

*Rachel Glennerster, Michael Kremer, and Heidi Williams*

# Creating Markets for Vaccines

*Innovations Case Discussion:  
International AIDS Vaccine Initiative*

Malaria, HIV, and tuberculosis kill five million people each year, almost all of them in poor countries. Relative to the social need, there is a dearth of research and development (R&D) on health technologies for these and other diseases concentrated in poor countries. One commonly cited estimate is that half of all global health R&D in 1992 was undertaken by private industry, but that less than 5 percent of that was spent on diseases specific to poor countries.<sup>1</sup> It is estimated that in 2004, private industry was responsible for only 10 percent of the total \$682 million in global HIV vaccine R&D investments.<sup>2</sup>

Private biotechnology and pharmaceutical firms are unlikely to invest in R&D on products which they expect to be unable to sell at prices that would cover their risk-adjusted costs. As we will discuss, low expected prices for products such as an HIV vaccine reflect both the poverty of the relevant populations as well as severe distortions in the markets for drugs needed for poverty-related diseases.

One proposal to incentivize private sector R&D investments in products for diseases concentrated in poor countries is for sponsors (rich-country governments, private foundations, or international organizations such as the World Bank) to undertake “advance purchase commitments” for desired products, such as an HIV vaccine. A commitment to purchase these products in advance of their development would create market incentives for firms to develop needed vaccines. Advance purchase commitments can also be structured to ensure access to these vaccines, if and when they are developed, for the people who most need them (in both the short and long term). If no vaccine is developed, no donor funds would be spent; if a desired vaccine is developed, an advance purchase commitment would be an extremely cost-effective expenditure from a public health perspective, saving more lives than virtually any comparable health expenditure.<sup>3</sup>

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The idea of advance purchase commitments for vaccines has recently been gaining political momentum. In 2003 the Center for Global Development (CGD), with financial support from the Bill and Melinda Gates Foundation, convened a working group to explore the details of how this type of proposal could be implemented.<sup>4</sup> In November 2004, U.K. Chancellor of the Exchequer Gordon Brown announced that the U.K. government, working in cooperation with other donors, would be willing to enter into an advance purchase commitment for a malaria vaccine.<sup>5</sup> The Chancellor later announced that the U.K. will also explore the use of

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advance purchase commitments for HIV vaccines. In April 2005 the CGD working group published a report recommending how advance purchase commitments for vaccines could be implemented;<sup>6</sup> in December of that year the G-7 finance ministers announced an agreement to work with others on developing a pilot advance purchase commitment during the 2006 calendar year.<sup>7</sup>

Innovations in health technologies (in particular, vaccines) have, in the past, had a profound impact on

global health, in rich countries as well as poor. Yet capitalizing on the full potential of vaccines to improve the health of individuals in poor countries requires tackling a host of complex issues. Advance purchase commitments are intended to address one part of this important issue, and a number of other existing institutions are making notable progress on complementary fronts. For example, the Global Alliance for Vaccines and Immunization (GAVI) is making critical and needed investments in strengthening health care systems in poor countries. More directly relevant for our discussion in this article is the work of Product Development Public-Private Partnerships (PDPPPs) such as the International AIDS Vaccine Initiative (IAVI) and the Malaria Vaccine Initiative (MVI).

As discussed by Seth Berkeley in his article in this issue of *Innovations*, as well as in a recent policy brief by IAVI,<sup>8</sup> advance purchase commitments hold great potential promise as an important complement to the work being done by IAVI and other PDPPPs. For diseases prevalent in rich countries, a combination of “push” and “pull” measures help to provide incentives for the development of drugs and vaccines. Applying the same principle to vaccines and drugs for diseases concentrated in poor countries would suggest using push programs (such as funding through IAVI and other PDPPPs) for basic research and for clinical development, and using pull programs to encourage biotech and pharmaceutical firms to turn this research into

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needed health technologies and to help ensure that the products are affordable and used by poor countries once developed. By increasing the probability that the results of public- and philanthropic-funded research will be picked up, translated into useable products, and widely distributed, advance purchase commitments can provide a critical and complementary approach to, but do not substitute for, the important work being done by IAVI and other PD-PPPs on vaccines for diseases concentrated in poor countries.

