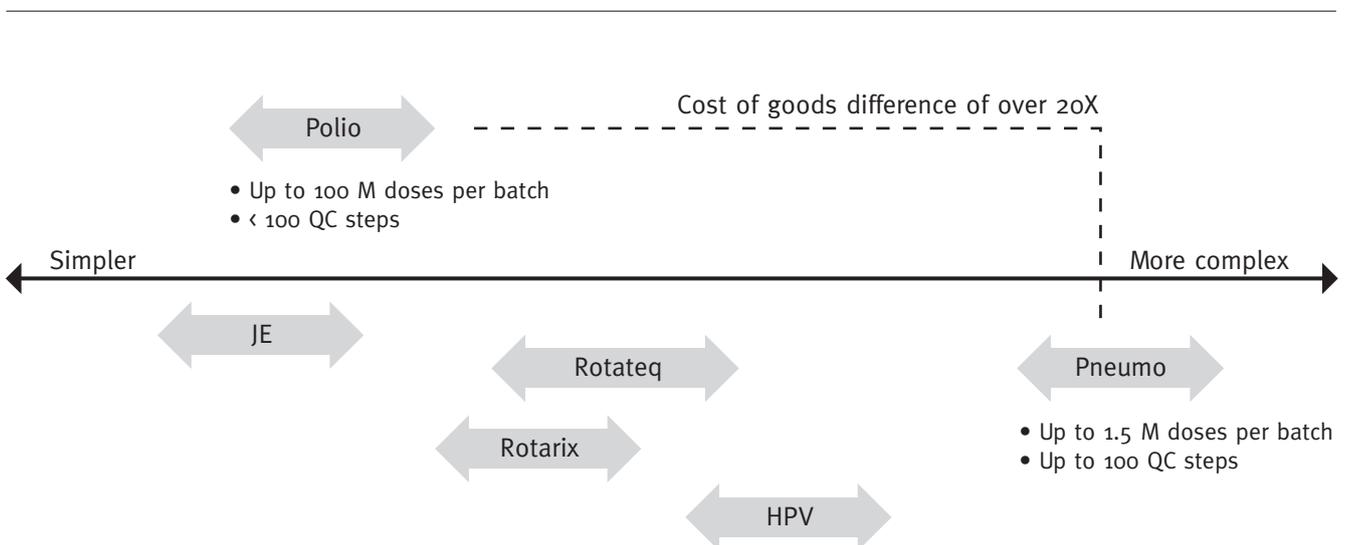
Presentation: The form in which vaccines are packaged and the number of doses per unit can also contribute significantly to cost: pre-filled syringes are more expensive than single dose vials (and less suitable for developing countries); 10-dose vials are cheaper per dose than 1-dose vials. The relative contribution of presentation to total cost is greater for cheaper vaccines. With more expensive vaccines, the risk of wastage can outweigh the cost benefits of multi-dose presentations.³⁴

Scale of operations and capacity utilization: Because of the importance of fixed costs, a plant producing 100 million doses per year will in general have lower costs per dose than a plant producing 50 million doses per year. As a rule, emerging suppliers serving high-volume, low-margin markets tend to build larger plants. This can have a significant impact on vaccine production costs.

These gains from scale are realized only if plants produce at full capacity: per dose costs will be higher to the extent that capacity is underutilized.

Location of operation: Lower costs of brick and mortar construction generally make vaccine plants cheaper to build in developing countries, even if much of the equipment has to be imported. The labor costs of operating a plant are also significantly lower in India or China than in Europe or the U.S.³⁵ In addition, the EMEA/FDA regulatory environment imposes some additional quality control and operations costs. With increasing harmonization in good manufacturing practices (GMP) standards and increasing labor costs however, this difference is shrinking.

Figure 2: Relative complexity of different types of vaccines



Determining the cost of a specific manufacturing plant is difficult, mainly because manufacturers often build plants that produce multiple vaccines, making the attribution of the portion of the plant that deals with a single vaccine difficult. Further, the number of doses produced by a plant is often kept vague. However, a review of facilities constructed in the past decade³⁶ suggests that costs for multinational firms range from \$200 to \$400 million, with additions to existing facilities costing less than \$200 million and multiple vaccine plants up to \$700 million. Emerging manufacturers generally have much lower costs, which are usually less than \$100 million and can range from less than \$50 million up to \$150 million.

Barriers to new entrants

Facilitating the entry of new suppliers is the most powerful way to accelerate the decline in prices of new vaccines in developing countries. But would-be producers of versions of new vaccines, especially emerging suppliers, face a more complicated set of obstacles than generic drug producers.

Increasing complexity of, and regulatory stringency towards, new vaccines work together with know-how and intellectual property (IP) obstacles to delay the entrance of competitors and preserve markets for the largest companies.

Technological sophistication and access to know-how: Although patent barriers are becoming more important (see below), the primary obstacle to the development and production of newer, more complex vaccines by emerging manufacturers has been lack of technological capacity. While the leading manufacturers in India, China, and Brazil are investing more in R&D and closing the technology gap, their capability still lags well behind that of the multinational companies. This slows or prevents the development of versions of existing vaccines as well as entirely new vaccines. Unlike small-molecule drugs, vaccines are not easily reverse-engineered, as the greatest challenges often lie in details of production processes that cannot be inferred from the final product. Thus proprietary “know-how” is often the greatest impediment to the entry of new suppliers into markets for sophisticated vaccines.

Lack of a generic pathway: Vaccines, like biologic drugs, cannot be licensed on the basis of “bioequivalence” to already licensed products, essentially because it is in general impossible to certify that vaccines made by different manufacturers are identical. Even when a new vaccine is closely modelled on an existing one, its safety and efficacy must be independently demonstrated in clinical trials. Thus, there is technically

no such thing as a generic vaccine. Although the WHO prequalification process works quite well to endorse follow-on versions of vaccines, in some cases with abbreviated requirements for trials, this remains an important distinction between drugs and vaccines.

Regulatory requirements: The most ambitious emerging suppliers, who hope to gain access to high-income markets, are preparing to meet increasingly stiff regulatory requirements. Moreover, there is some tendency for the standards set by national regulatory authorities in developing countries and by the WHO in its prequalification process to converge with those of the FDA and EMEA, especially in the area of good manufacturing practices (GMP). Meeting these standards increases costs. But the WHO prequalification process has been highly successful, and it remains a practical way for developing country firms to sell their vaccines to UN agencies and enter markets in other low- and middle-income countries. The weakness of national regulatory authorities (NRAs) remains a problem, however, both because approval by a functioning regulator in the manufacturing country is a requirement for WHO prequalification (which is in turn a requirement for all vaccines procured by UNICEF/GAVI), and because many vaccines purchased from domestic manufacturers are not prequalified.

