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Challenges and potential solutions to innovative vaccine development for developing countries

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Abstract

Introduction. One of the barriers to meeting Millennium Development Goal Number 4 is access for large populations of developing countries to vaccines against their most serious and common diseases. Innovative vaccines have been more readily available at affordable prices once more producers enter the market, but this means that there will be a delay in access until these manufacturers can access the technology. Several solutions to enhance access have been proposed; none so far is optimal.

Methods. The factors relating to competition in the market and an affordable price were examined. Historical price data to countries were reviewed. Various explanations for lack of competition were also analyzed, including unequal access to financing, lack of optimal research and development capacity, barriers to technology transfer, issues in accessibility to intellectual property.

Results. Differences in vaccine scale up, know-how, GMP practices and regulatory oversight are decreasing between emerging suppliers and established multinationals. Developing country vaccine prices are at about the same levels for all manufacturers, but the level of vaccine development is lower for emerging suppliers who have few high priced markets to offset investments. There appear to be three major differences between multinational manufacturers and emerging suppliers:

- (1) limited access to research results that lead to new vaccine constructs;
- (2) barriers to vaccine technology development relating to blocking intellectual property;
- (3) inability to spread the investments that would be incurred in addressing issues (1) and (2) over a large enough financial base.

In terms of pricing, experience with early adopting countries has shown that other factors may overcome the perceived pricing barrier: that is, willingness to pay appears not to correlate with country wealth.

Conclusions. Based on these analyses it appears that the interventions of the international community might be better directed to achieve vaccine access.

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Keywords: vaccine access; vaccine pricing; vaccine development; willingness to pay; innovation

1. Main text

Currently vaccine development is in a vicious cycle (see Figure 1).

Figure 1. The vicious cycle of vaccine access. The three components of the cycle are low access, monopoly or few suppliers and high prices. Traditionally proposed inputs are to increase the number of suppliers to increase competition, to lower prices to increase uptake, and to increase demand to make the market more interesting.

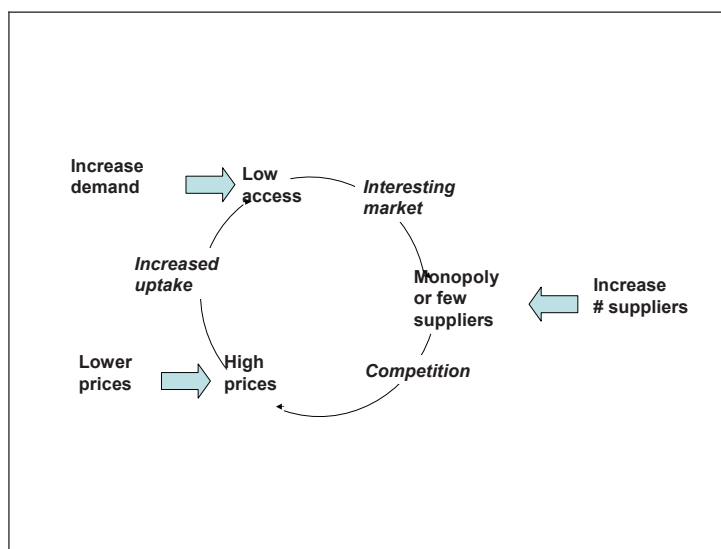


Figure 1 implies that there are several options to increase availability of priority vaccines: increasing competition, increasing uptake, and making the market more interesting. This paper will look at the information available on the impact of all three approaches on improving access to these products, as a step towards defining solutions.

Addressing monopoly or few suppliers to increase competition. One approach that has been suggested is to address the issue of only a few suppliers in a particular market, so that competition between suppliers will be increased. The first issue to address is that of why there are few suppliers? There could be several reasons for this: the market is not interesting, the technology is too risky, or the science is not yet ready. Given these reasons, there are several approaches that could be taken to address them.