This paper discusses the key issues involved with how advance purchase commitments can be designed to “create markets” for vaccines against diseases like HIV which are concentrated in poor countries. The paper outlines a proposed structure for advance purchase commitments, and outlines some key design issues which can be used to evaluate advance purchase commitments as relative to other forms of pull incentives.

The paper draws upon prior work by the authors and others. Kremer and Glennerster<sup>9</sup> lay out the rationale for advance purchase commitments and discuss design issues in more detail. Berndt and Hurvitz<sup>10</sup> discuss some of the legal and economic practicalities of structuring advance purchase commitments. Towse and Kettler<sup>11</sup> discuss design issues for advance purchase commitments.

### MARKET FAILURES FOR NEEDED VACCINES AGAINST DISEASES CONCENTRATED IN POOR COUNTRIES

The need for accelerated development of new health technologies targeted to and appropriate for epidemiological conditions and health systems of poor countries cannot be understated.

Vaccines are perhaps the paradigmatic example of a cheap, easy-to-use technology that can have tremendous health impacts even in very poor countries with weak health care infrastructures. Vaccines (relative to drug treatments) require little training or expensive equipment to implement, do not require diagnosis for use, can be taken in a few doses instead of in a longer-term regimen, and rarely have major side effects. They can be prescribed and delivered by health care workers with very limited training, and resistance rarely develops against vaccines.

In recent decades much of the improved health in poor countries has been due to the widespread adoption of vaccines that were developed in response to incentives provided by the prospect of sales in rich country markets. Seventy-four percent of the world’s children now receive a standard package of cheap, off-patent vaccines through the World Health Organization’s (WHO) Expanded Programme on Immunization (EPI). These vaccines save some 3 million lives per year—almost 10,000 lives a day—and protect millions more from illness and permanent disability.<sup>12</sup>

Poor countries have benefited enormously from such vaccines, but these benefits have for the most part been a fortunate byproduct. Little public- or private-sector R&D is targeted toward developing new health technologies for diseases concentrated in poor countries. Of the 1,233 drugs licensed worldwide between 1975 and 1997, only 13 were for tropical diseases; of these 13, five came from veterinary research, two were modifications of existing medicines, and two were produced for the U.S. military—only four were developed by commercial pharmaceutical firms specifically for tropical diseases of humans.<sup>13</sup> Even for diseases that are major health issues in rich countries, R&D on these diseases may not result in products that easily spill over to the epidemiological conditions and health systems of poor countries. For exam-

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ple, in the case of HIV most R&D is focused on the strain of the virus common in rich countries, and on drug treatments rather than vaccines—treatments which are much more difficult than vaccines to deliver in poor countries with weak health care infrastructures.

Although the scientific challenges associated with developing products such as an HIV vaccine are formidable, many very difficult challenges have been overcome to develop products

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needed in rich country markets, whereas even when there exist potentially promising candidate products for diseases concentrated in poor countries, these candidate products often remain “on the shelf” and are not pursued. Despite the enormous potential benefits in terms of lives saved, biotechnology and pharmaceutical firms have little incentive to undertake R&D on technologies that will primarily be used in poor countries. One reason is that the potential

consumers (patients and their governments) are poor. But there are also two key market distortions that reduce the incentives for R&D on new products for these diseases.

First, the scientific and technological advances generated by R&D on these diseases spill over to many nations, so none of the many small countries that would benefit from (for example) a malaria vaccine has an incentive to encourage R&D by unilaterally offering to fund R&D directly or to pay higher prices for new products.

Second, governments and other institutions that purchase vaccines for these diseases face a “time-inconsistency” problem. Once pharmaceutical companies have made the R&D investments necessary to develop vaccines, governments and aid institutions often use their powers as dominant purchasers and arbiters of intellectual property rights to keep prices close to marginal cost in the interest of using limited budgets to increase access to life-saving products. However, because the largest part of the industry’s expenditures lies in the initial R&D cost, prices that cover the (typically modest) variable costs of production will likely not enable companies to recover their R&D investment, thereby deterring industry from investing in such R&D in the first place.