Intellectual property: Historically, patents were not considered as important a barrier to follow-on vaccine suppliers as access to technology and proprietary know-how. But patents are apparently an impediment in the case of HPV vaccines, for example, and IP barriers, as well as data exclusivity provisions, are likely to grow in importance. Developing country manufacturers state that circumventing these barriers may in some cases delay their efforts to introduce competing vaccines by years. As is often the case, the new technologies that underlie the HPV vaccines were developed in publicly-funded academic labs, and the adoption by universities of more open licensing policies that facilitated production by multiple suppliers in developing-country markets would be an important step. Governments need to examine the impact of patents on vaccine availability and make use of flexibilities enshrined in the TRIPS agreement to limit the negative impact of patents. Manufacturers in developing countries will also have to build their capacity to manage IP.

In some cases, the formation of ‘patent thickets’ can impede the development of new classes of vaccines as well as the entry of competitors.³⁷

Capital: Interestingly, private-sector emerging manufacturers do not describe access to capital as a barrier to entry, although it is an issue for many publicly-owned manufacturers.

Summary of access challenges

- GAVI has greatly improved access to vaccines such as Hep B and Hib in low-income countries, but a dramatic funding shortfall is endangering its commitment to introduce the pneumococcal and rotavirus vaccines, as well as its plans to support purchase of HPV and other important vaccines. The impact of the economic crisis on donors and the high prices of these new vaccines, which are still supplied only by multinationals, are the main causes of GAVI's financing troubles. A truly competitive market for pentavalent, another important GAVI vaccine, has also been slower to emerge than expected, contributing to persistently high prices.
- Most middle-income countries are not eligible for GAVI support, and growing market segmentation has led to a conflict between GAVI and PAHO over pricing of new vaccines. Any efforts to promote access and affordability must keep middle-income countries in mind. A more comprehensive approach could include new pooled procurement mechanisms (modeled on PAHO's Revolving Fund), access to GAVI prices for some countries that might not qualify for subsidies, regional exports by government-owned producers such as Brazil's BioManguinhos, and forms of tiered pricing acceptable to middle-income countries.
- Shortening the time it takes for competitive products to reach market is probably the most promising strategy to make vaccines more affordable for countries and donors. Strategies that could help to reduce barriers to entry include:
 - Mechanisms for facilitating technology transfer;
 - Mechanisms for preventing or removing patent barriers, including open licensing policies on the part of universities and government research bodies and the use of TRIPS flexibilities when appropriate; and
 - Procurement policies that support competition and, at a minimum, do not inadvertently reinforce the dominance of the handful of established multinational suppliers.

Vaccine research and development

Although ensuring access to the many useful vaccines we already have is an immediate priority, new vaccines are also urgently needed. There are no licensed vaccines against HIV, malaria, dengue, or any of the other tropical parasitic diseases, and only a grossly inadequate vaccine against tuberculosis. Improved vaccines are needed against cholera and typhoid fever, as well as new vaccine formulations and presentations more suited to use in low-income settings.

This section begins by reviewing the current system of vaccine R&D. It then outlines some of the obstacles to development of needed vaccines for low- and middle-income countries and a range of possible solutions.

Because the entry of new suppliers into vaccine markets is one of the most important ways to drive down prices and ensure access, and because new suppliers of vaccines (unlike generic drug producers) must carry out substantial development and testing of their products, many of the issues raised in this chapter are relevant to access as well as to the development of entirely new vaccines.

Overview of vaccine development

Vaccines are very different from drugs: vaccines are highly complex macromolecules or whole organisms designed to stimulate the immune system to fight disease pathogens, while most drugs are small molecules that directly inhibit disease processes. But vaccine research and development, like drug

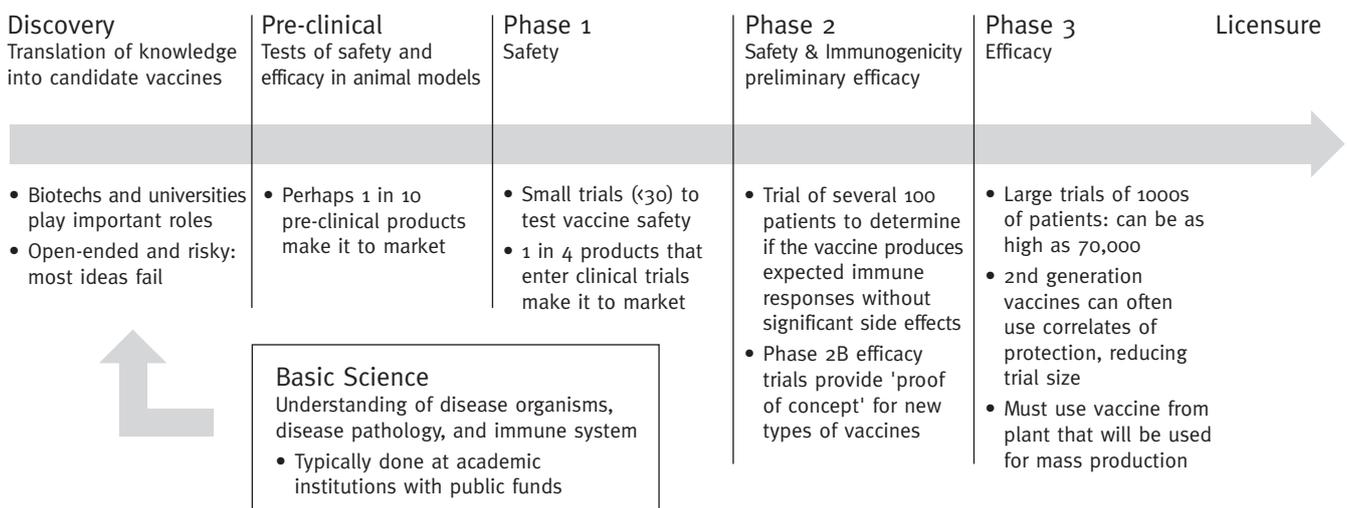
development, involves progression through a series of increasingly expensive phases, from exploratory research in the laboratory to large-scale clinical trials and development of manufacturing processes. Candidate vaccines can fail at any stage, making R&D a very risky undertaking. Perhaps a quarter of products that enter clinical trials reach market. Figure 3 provides a snapshot of the research and development process for vaccines.