The first is to guarantee a market. This is the reasoning behind the development of the Advance Market Commitment (AMC), in which a significant sum of money in the form of purchase commitments is reserved for the first manufacturer to bring to market a product which meets pre-established characteristics (the Target Product Profile - TPP). Currently a pilot AMC is in progress, which proposes to make US\$1.5 billion in market guarantees available to the first manufacturers that develop a product meeting this TPP.¹ A second example is the Meningitis Vaccine Project, which, through a coordinated technology transfer and development project with a developing

¹ <http://www.vaccineamc.org/>

country manufacturer, proposes to bring to market a conjugate meningitis A vaccine for the African meningitis belt at a target price of \$0.50 per dose.² Finally, the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) has provided high levels of funding to the poorest countries of the world in order to help them introduce priority new vaccines that are public health priorities.³ One of the impacts of increasing this market for such vaccines is expected to be an increased number of potential suppliers of these products.

The second approach to addressing the potential number of suppliers is to make difficult technology available. In fact, the Meningitis Vaccine Project, mentioned above, did just that, by overseeing a transfer of polysaccharide conjugate technology, which is the cornerstone of several high priority vaccines. Other approaches have been used, for example, through the Developing Country Vaccine Manufacturers' Network, to increase the availability of difficult technology.⁴

Finally, the third approach is to support basic research to answer the basic questions of feasibility. This approach has rarely been that taken with the ultimate goal to increase access to priority vaccines, because it involves a very long term goal. But this is just the approach now being taken to address the issue of HIV vaccines, where clinical approaches have been disappointing.

Have these approaches worked to increase the number of suppliers? Guaranteeing a market can help if the technology is available and the science is ready. Secure financing has slowly resulted in more suppliers, and this can be seen with the vaccines promoted by GAVI. While at the beginning of its activities, only one *Haemophilus influenzae* type b (Hib)-containing combination (pentavalent) vaccine was available, currently four are available, three of which are manufactured in developing countries.⁵

Transfer of technology has also worked to help increase the number of manufacturers for a particular vaccine. The example of the Meningitis Vaccine Project has been given above. Other examples of technology transfer include the agreement between Instituto Butantan and Sanofi-Pasteur for influenza vaccine production, and other examples in countries such as Brazil and India.⁶

Competition is increasing, but there is still a research lag for developing country manufacturers. Most of these, although they are adept at product development research, do not have basic research and development facilities, nor do they have active research acquisition programs, although there are some exceptions.⁶

Addressing high prices to increase uptake. It has generally been asserted that as competition increases vaccine prices will decrease. This statement may not be entirely true in the case of vaccines, which are a fixed cost business.⁷ In fact, the record shows a mixed performance. In the case of hepatitis B vaccine, when Korean manufacturers entered the market, prices dropped quickly to under \$1/dose. The price now is about \$0.20.⁸ However, for Hib-containing vaccines, as shown in Table 1, this has not happened.

² <http://www.meningvax.org/faq.htm>

³ <http://www.gavialliance.org/>

⁴ Jadhav S, Datla M, Kreeftenberg H, Hendriks J. The Developing Countries Vaccine Manufacturers' Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries. *Vaccine*. 2008 Mar 20;26(13):1611-5. Epub 2008 Feb 6.

⁵ http://www.who.int/immunization_standards/vaccine_quality/pq_vaccines/en/index.html

⁶ Milstien, Julie B, Gaulé, Patrick, Kaddar, Miloud. Access to vaccine technologies in developing countries : Brazil and India. *Vaccine* 2007, 25 (44): 7610-7619.

⁷ Batson, A. and Whitehead, P. Vaccine economics: assuring vaccines are developed for, and available in, developing countries. *In press*. *New Generation Vaccines*, 4th edition, eds MM Levine et al. New York: Marcel Dekker, Chapter 7.

⁸ http://www.unicef.org/supply/files/Product_Menu_23_Sept_2008.pdf

Table 1. Evolution of Hib-containing vaccines prices (Source: PAHO)

Year	Product	
	Hib mono	Pentavalent
1997	\$6-\$8.20	--
1998	\$2.18-\$2.60	--
2000	\$3-\$3.11	\$3.50
2001	\$2.80-\$2.65	\$3.50
2004	\$3	\$3.85
2008	\$3.35	\$3.92-\$3.95

Currently the price for monovalent Hib vaccine is \$3.50, while that of the pentavalent vaccine is \$3.41-\$3.50.⁸ So increasing competition does not necessarily decrease prices.