As we will discuss, although the goals of creating incentives for R&D on new pharmaceuticals (which requires high prices) and ensuring wide access to pharmaceuticals once developed (where low prices enable budgets to go further) are often pitted against each other, well-designed incentive mechanisms can de-couple these goals and promote both effectively.

It is important to note that many lives in poor countries could be saved with improved access to existing health technologies; for example, three million people die every year of diseases preventable with existing vaccines. The paper by Lanjouw in this issue of *Innovations* addresses the issue of access to existing health technologies. Although society has not capitalized on the full potential of existing vaccines, as discussed above there is an urgent need for the development of new vaccines against the diseases which most heavily burden poor countries, such as HIV.

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### THE ROLES OF “PUSH” AND “PULL” IN DEVELOPING NEW HEALTH TECHNOLOGIES

Incentive systems to encourage the development of new products can be broadly classified as “push” programs, which subsidize research inputs, and “pull” programs, which reward developers for actually creating desired products.

Government- and philanthropic-directed push programs are well-suited for basic research, but for later, more applied stages of research the incentives provided by pull-like mechanisms are critical in producing useable health technologies. With pull programs, money changes hands only after a successful product is developed—thus giving researchers strong incentives to self-select projects with the best prospects for success as useable products. Pull programs also create incentives for researchers to focus on developing a vaccine, rather than pursuing ancillary goals such as publishing journal articles.

For diseases prevalent in rich countries, a combination of push and pull measures help to provide incentives for R&D. Push funding from institutions such as the U.S. National Institutes of Health and the Wellcome Trust supports basic scientific research and some clinical development, while the prospects of profits in rich country markets provide pull incentives for private sector firms to transfer basic research into useable products.

Applying the same principle to vaccines and drugs for poor countries would suggest using push programs for basic research and for clinical development, and using pull programs to encourage biotech and pharmaceutical firms to turn this research into needed health technologies. For diseases concentrated in poor countries, push funding is being provided from a number of institutions, notably Product Development Public Private Partnerships (PD-PPPs) such as the Malaria Vaccine Initiative (MVI) and the International Aids Vaccine Initiative (IAVI). While more push funding is needed, a major stumbling block remains the lack of a market pull incentive to turn basic R&D into useable products.

Pull programs offer the opportunity to harness the energy and creativity of the private sector through an open, transparent approach that is difficult for special interests to capture. Private sector R&D would be attracted to worthwhile products through a market-oriented approach, with donor dollars rewarding success without micro-managing the research process.

#### PRECEDENTS FOR PULL INCENTIVES

A sizeable academic literature as well as several historical precedents suggest market-based pull incentives are effective in stimulating R&D investments and innovation in rich country markets.

A long academic literature relating back to Schmookler<sup>14</sup> and Griliches<sup>15</sup> finds technological change to be closely linked to expected market size. More recently, Vernon and Grabowski,<sup>16</sup> Scott Morton,<sup>17</sup> Reiffen and Ward,<sup>18</sup> and Acemoglu and Linn<sup>19</sup> have provided evidence of this trend specific to the pharmaceutical industry. For example, Acemoglu and Linn<sup>20</sup> analyze the effect of expected market size on the entry of new drugs through examining variations in market size for pharmaceuticals linked to demographic changes, and find that a 1 percent increase in the potential market size for a drug category leads to a 4 to 6 percent increase in the number of new drugs in that category.

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Several historical precedents reinforce the view that policies increasing the value of markets for pharmaceuticals can encourage R&D. For example, the U.S. Orphan Drug Act, which went into effect in 1983, created a number of financial incentives for pharmaceutical companies to develop drugs for rare diseases like Huntington's, ALS (Lou Gehrig's disease), and muscular dystrophy—diseases which affect fewer than 200,000 people in the USA and therefore have a limited market. The primary attraction for companies under this legislation is a promise of seven years of market exclusivity. Although before/after comparisons are difficult to make, over 200 orphan drugs have been developed since 1983, while fewer than ten were introduced in the decade preceding passage of the act.<sup>21</sup> Kettler<sup>22</sup> argues biotechs in particular responded to the incentives provided by the U.S. Orphan Drug Act; Kettler and Marjanovic<sup>23</sup> note that as of 2000, biotechnology companies had sponsored 70 percent of the more than 900 orphan-designated projects in the U.S., and 50 percent of all approved biotechnology products had orphan status.