Although the later stages of vaccine development are now carried out largely by industry, and in particular by a handful of multinational firms, the public sector plays a very important role. Most basic research is done at universities and public laboratories,³⁸ which also contribute to discovery in many cases. Biotech companies are also increasingly important in early stage R&D. The R&D capacity of emerging suppliers in developing countries is growing rapidly, and public sector manufacturers remain important in several important middle-income countries, including Brazil, India, China, Indonesia, and Mexico. Historically, the public sector played a more important role in vaccine development in the U.S. and Europe, as well – the U.S. Army in particular developed many important vaccines. Rebuilding public sector capacity to develop and test needed vaccines may be an important element of a public health strategy.

Regulatory approval of vaccines

Like drugs, vaccines are licensed by national regulatory authorities (NRAs), which require evidence of efficacy (in this case prevention of infection or disease), safety,

Figure 3: Stages of vaccine research and development



and quality, including proof of good manufacturing practices (GMP). New vaccines developed by the big multinational firms are typically licensed first by the U.S. FDA or the EU's EMEA, while vaccines produced by developing country firms are usually approved first by their own NRAs.

Manufacturers from either developed or developing countries hoping to supply developing countries (other than their home market) must also be prequalified by the WHO. Prequalification, which is required for purchase by UN agencies, including UNICEF and PAHO, is intended to ensure that vaccines used in national immunisation services are safe and effective for the target populations and that packaging and presentation are appropriate. The WHO standards are rigorous but distinct from those set by the FDA and EMEA, and the prequalification process is thus a vital alternative to approval by a rich-world regulator.

For a vaccine to be considered for prequalification, the national regulatory authority in the country of manufacture must be considered functional by WHO. Strengthening regulatory agencies, especially in the key exporting countries, is thus crucial to a strategy that relies in large part on the emerging suppliers.

A few points are worth noting:

1) Demonstration of efficacy for an entirely new vaccine or class of vaccines requires a large placebo-controlled trial, in which rates of infection or disease in people who receive the vaccine are compared to rates in the placebo group. Developers of subsequent vaccines against the same disease and relying on the same mechanism of protection may not have to demonstrate reduced incidence. If study of previous trials has established a so-called correlate of protection (a level of immune response to the vaccine above which individuals are protected), regulators will accept evidence that the new vaccine consistently produces this protective response in lieu of incidence data. This can sometimes make much smaller trials possible.

2) Safety standards for vaccines have become almost absurdly stringent in recent decades, especially in the U.S., in part because the public in high-income countries is no longer particularly concerned about the diseases vaccines are intended to prevent. As a result, there is no longer the sense that safety risks should be balanced against benefits. While from a public health perspective this may be unfortunate for the U.S. and Europe, it is a much more serious problem for developing countries, which might set this balance differently but find it technically and politically challenging to set a different safety standard than is used in the U.S. and Europe.

The most well-known case of regulatory stringency is that of Wyeth's rotavirus vaccine RotaShield, which was approved in the U.S. in 1998. The vaccine was taken off the market one year later after 15 children developed intussusception, a serious side effect. As a result, developing countries, where rotavirus infection is estimated to kill more than half a million children every year, were also unwilling to use RotaShield. A recent study by the CDC showed that the number of lives saved in high-burden countries by a vaccine like RotaShield would greatly outnumber new cases of fatal intussusception.³⁹

But the cost of excessive regulatory stringency is not only that a particular vaccine will not come to market but also that all vaccines become more expensive. The developers of the next generation of rotavirus vaccines had to conduct trials of unprecedented size in order to rule out this very rare side effect (GSK did a trial involving 61,000 children), and developers of all vaccines are aware that side effects too rare to be detected in trials of ordinary size could result in their vaccines being taken off the market.

3) As with drugs, there is no completely satisfactory regulatory pathway for new vaccines that have no market in the U.S. or Europe. Although the WHO prequalification programme works well for "follow-on" vaccines, most developing country regulators still lack the capacity to rigorously evaluate wholly new vaccines. One option is the EMEA's new Article 58 procedure, under which the agency will offer an "opinion" on a vaccine that will not be marketed in Europe. This is the route that GSK and the Malaria Vaccine Initiative (MVI) will take with the RTS,S malaria vaccine. The FDA has announced a similar programme. In the long run, the best solution is to build the capacity of regulatory agencies in the countries where new vaccines will be used, and in countries such as India, Brazil, and China that can produce and increasingly develop new vaccines for use in developing countries. One promising route to this end is regional regulatory harmonization or even consolidation. An example is the use of the South African Medicines Control Council as a regional regulatory reference in southern Africa.

R&D costs

The costs of each of the stages of vaccine development vary greatly, accordingly to the scientific difficulty, technology, trial sizes, and the type of product developer. Table 2 gives ranges for each stage.

Although actual expenditure on a particular licensed vaccine can be determined ex post by adding up the costs of each stage of research and development, such an approach underestimates the true cost of vaccine R&D (and the likely cost of developing a new vaccine) because it leaves out the cost of failure: expenditures on vaccine candidates that didn't make it to market. Taking the risk of failure at each stage into account gives the following formula for average total expenditure on clinical development per licensed product:

$C = (C1 + C2 * P1 + C3 * P1 * P2) / (P1 * P2 * P3)$, where C1, C2, C3 and P1, P2 and P3 are the costs and probabilities of success of the different phases of clinical trials. The formula is easily extended to include discovery, preclinical and licensure phases.

Using this approach and the probabilities and cost ranges presented in Table 2 gives an estimate of total risk-adjusted R&D cost of \$135-\$350 million, not including basic research or the cost of building a manufacturing plant.

These estimates are at best gross averages. Very challenging vaccines such as malaria and TB (not to mention HIV) can be expected to cost more, while "easy" vaccines or those that are substantially based on already licensed vaccines, will cost much less to develop, as trials may be smaller and chances of success at each stage much higher. Discovery costs are particularly variable, as this phase can be quick for new versions of existing vaccines but essentially open-ended for research into entirely new classes of vaccines.