There are, however, additional approaches which could help lower prices. One of these is a reiteration of the message of public responsibility. In fact, recently IFPMA and major vaccine manufacturers have stated their commitment to ensure affordable prices to the developing world.⁹ A second way is for the public sector to develop early and accurate demand forecasts which would allow vaccine manufacturers to install sufficient excess capacity up front to provide the needs of the developing world. Manufacturers reduce manufacturing costs through economies of scale and experience, and traditionally these cost reductions have been passed on to developing country consumers. The most important mechanism of lowering prices for vaccines has been through price tiering, a strategy through which manufacturers charge prices to cover fully loaded costs to the high end market, and so recoup research and product development spending and overheads, while charging an amount closer to unit cost for each additional dose for the public market. Table 2 shows examples of price tiering for hepatitis B monovalent vaccines in 2001.

Table 2. Hepatitis B Monovalent Vaccine Prices, 2001, for Different Country Categories (Sources: UNICEF, PAHO Revolving Fund, country data to WHO)

Country Classification	Price Range, US\$ (#)
Low, includes PAHO and UNICEF	0.32-1.70 (3)
LMI	0.65-12.78 (8)
UMI	3.40-3.55 (4)
High	8.03 (1)

⁹ <http://www.guardian.co.uk/business/2009/feb/13/glaxo-smith-kline-cheap-medicine>; IFPMA, Industry Commitment to Global Access. Statement May 5, 2008

In general, prices to the poorest countries are lower, which should stimulate increased uptake, and this is mainly achieved by price tiering. However, in the case of developing country manufacturers, they may not have a wealthier market over which to recoup costs; on the other hand they have lower research and development costs. Thus price tiering may be less obvious for vaccines from developing country manufacturers, although they have traditionally been priced at lower levels.

Addressing vaccine uptake to improve the market. If prices are lower, will countries more readily introduce new vaccines? Maybe, since some countries cite price as the main barrier. Maybe not, since countries are becoming more knowledgeable on priorities: some countries are paying premium prices to buy vaccines that are priorities for them, while others are refusing to buy vaccines that they do not consider priorities. Figure 2 shows that when the price of pentavalent vaccine was high, at \$7.20/dose, no Latin American countries had introduced the vaccine by 1998. The lowering of the price in 1999 to about \$3.50 per dose resulted in four countries introducing the vaccine. However, as the price gradually increased over the next seven years to just under \$4 per dose, there was a steady increase in the number of countries introducing the vaccine, up to a total of 31 by 2007. Only one of these 31 countries was helped by GAVI funds. This figure shows that in the Americas, once the price was initially lowered to one that was apparently considered “affordable,” vaccine introduction proceeded seemingly independent of price.

Figure 2. Uptake of pentavalent vaccine in the Americas (Source PAHO)

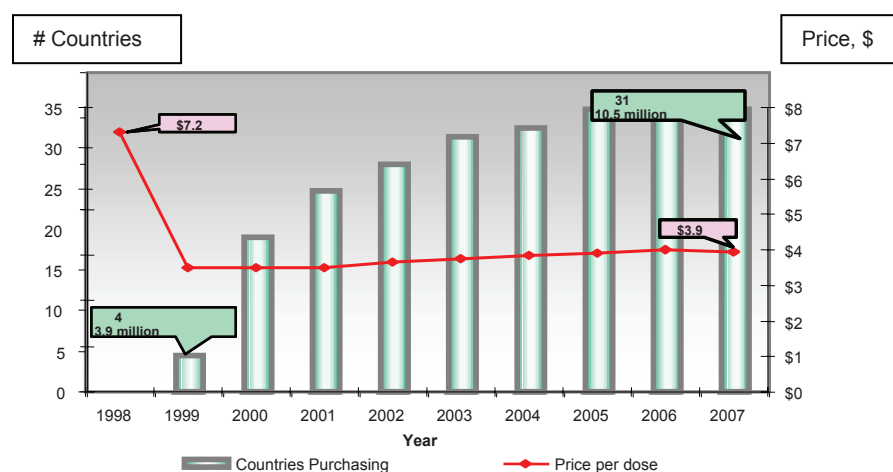


Figure 2 implies that lower prices alone will not increase demand in all countries. Other factors, besides sustaining affordable pricing, which have been postulated to play a role, include advocating the value of the vaccine to Ministers of Finance and other national and political leaders, demonstrating vaccine impact through reliable disease surveillance systems, and supporting processes that encourage independent country decision making. Two examples can show the impact of such activities for the pentavalent vaccine. The first example is the story of Mali. When a national laboratory examining isolates from spinal fluids of children presenting with meningitis found a high rate of Hib-related meningitis in infants under one year of age,¹⁰ the president of Mali pushed the health authorities of the country to apply for GAVI funds to introduce this vaccine.¹¹ A second example has to do with the WHO