Another set of precedents for the case of vaccines are the recommendations from the U.S. Advisory Committee on Immunization Practices (ACIP). ACIP's recommendations typically set policy for immunization requirements in the U.S., and hence if a vaccine is recommended by ACIP the producers of that vaccine are assured of a reasonably large market. Finkelstein<sup>24</sup> investigates the private sector response to health policies such as the ACIP recommendations that, in attempting to increase immunization rates, also increased the expected profits from new vaccines. Her work estimates the change in investment in vaccines against those diseases, using changes in investment for vaccines against carefully selected diseases that were not affected by the policies to control for underlying secular trends in R&D in the vaccine market, and finds a strong positive impact of these policies on private sector R&D activity on affected vaccines.

## ADVANCE PURCHASE COMMITMENTS

Pull programs that reward successful R&D on needed global health products could take a variety of forms. Given the current huge disparities between private and social returns to R&D on diseases concentrated in poor countries, any program that committed to compensate private developers of needed products would likely be an improvement on the status quo.

In this section we argue that advance purchase commitments may be particularly well suited to encouraging R&D on diseases concentrated in poor countries. We first outline the basic structure of an advance purchase commitment, as developed by Kremer and Glennerster<sup>25</sup> and the Center for Global Development.<sup>26</sup> We then discuss several key issues that arise in the design of pull programs, and use these to evaluate advance purchase commitments as relative to other pull mechanisms. We do not here discuss alternative pull programs in detail; for more discussion on this topic, see Kremer and Glennerster<sup>27</sup> and Barder et al.<sup>28</sup>

### **The Structure of an Advance Purchase Commitment**

In advance purchase commitments, sponsors commit (in advance of product development and licensure) to fully or partially finance purchases of vaccines for poor countries at a pre-specified price. A program sponsor or coalition of sponsors that potential investors in R&D would find credible (*i.e.*, sponsors that are financially solvent and are thought to be unlikely to

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Advance market commitment	Example for malaria vaccine
Legally binding contracts, enforceable by law	Offer made by a group of sponsors
Total market value approximately equal to sales revenues earned by average new medicines	Total market size of \$3 billion (net present value, 2004 US dollars)
Sponsors under-write a specific price	\$15 per treatment (e.g. \$5 per dose for 3 doses)
Price guarantee applies to a maximum number of treatments	Guarantee for first 200 million treatments
Treatments sold in eligible countries	Vaccine Fund eligible countries <sup>35</sup>
In return, the developer guarantees to sell subsequent treatments at a low price	\$1 per treatment
Recipient country makes a co-payment for the products they buy (or asks a donor to do so)	\$1.00 paid by recipient \$14.00 paid by sponsors
Successful developers receive \$15 per treatment sold.	
Subsequent products are also eligible for the guaranteed price, if superior to existing products—as developing countries can switch their demand to these subsequent, superior products.	
An Independent Adjudication Committee oversees the arrangement.	

**Figure 1.** Example structure of an advance purchase commitment.

Source: Barder et al. (2005)

For those readers who may be unfamiliar, the Vaccine Fund is the financing arm to the Global Alliance for Vaccines and Immunization (GAVI). More information is available online at <<http://www.vaccinealliance.org>>.

renege on a commitment) would sign a contract underwriting a guaranteed price for the supplier. Poor countries would decide whether to buy a product at a low and affordable price (say, \$1 per treatment), and sponsors would guarantee to top-up to a guaranteed price (say, \$15 per treatment)—thus providing market returns for the developer which are comparable to other, average-revenue pharmaceutical products. Once the full number of treatments has been purchased at the guaranteed price, the supplier would, in return, be committed to either selling further treatments at an affordable price in the long term, or later licensing their technology to other suppliers. Although not part of the contract, there would be nothing to stop the original sponsors or other donors from covering the \$1 price on behalf of poor countries at the time of purchase.