A final issue in considering the cost of R&D is the cost of capital. Private sector developers, who must raise money in capital markets to finance vaccine development, take into account the cost of this money

(essentially an interest rate) in calculating total R&D costs.⁴² Governments and foundations do not bear these expenses in the same way, although a rigorous accounting of the true public sector cost should at least include the cost of public borrowing.

Alternative models for R&D

The current profit-driven system of pharmaceutical R&D has worked fairly well to deliver new, albeit increasingly expensive vaccines with large markets in the developed world. But the system does not work to generate vaccines for diseases that affect predominantly low- and middle-income countries, whose markets do not offer sufficient revenues to motivate industry investment in R&D on the necessary scale. This problem is well recognized; a variety of solutions have been proposed and some are being tried. Even in the case of diseases that affect both high-income and developing countries, such as pneumococcal disease or HPV, the current system has important deficiencies. Because vaccines against these diseases are developed primarily for rich-world markets, they may not be well suited to low- and middle-income countries, where the distribution of disease serotypes may be different and different presentations may be needed.⁴³ Perhaps most importantly, the new vaccines may be very expensive to manufacture, even though an R&D strategy that considered cost from the start might have led to far less expensive, but still useful, vaccines.

Ideally, then, alternative models of vaccine R&D would result in new vaccines against "neglected" diseases of developing countries as well as versions of existing vaccines more suited to developing countries needs and circumstances. Some proposed approaches are designed to fill specific gaps in the current pharmaceutical R&D system, while others promise a more sweeping transformation that would align R&D investment with public health need and eliminate many of the distortions of the current system. This section provides a brief overview of some of these mechanisms.

Table 2: Estimated costs of research and development (U.S.\$ millions)⁴⁰

Stage	Discovery ⁴¹ & Preclinical	Phases 1 & 2	Phase 3	Licensure	Total
Cost	5 – 15	4 - 10	50 - 120	2 - 3	60 - 145
Chance of success	40%	33%	75%	N/A	10%
Risk-adjusted cost					135-350

Most solutions to the lack of neglected disease R&D involve public or philanthropic funding to compensate for the lack of commercial investment, but this funding can come in a variety of forms. Direct grants to universities, public researchers, or firms to carry out R&D are often called “push” funding: funding of this type pays directly for R&D or reduces the costs or risks to commercial product developers. “Pull” mechanisms, in contrast, seek to increase the reward to successful development of a new drug or vaccine in the hope of motivating developers, typically private sector firms, to invest their own resources in R&D. (Rich-world markets can themselves be considered a powerful pull mechanism, especially when the reward to innovators is increased by the temporary market exclusivity conferred by patent protection.) While push funding remains the mainstay of neglected disease R&D funding, several innovative pull mechanisms have been implemented or proposed in recent years. The following sections will consider several promising financing models.

While funding is essential to any strategy for neglected disease R&D, access to technology is also crucial. Some ideas in this area are outlined in the last section.

Push funding

In addition to public funding of university research, the leading approach by which governments and foundations currently try to drive development of vaccines for the developing world is the “product development partnership” or PDP. Vaccine PDPs, which include the Malaria Vaccine Initiative, the Aeras Global TB Vaccine Foundation, and the International AIDS Vaccine Initiative, channel funding from donor governments and foundations, especially the Gates Foundation, toward a portfolio of discovery and clinical development partnerships with universities, biotechs, and pharma companies. PDPs are popular with donors and with industry, but it is too early to know if they will prove successful in the long run: no licensed vaccines have yet resulted from their efforts. The Malaria Vaccine Initiative can serve as an example of a vaccine PDP.

The Malaria Vaccine Initiative (MVI)

MVI, established by PATH with funding from the Gates Foundation, seeks to accelerate the development of malaria vaccines and ensure their availability and accessibility. MVI manages a series of partnerships with universities, biotechs, the U.S. military, and big pharma. Its most clinically advanced candidate is RTS,S, a product originally developed by the U.S. military in the 1980s and now owned by GSK. After several phase 2b trials, it is now being tested in a large phase 3 trial in several African countries. MVI

is sharing the costs of these trials with GSK, using a grant of just under \$200 million to MVI from the Gates Foundation. In exchange, GSK has agreed to an undisclosed set of volume-dependent price ceilings. It is difficult to know if these prices are substantially different from the prices GSK would have asked if it had developed the vaccine without help from MVI.

Trials conducted to date suggest that RTS,S will be at best an imperfect vaccine, with an efficacy of approximately 50% against clinical disease and relative short duration of protection. It could nonetheless have a significant impact, given the enormous toll of malaria in sub-Saharan Africa.

MVI’s role in the development of RTS,S has been primarily to subsidize clinical development by GSK. Although it is impossible to know for sure what path the vaccine would have taken without this subsidy, it is likely that development would have been abandoned or greatly slowed: GSK had apparently terminated work on RTS,S until MVI began to share costs.⁴⁴ Malaria vaccines in general have at best modest rich-world markets among travelers and the military; RTS,S will have no market at all outside Africa. GSK will derive an important indirect commercial benefit from testing RTS,S, however, because the vaccine includes a new adjuvant that could be used in other vaccines with big markets.

MVI became involved with RTS,S late in the game and played little or no role in the design of the candidate or in supplying needed technologies. It was thus not in a position to choose a development partner or to influence production costs. But given the difficulty of developing a malaria vaccine – a challenge that has defeated researchers for decades – working with GSK on RTS,S was the only option available to MVI likely to result in a licensed vaccine in the next decade. MVI is working with a number of partners on other R&D projects, but all of these are at quite early stages and none are assured of success.

The Meningitis Vaccine Project (MVP)

The Meningitis Vaccine Project (MVP) is an intriguing model of vaccine development for developing countries, in which a vaccine with specific characteristics tailored to a particular population is developed at a modest cost and provisions to ensure sustainable access are built in from the start. Although similar to the larger vaccine PDPs, its approach has differed in several ways.

The MVP was established in 2001 by PATH and WHO to develop an effective and affordable vaccine to combat the epidemics of bacterial meningitis, caused mostly by group A strains of *Neisseriameningitidis*

(“meningococcus”), which plague the so-called “meningitis belt” in sub-Saharan Africa.⁴⁵ While polysaccharide vaccines have been available for many years, they have limited duration of protection and are not effective in very young children.⁴⁶ So-called “conjugate” vaccines, like the one produced by Sanofi, in theory overcome these disadvantages. But the Sanofi conjugate vaccine, an ACYW-strain tetravalent, is more expensive to produce (four conjugate vaccines instead of just one). Even at a heavily discounted price, it would likely remain far more expensive than a monovalent vaccine.