¹⁰ Sow SO, Diallo S, Campbell JD, Tapia MD, Keita T, Keita MM, Murray P, Kotloff KL, Levine MM. Burden of invasive disease caused by *Haemophilus influenzae* type b in Bamako, Mali: impetus for routine infant immunization with conjugate vaccine. *Pediatr Infect Dis J.* 2005 Jun;24(6):533-7.

¹¹ http://www.gavialliance.org/performance/country_results/index.php?contID=1&countID=42 – proposal October 2004 for pentavalent vaccine

recommendations on Hib use. When WHO changed its longstanding recommendation to include countries in Asia,¹² many of these countries then added Hib vaccine, despite the steadily increasing prices shown above.¹³

Characteristics of vaccine manufacturers in developing countries as compared to those in industrialized countries. Previously, there were large differences between established multinational vaccine manufacturers in industrialized countries and emerging suppliers located in developing countries in vaccine scale up, know-how, GMP practices and regulatory oversight. These differences are decreasing,^{6, 14} and significant numbers of doses, even of relatively innovative vaccines, are now available and WHO-prequalified from emerging suppliers.⁵ Developing country vaccine prices for the UNICEF market are at about the same levels for all manufacturers,⁸ but the level of vaccine development is lower for emerging suppliers who have few high priced markets to offset investments. At the moment, the major differences between multinational manufacturers and emerging suppliers in relation to development of innovative priority vaccines for developing countries are:

- (1) limited access of emerging suppliers to research results that lead to new vaccine constructs;⁶
- (2) barriers to vaccine technology development relating to blocking intellectual property;⁴
- (3) inability to spread the investments that would be incurred in addressing issues (1) and (2) over a large enough financial base.⁷

Lessons learned. The conclusion of these observations is that increasing access will not be as simple as assuring increased competition and lower prices by transferring new technologies to developing country manufacturers. Such a premise relies on the idea that lowering vaccine prices will assure access, and we have seen above that that is not always the case. Rather national prioritization based on disease burden, competing priorities, and ability to demonstrate a quantitative impact appears to play a larger role than price, below a certain price point. Thus, achieving enhanced access will require significant work on the demand side.

On the supply side, although previous work to make technology available through partnerships and technology transfer has indeed had an impact, for future vaccines, especially where the science is not yet mature, enhanced research and development will play a major role. If only multinational companies in industrialized countries have this ability, this implies a change in direction for the international community: more efforts targeted at ensuring relevant clinical trials, sustainable pricing, and global capacity investments early in the life cycle for innovative developing country vaccines.

This also means a supply side strategy change if emerging suppliers are to provide part of this supply, especially to their own constituencies. They will need to increase investment in accessing relevant research results. Although some vaccine manufacturers located in developing countries are increasing their research and development capacities, this is a long term process. In the meantime, manufacturing costs for these emerging suppliers are continuing to increase as their standards are becoming increasingly more stringent. Without a range of markets over which to tier prices, their prices for new vaccines will of necessity increase, despite some advantages based on labor, construction, and clinical trial costs. This means that a long range strategy for an emerging supplier will need to be entry into the international marketplace – with the concomitant needs for innovation and regulation.

¹² World Health Organization. WHO Position Paper on Haemophilus influenzae type b conjugate vaccines. *Wkly epidemiol rec* 2006 Nov 24;81(47):445-452.

¹³ Data from Hib Initiative staff and website, <http://www.hibaction.org/>, accessed Nov 3, 2008.

¹⁴ Milstien J, Costa A, Jadhav S, Dhare R. Reaching International GMP Standards for Vaccine Production: Challenges for Developing Countries. Expert Review of Vaccines 2009, *in press*.