The advance purchase commitment structure as recommended in the Center for Global Development report is presented in Figure 1.

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For firms, this type of advance purchase arrangement would reduce economic uncertainty and give investors confidence about the returns they can expect if the relevant scientific challenges are overcome. It is important to note that advance purchase commitments would not eliminate all risk to developers. In particular, the scientific challenges and associated risks (as in markets for diseases prevalent in rich countries), would be considerable and the risk of failure high. But advance purchase commitments would greatly reduce the risks that are currently unique to the markets for diseases concentrated in poor countries—such as the risk that once R&D investments had been made, a company would face enormous pressure to sell the product at a very low price. Advance purchase commitments would thereby put diseases like malaria on more equal footing with health conditions prevalent in affluent populations in R&D allocation decisions.

One reasonable approach to setting the size of an advance purchase commitment, as in the CGD proposal, is to create a market comparable to that of the lifetime sales of an average existing pharmaceutical product. Specifically, the total recommended market size of \$3 billion (in net present value, 2004 U.S. dollars) represents the net present value of lifetime sales for the average pharmaceutical in a sample of recently launched commercial products, adjusted for lower marketing costs. In general, the larger the commitment, the more private firms will likely enter the search for a vaccine, and the faster a vaccine is likely to be developed.

For advance purchase commitments, donor funds are spent only if desired products are developed. If desired vaccines are developed, advance purchase commitments would be an extremely cost-effective expenditure from a public health perspective. For the case of a malaria vaccine, a purchase commitment of \$3.1 billion (comparable to the average revenue for existing commercial products) would cost an estimated \$15 per life-year saved—very cost effective compared to other health or development expenditures.<sup>29</sup> The estimated cost-effectiveness of similar-sized commitments for vaccines for HIV and tuberculosis would be \$17 and \$30 per life-year saved, respectively.

To put this \$15 per life-year saved figure in context, it is worth giving some benchmarks for cost-effectiveness comparisons. Health interventions in the poorest developing countries that cost about \$100 per life-year saved are generally regarded as highly cost effective.<sup>30</sup> More recently, a country's gross national product (GNP) per capita has also been used as a benchmark,<sup>31</sup> and in the U.S., the cost-effectiveness threshold is estimated to be as high as \$50,000 to \$100,000 per life-year saved.<sup>32</sup>

The \$15 per life-year saved estimate discussed above demonstrates that once a vaccine is developed, purchasing vaccine at the pre-specified price would be a very cost-effective expenditure. There is little reason to fear, therefore, that a vaccine commitment would tie donors to future purchases that would not be worthwhile, if a vaccine were developed. A somewhat more complex issue is the value of a commitment in accelerating the development and distribution of a vaccine that would have been developed at some later date in absence of a commitment. Berndt et al.<sup>33</sup> examine this case, and their estimates suggest that even in the conservative case in which an advance purchase commitment accelerated vaccine development by only one year and adoption in poor countries by only two years, the commitment would still cost only about \$80-\$90 per additional life-year saved—still very cost-effective relative to other health and development interventions, and still below the common \$100 per life-year saved benchmark.



### Key issues in Designing Pull Programs

In this section we discuss several key issues which are relevant to evaluating the relative appropriateness of various pull program designs, with a focus on advance purchase commitments.

#### (1) Which mechanisms will be seen as credible to industry?

Some argue that non-binding promises to purchase vaccines, or a consistent pattern of buying increased volumes of existing vaccines, would be enough of an incentive to encourage more investment into products such as an HIV vaccine.

Buying and distributing existing vaccines which are not now being fully utilized would be a very cost-effective way of saving lives, and therefore is a very valuable policy in its own right. However, it seems unlikely that simply purchasing more of existing products would significantly increase investment into new products needed primarily in poor countries. In the case of products which do not yet exist, manufacturers must be willing to invest in R&D that may take many years to reach fruition, over which time government and international priorities could easily shift. Hence, creating contractually binding mechanisms will be vital.