After identifying and licensing an appropriate conjugation technology from the U.S. FDA and negotiating with several possible industrial partners, the MVP reached agreement with Serum Institute of India (SII) to produce the new monovalent meningitis A conjugate vaccine at an affordable price for the African market. In exchange for price and supply commitments, SII benefited from transfer of technology and know-how. PATH funded the clinical trials.

Significant progress has been made. In December 2009 market authorization for the Men A conjugate vaccine was granted by the Drugs Controller General of India and the WHO prequalification process has begun. Plans are being made for introduction at public health scale in Burkina Faso in late 2010.

The total research and development costs for this vaccine are estimated to be about \$60 million, not including the cost of the manufacturing plant; SII has committed about \$15 million to the project.

The MVP’s approach differs in some respects from that of the larger PDPs:

- Focus on low cost: Consultations at the start of the project established that to ensure long-term access a vaccine should cost no more than \$0.50/dose. MVP emphasized this requirement in discussions with vaccine manufacturers. The agreement between SII and MVP is also notable for its transparency: although all PDPs include access provisions in their agreements with industrial partners, these provisions are generally not made public.
- Focus on a single candidate and single supplier: Unlike most product development partnerships that maintain a portfolio of vaccine candidates, MVP focused on a single candidate and on SII as the sole supplier. The relatively high probability of success in making a monovalent conjugate vaccine lowered the risk when compared to a malaria or TB vaccine, where the risks of R&D failure are high.
- Partnership with an emerging supplier: The choice of an emerging supplier was critical to achieving

the goal of low cost, in part because the access to technology and visibility associated with the project made the partnership more attractive to SII than to a multinational firm. In addition, producing for a high-volume, low-margin developing country market was consistent with SII’s established business model.

- Public sector technology transfer: The transfer of a non-exclusive license for an efficient conjugation technology through the NIH Office of Technology Transfer, coupled with active transfer of know-how, was central to the success of the project.

To a great extent, these choices were made possible because several meningococcal conjugate vaccines had already been developed, the technologies were well understood, and correlates of protection for Meningitis A were known. These data made focusing on one candidate a reasonable bet, allowed emerging suppliers to be considered as manufacturing partners, and kept costs relatively low. The MVP model is therefore particularly suited to the development of adapted versions of vaccines based on established technologies, such as for rotavirus, pneumococcal or HPV vaccines. On the other hand, the development of AIDS, TB and malaria vaccines is far more challenging and probably requires different models.

Other forms of push funding for vaccine development are under discussion, including new funds that would pool donor resources and allocate them among PDPs and possibly firms, proposals to use bond markets to raise long-term funding for PDPs, as well as currency transaction levies or financial transaction taxes.

An alternative to the PDP model of publicly subsidized collaboration with the private sector would be to rebuild capacity in the public sector to develop and test vaccines. The public sector, notably the U.S. Walter Reed Army Institute of Research, played the leading role in the development of several important vaccines, including vaccines against influenza, mumps, and meningitis, especially in the decades following World War II.⁴⁷

Pull funding

A simple example of pull funding is the existence of an organisation like GAVI, which, by obtaining commitments of several billion dollars from donors, served to signal to industry that the poorest countries could be a viable market. However, the existence of this subsidised but still low-margin market is not sufficient to drive the development of new and sophisticated vaccines, although it has almost certainly accelerated the introduction of follow-on vaccines from emerging suppliers.

Advance Market Commitments

The pilot AMC for pneumococcal vaccines, discussed above, is primarily a procurement mechanism. However, AMCs were originally proposed as a way to stimulate the development of new vaccines for developing countries by creating an artificial market sufficient to motivate private investment in R&D. If a second AMC is created – and discussions among GAVI, the World Bank, and certain donors have begun – it is likely that it would seek to test the value of this mechanism for earlier-stage vaccines. The daunting scientific obstacles facing HIV vaccines make them an unappealing choice; this leaves malaria and tuberculosis vaccines as the front-runners, although other diseases are also possible (see below).⁴⁸ In fact, the original expert committee that chose pneumococcal vaccines for the pilot suggested that malaria should be chosen if a second AMC were funded.

At least in theory, AMCs are an elegant solution to the problem of lack of private-sector investment in developing-country vaccines without large markets. But an early-stage AMC would face several serious challenges that did not have to be considered in designing the pneumococcal AMC.⁴⁹ First, the terms of an early-stage AMC, especially its size, are difficult to set, since costs, risks, and potential returns cannot be estimated with any precision, and neither the identities nor the number of likely competitors is known. Second, it is not clear that the university labs or biotech companies whose participation in R&D is most needed at early stages can be easily reached by the distant pull of an AMC. Third, an AMC, as an inherently competitive mechanism might interfere with the networks of collaboration and information-sharing that have been built by PDPs and other neglected disease R&D funders. Finally, and perhaps most importantly, an AMC of this kind would almost certainly have to be very large to attract substantial investment – potentially so large as to be politically infeasible. The very high discount rates used by industry, coupled with the long time to market and the very high risks, mean that only the prospect of very large returns could drive decisions to invest on purely commercial grounds.⁵⁰

Given these difficulties, AMCs by themselves are probably not a practical way to drive R&D for challenging early-stage vaccines or those facing substantial scientific obstacles. They could have a role, however, as a complement to public sector research funding, PDPs, and other push mechanisms. Some assurance that donors would pay a respectable price, at least enough to cover the costs of plant and manufacture and phase 3 trials might help to ease the hand-over from public sector researchers or PDPs to a firm capable of bringing a new vaccine to market, once the major

obstacles had been overcome. There may be a role for well-designed AMCs in mid-stage or less difficult vaccines, those that have demonstrated some promise in preliminary efficacy trials or for which similarity to existing vaccines offers a likely path to success.

FDA Priority Review Vouchers

According to this new U.S. programme, launched in 2008, any organisation that wins FDA approval for a new drug or vaccine against a defined list of neglected diseases is eligible for a “priority review voucher” (PRV) entitling the holder to expedited FDA review of another new drug application. The voucher is transferrable: it can be sold to and used by another organisation. Since priority review allows a new product to be marketed sooner – and thus extends the period of market exclusivity—the voucher could substantially increase returns from a blockbuster drug: one study estimated that it could be worth as much as \$300 million.⁵¹ In theory, then, the prospect of winning a PRV could be a powerful incentive for firms to pursue neglected disease R&D. Like an AMC or a prize, the PRV is a pull mechanism focused primarily on motivating neglected disease R&D by the for-profit pharmaceutical industry. One PRV has been awarded so far, for Novartis’ malaria drug combination Coartem. Since Coartem has been on the market for several years outside the U.S., in this case the PRV did not reward new neglected disease R&D.

It is too early to say whether PRVs will prove an effective incentive for neglected disease vaccine development. An important flaw in the legislation is that it includes no access provisions: firms are not required to manufacture or distribute a winning product, let alone make it available in developing countries at an affordable price, or, as an alternative, to permit generic supply.

Prize funds

The current pharmaceutical R&D system depends primarily on high prices in rich-world markets, buttressed by patent-protected market exclusivity, to cover R&D costs. Although this system has provided a strong incentive for the development of some important vaccines, it distorts both R&D priorities (toward products with large markets) and prices (which are kept well above marginal cost of production). Some advocates have proposed a system of large prizes for new drugs and vaccines as a way to solve both problems. Incentives would be aligned with social benefit by making the amount of the payoffs proportional to public health benefit, while access (and economic efficiency) would be maximized by facilitating or requiring prices close to marginal cost. Prizes are therefore a pull mechanism that allows the cost of R&D to be uncoupled from the price of

the product. The prizes would come from a large and regularly replenished public fund. These ideas were first developed by Knowledge Ecology International (KEI);⁵² a more recent proposal called the Health Impact Fund is derived from the KEI proposal but differs from it in several ways.⁵³

If prize funds could be implemented and managed successfully, they would offer comprehensive reform of the pharmaceutical R&D system, aligning R&D investment with public health need and driving down prices of new medicines. These ideas face formidable political, financial, and practical challenges to implementation on a large scale. They are so compelling, however, that they should be tested on a smaller scale.

Prize mechanisms that rely on open licensing and generic competition to ensure low prices face additional challenges, especially for vaccines. First, removing patent barriers will not in many cases be sufficient to allow new manufacturers to produce versions of new vaccines—a mechanism for transferring know-how as well as an abbreviated regulatory pathway would also be needed. Second, markets for some new vaccines might be too small to attract multiple suppliers even if a patent pool and transfer of know-how substantially reduced R&D costs for follow-on manufacturers. If open licensing and competitive generic supply are not feasible, a prize would need to include mechanisms to ensure low prices and supply, such as assurances from manufacturers, backed by financial guarantees, that the product would be manufactured in sufficient quantities and provided at an affordable cost.

Access to technology

Funding for R&D, either through grants or pull mechanisms like AMCs, or prizes, is necessary to make up for the lack of market returns, especially for challenging vaccines needed primarily in low-income countries. But greater access to technology would greatly expedite the entry of new suppliers into markets for existing kinds of vaccines and increase the capacity of firms in developing countries to contribute to the development of new classes of vaccines. The technological sophistication of some emerging suppliers is already growing quite rapidly, but new mechanisms can accelerate this process, especially for specific vaccines.

The Meningitis Vaccine Project is an example of two useful approaches to technology transfer. First, it demonstrates the importance of linking technology transfer to patent licensing: the license for NIH's conjugation technology would have been much less useful without the transfer of know-how. The idea of bundling vaccine patents and know-how, perhaps in

an expanded type of patent pool, has been proposed by Universities Allied for Essential Medicines⁵⁴ and by Anthony So of Duke University, in his concept of a “technology trust”⁵⁵. Second, the MVP shows the value of donor funding for focused technology transfer. Another Gates-funded PATH project, the Pneumococcal Vaccine Project, is assisting emerging suppliers to develop pneumococcal vaccines suitable for developing countries.

The big firms also sometimes transfer technology to manufacturers based in developing countries; the agreement between GSK and Brazil's publicly-owned BioManguinhos on the new pneumococcal vaccine is a notable example. But this happens only when technology-owning firms find it in their commercial interest, for example when tech transfer is a condition for entering potentially lucrative markets.

As an alternative to bilateral tech transfer to individual firms, the WHO and the Netherlands Vaccine Institute (NVI) are establishing a “technology hub” for influenza vaccines that will enable multiple manufacturers to acquire the necessary know-how and materials.⁵⁶ The NVI also played an important role in the development of Hib-containing vaccines by Indian manufacturers.

Summary of R&D challenges

- The current, market-based R&D system has failed to develop vaccines for diseases such as TB and malaria that affect large numbers of people as well as vaccines for smaller markets such as dengue or Meningitis A. In addition to new vaccines, there is also a need for improved, cheaper, and more suitable versions of existing vaccines.
- Although there has been progress and a number of promising initiatives, these efforts still depend too much on the established multinational firms, who fund and conduct most late-stage vaccine R&D. There is a great opportunity to exploit and expand developing country capacity to develop needed vaccines.
- Much vaccine technology is initially developed in government and academic institutions, but these inventions are typically licensed to big pharma for rich-world applications.
- New mechanisms are needed to support technology transfer and fund vaccine development.

Conclusions & policy objectives

Securing access to existing new vaccines for developing countries, and stimulating R&D for needed and better-adapted vaccines, currently present a formidable public health challenge. This is the right moment to engage public health advocates, donors and governments on the issue of vaccines, drawing upon the momentum gained from the ongoing effort to secure access to medicines.

Emerging suppliers critical to broader vaccine access

The recent development of three crucial new vaccines opens the door to helping prevent millions of additional deaths over the coming years in developing countries. However, GAVI will not be able to provide these new vaccines to the poorest countries unless prices come down dramatically, and its funding crisis – partly caused by high vaccine prices – is addressed. It has become apparent that predictable demand alone is not sufficient to accelerate the entry of additional producers to the market, thereby lowering prices.

Therefore, more attention should be paid to ensuring that donor funds are used to proactively bring down the prices of vaccines. In the meantime, donors must urgently stave off GAVI's funding crisis by replenishing its coffers. An unacceptable and alarming alternative is already being planned, whereby a smaller number of countries will be introducing fewer vaccines on a longer timetable.

For middle-income countries that are not eligible for GAVI support, company tiered pricing has demonstrated its limits, leading to rationing of newer vaccines. Until increased market competition forces prices down, pressure must be exerted on companies to lower prices further for middle-income countries. Extending GAVI negotiated prices to countries that have or will soon 'graduate' from GAVI will be a critical part of this strategy. Otherwise, these countries will face the difficult choice of cutting budgets for other health priorities, or simply not introducing new vaccines at all. At the same time, middle-income countries should be encouraged to explore opportunities to collectively negotiate for reduced prices, as with the PAHO Revolving Fund's pooled procurement mechanism. Another option to explore would be regional exportation of vaccines from government-owned producers, such as Brazil's BioManguinhos.

Expediting the market entry of competitive products is vital to pushing prices down, thereby increasing vaccine access in developing countries. Significant investment in transfer of know-how is needed to overcome barriers that prevent emerging suppliers from entering the

market. The technology transfer 'hub' approach uses training platforms as an alternative to more typical provider/recipient tech-transfer relationships, and has been used successfully in the context of the influenza vaccine. This hub model should be utilized additionally for the development of needed vaccines by emerging suppliers. Publicly-owned or funded bodies, e.g. EU vaccine institutes, could provide an ideal base for such technology transfer hubs.

Facilitating emerging supplier market entry will also require mechanisms to overcome patent barriers: universities and public research institutions should be encouraged to adopt open licensing policies. Moreover, countries should be advised on how to make full use of flexibilities enshrined in the TRIPS agreement. Procurement policies should also encourage competition, not reinforce the dominance of several multinational suppliers.

Alternative models needed to close vaccine R&D gap

On the R&D front, the market-based system is failing to develop needed vaccines for diseases such as TB and malaria. It has also failed to develop more affordable and suitable versions of existing vaccines for developing countries, for example vaccines that do not need refrigeration. There is an opportunity to augment the role emerging suppliers play in vaccine R&D, and several efforts to that effect have proven successful.

While much of the basic research for vaccine development is carried out by government institutions and universities, the discoveries are then typically licensed to multinational pharmaceutical companies to finish developing products. These companies, in turn, tailor the products to developed country markets where they can charge the highest prices. This leaves many global health needs unmet. To break this pattern, public institutions should be encouraged to adopt more open licensing policies, so that emerging suppliers can produce products that specifically address the needs of developing country populations. In addition, reexamining the capacity of the public sector itself to again play an important role in vaccine R&D will be critical.

There is a great need for increased investment into not-for-profit R&D to meet the health needs of developing countries. WHO is uniquely positioned to play a key role here, particularly with regard to its legitimacy in priority setting. Furthermore, models to promote needs-based R&D must rely on funding that is predictable and sustainable, and conditions for

affordable access to developed products should be negotiated in advance.

A number of ‘push’ and ‘pull’ R&D mechanisms have shown initial promising results. Several projects are now close to delivering vaccines to children in developing countries, notably the PATH/WHO Meningitis Vaccine Project and the pneumococcal advance market commitment (AMC). The Meningitis Vaccine Project has been a highly-effective and cost-efficient model that has resulted in an innovative adaptation of an existing vaccine. This model should be replicated where appropriate.

On the other hand, the AMC has been criticized as too expensive and too complex, and is ultimately resulting in the procurement of a vaccine already in its final stages of development, in lieu of generating an innovative new product. It will be important to follow closely the evolution of these projects and to examine how lessons learned can be applied to potential future candidate projects. Given the difficulties with the current AMC, caution should be exercised before embarking on a new one. If a new AMC is considered, it should be designed as a true pull mechanism for vaccine R&D, rather than a procurement system, as with the pneumococcal AMC. Additionally, prize fund proposals for vaccines should be explored that would address the R&D gap, while also securing sustainable access through affordable prices.

GAVI will be redefining its strategy during this, its tenth, year. It will be critical for GAVI to include measures to encourage competition; find better ways to leverage price reductions; and support mechanisms that foster both the development of new vaccines and the adaptation of existing ones. Ensuring that the world’s children receive new and better-adapted life-saving vaccines is a challenge that will demand strong commitment from governments, donors and public health advocates alike.

Abbreviations and Acronyms

AIDS

Acquired Immunodeficiency Syndrome

AMC

Advance Market Commitment

CDC

U.S. Centers for Disease Control

DTP

Diphtheria, Tetanus, Pertussis vaccine

EMA

European Medicines Agency

EPI

Expanded Programme on Immunization
(World Health Organization)

FDA

U.S. Food and Drug Administration

GAVI

Global Alliance for Vaccines and Immunization
(GAVI Alliance)

GMP

Good Manufacturing Practice

GNI

Gross National Income

GSK

GlaxoSmithKline

Hib

Haemophilus influenzae type b

HIV

Human Immunodeficiency Virus

HPV

Human Papillomavirus

IFFIm

International Finance Facility for Immunization

IP

Intellectual Property

MVI

Malaria Vaccine Initiative

MVP

Meningitis Vaccine Project

NIH

U.S. National Institutes of Health

NRA

National Regulatory Authority

PAHO

Pan American Health Organization

PDP

Product Development Partnership

R&D

Research and Development

TB

Tuberculosis

TRIPS

Trade-related Aspects of Intellectual Property Rights
agreement

UNICEF

United Nations Children's Fund

WHO

World Health Organization

Glossary⁵⁷

Advance market commitment (AMC)

An advance market commitment (AMC) is an innovative financing model that provides an incentive for pharmaceutical companies to develop and produce new vaccines by creating a subsidized market for needed products. The subsidy is meant to reduce the risk for pharmaceutical companies of investing in products for developing country markets with limited purchasing ability, and is only paid once a vaccine meeting certain specifications is purchased by eligible developing countries (or donors on their behalf) at a pre-set price. The subsidy covers an agreed volume of vaccines, after which a predetermined and more affordable long-term price (also called 'tail price') is offered to countries. This aims to ensure the vaccine's use is sustained beyond the duration of the subsidy.

Co-financing

Co-financing, introduced by GAVI in 2007, means countries share the cost of the vaccines supplied by the GAVI Alliance. The intention is to ensure immunisation programmes are sustainable in the long-term. GAVI-eligible countries have been grouped according to their expected ability to pay, and the co-financing levels vary across the different groups.

Combination vaccine

Combination vaccines are formulated with antigens against several infectious agents or pathogens in one injection (for example DTP, DTP-Hep B, or DTP-Hep B+Hib).

Conjugate vaccine

This is a vaccine that is formulated by chemically linking sugar chains derived from the pathogen to a protein backbone. Conjugate vaccines supported by GAVI include Hib and pneumococcal vaccines.

Frontloading

Fontloading is based on the concept that substantial initial investments lead to proportionally greater impact than investments distributed evenly over time. The International Finance Facility for Immunisation (IFFIm) is based on the concept of frontloading.

GAVI-eligible country

There are 72 countries with a GNI per capita of U.S.\$ 1,000 or less in 2003 which are eligible to apply for GAVI support.⁵⁸

Good Manufacturing Practice (GMP)

A quality system that outlines how active pharmaceutical ingredients, diagnostics, foods, pharmaceutical products and medical devices are produced and tested. GMP are guidelines, but can also be regulations in some countries, such as the USA.

Expanded Programme on Immunization (EPI)

Since its inception in 1974, the Expanded Programme on Immunization has brought together partners under the auspices of the World Health Organization to increase immunisation coverage from the then low levels of 5% to the current levels, which are close to 80%. The traditional EPI vaccines are BCG (Bacille Calmette-Guérin, against tuberculosis), DTP (against diphtheria, tetanus, and pertussis), oral polio vaccine (OPV), and measles.

Haemophilus influenzae type b (Hib)

Hib is a bacterial infection which mainly affects children under five and can lead to life-threatening meningitis and pneumonia. Safe and effective Hib conjugate vaccines were first licensed in the early 1990s and are now being introduced in GAVI-eligible countries.

Hepatitis B (Hep B)

Hepatitis B is a serious disease caused by a virus that attacks the liver, potentially causing liver cancer, liver failure, and death in otherwise healthy adults. A safe and effective vaccine was first licensed in 1982, but had not been widely used in developing countries until GAVI provided funding beginning in 2000. GAVI supports hepatitis B vaccine in combination with other vaccines such as DTP and Hib.

International Finance Facility for Immunisation (IFFIm)

The International Finance Facility for Immunisation (IFFIm) is a new multilateral development institution created to accelerate the availability of predictable, long-term funds for health and immunisation programmes. IFFIm's financial base consists of legally binding grants payments from its sovereign sponsors, on the basis of which IFFIm issues AAA/Aaa/AAA-rated bonds in the international capital markets. The World Bank is the Treasury Manager for IFFIm. IFFIm's inaugural bonds of \$1 billion were issued on 14 November 2006. IFFIm funds are provided as grants – not loans – through the GAVI Alliance and all GAVI eligible countries can benefit from these funds. IFFIm's anticipated investment of \$4 billion over the next 10 years is expected to provide immunisation for an additional half a billion people, and avert as many as 10 million deaths. IFFIm was established as a charity with the Charity Commission

for England and Wales and is registered in England and Wales as a company. By the end of 2007, the seven governments France, Italy, Norway, South Africa, Spain, Sweden, and the United Kingdom had committed funds to the IFFIm. Other donors are expected to follow suit. Brazil for example, has announced that it will pay \$20 million over 20 years.

Live attenuated virus vaccines

Live attenuated viruses are used to produce vaccines that mimic natural exposure while avoiding disease, with the expectation that immunologic memory and lifelong immunity will be induced. These vaccines generally require only one or two immunisations, since the immune responses they induce are very durable. Many licensed vaccines in use today are based on this concept, such as measles, polio, and yellow fever vaccines.

Meningococcal A/C conjugate vaccine

Meningitis (inflammation of the lining of the brain and spinal cord) can be due to viral or bacterial infection. The bacterium *Neisseria meningitidis* (meningococcus) is a leading cause of bacterial meningitis in all countries, particularly in the African “meningitis belt,” where the disease occurs in large-scale epidemics affecting the entire population every few years. There are many different serotypes of meningococcus. Presently, polysaccharide vaccines with limited effectiveness are used for outbreak response. Development of a more effective meningococcal A or A/C conjugate vaccine that can be given to infants is one of the three new vaccine priorities identified by the GAVI Board.

Monovalent vaccine

A monovalent vaccine is formulated against a single infectious agent or a single serotype of a related group of similar infectious agents.

Multivalent vaccine

A multivalent vaccine can refer either to a vaccine formulated against several serotypes of a given infectious agent or a combination of vaccines against a selection of very different pathogens (Please see “Combination vaccine” above).

Pentavalent vaccine

A pentavalent vaccine is a multivalent vaccine which includes five antigens. GAVI funds pentavalent vaccine against diphtheria, tetanus, pertussis, hepatitis B, and Hib disease (DTP- Hep B-Hib).

Pneumococcal disease

Pneumococcal disease is caused by *Streptococcus pneumoniae*. These bacteria can cause a range of infections – from relatively mild ear infections to fatal pneumonia, meningitis, and sepsis. Serious pneumococcal infections can occur throughout life, but children under two years old and the elderly are at highest risk. The World Health Organization estimates that more than 1.6 million people – including up to one million children under five – die every year from pneumococcal infections. In 2000, a new vaccine became available – a seven-valent pneumococcal conjugate vaccine – that is safe and effective in children under two years old. Two newer pneumococcal vaccines that are effective against additional serotypes – 10-valent and 13-valent versions – became available in March 2009 and February 2010, respectively.

Pull mechanisms

Pull mechanisms provide a market incentive for increased commitment to vaccine and drug research and development. An incentive for industry’s investment into product development is created by money only being paid out once a product has been developed. Should a manufacturer be unsuccessful, no funds are paid out. The AMC for pneumococcal vaccine is an example of a pull mechanism.

Push mechanisms

A push mechanism uses direct funding to accelerate the development of a vaccine (e.g. direct funding of research in laboratories or universities). Push and pull funding are complementary sources of investment. Push mechanisms are intended to reduce the risks and costs of R&D investment, paying before a product is available. GAVI does not fund push mechanisms at this time.

Rotavirus

Rotavirus is the most common cause of severe diarrhoea in young children worldwide. It can result in acute dehydration, vomiting, and fever and is responsible for nearly 600,000 child deaths each year, mostly in developing countries – more than one third of deaths from diarrhoea worldwide. Rotavirus is highly contagious. Vaccines to prevent rotavirus infections have been licensed for use in Europe, Latin America, and the United States.

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- 48 The GSK malaria vaccine RTS,S is well ahead of any other candidate and its development is already largely paid for. For these reasons a malaria AMC would probably exclude this candidate and focus on next-generation vaccines.
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