A key advantage of advance purchase commitments is that the agreements can be made credibly and contractually binding. Legal precedents suggest that such contracts are enforceable by contract law and existing legal institutions.<sup>34</sup>

#### (2) Which incentive packages will provide good value for the expenditure?

To achieve good value for expenditures, it is desirable to link the rewards received by innovators to the successful development of the desired products. This is in contrast to committing resources to products regardless of whether or not they are acceptable to the target populations and will actually be used. Sponsors do not wish to purchase products that, for whatever reasons, are not desired by the populations for which they are intended.

A related issue is that pull programs should be structured so as to provide incentives for firms to develop the best possible product. This implies a need to structure mechanisms so as to foster competition and encourage improved second-generation products.

Advance purchase commitments can be structured to cover the case in which more than one vaccine is developed, the rules for which should be set with several objectives in mind: first, fashioning incentives to appropriately reward development of the initial vaccine; second, creating incentives to improve on the original vaccine; and third, delivering the best available vaccines to patients. For example, from the standpoint of society as a whole, it is not a good use of resources to encourage development of second products that are different from but not superior to the first vaccine that is already in use. The CGD proposal, as detailed in Figure 1,

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If a commitment to purchase a vaccine needed primarily in poor countries failed to produce an effective vaccine, no donor funds would be spent; if it succeeded, tens of millions of lives would be saved at remarkably low cost.

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provides incentives for competition through allowing countries to switch their demand (and thus, the payment of the guaranteed price) to products that are developed subsequently and are superior to the initial product.

That advance purchase commitments can be structured so as to provide incentives for competition is a key advantage relative to many other types of pull mechanisms, such as “wild card” patent extensions, which by nature are structured as “winner-takes-all” rewards and hence do not provide incentives for follow-on innovations.

The open structure of advance purchase commitments is attractive to a wide range of firms—including small biotechnology companies, large pharmaceutical firms, and emerging market suppliers. All types of firms are eligible to compete and collaborate through creating whatever R&D structures they believe will be most effective in developing successful products. Rather than having sponsors dictate which R&D set-ups (or divisions of labor) among different firm types would be most effective, this open structure allows the firms themselves (which have much more information) to make these decisions and arrangements.

Although the only way to know for certain how firms would react to an advance purchase commitment is to implement one for a given vaccine and observe what happens, the available evidence suggests that, for early-stage products, the response to the “market” created by advance purchase commitments may be very similar to normal markets for pharmaceuticals.<sup>36</sup> Consultations undertaken by the Center for Global Development<sup>36</sup> suggest that for products in early stages, advance purchase commitment may initially motivate biotechs and potentially the venture capitalists which provide their funding, while some larger multinational pharmaceutical firms may get involved only later, at the licensing-in phase, after further advances in the science (perhaps led by biotechs). This finding is supported by anecdotal evidence that biotechs responded more enthusiastically than large pharmaceutical companies to orphan-drug incentives in the U.S.<sup>37</sup>

(3) *Which mechanisms can be structured to guarantee timely access to products, if and when they are developed, for individuals in poor countries?*

A key concern from the perspective of improving public health in developing countries is not just providing incentives for innovation but also linking incentives to access to products once they are developed. For example, when the hepatitis B vaccine was introduced at \$20 per dose, it was rarely used in poor countries;<sup>38</sup> more generally, the historical record suggests adoption of new vaccines in poor countries is often delayed by ten to fifteen years—thereby contributing to the three million annual deaths from diseases which are preventable with existing vaccines.

Many types of pull incentive structures do not directly address the issue of access to technologies once they are developed. A key advantage of advance purchase commitments, if structured correctly, is that they not only increase the likelihood of a new product being developed, but they also facilitate access to the desired technologies if and when they are developed. Consider the structure presented in Figure 1. In the short term, access to the vaccine in countries that need it most is facilitated through donor purchasers at the higher, pre-specified purchase price. In the long term, financially sustainable access to these technologies is facilitated through the contract provision which requires developers to commit to drop the price to a low level (close to marginal cost) or to license their technology to other suppliers after all high-price purchases have been made.

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### MOVING AHEAD WITH ADVANCE PURCHASE COMMITMENTS

Advance purchase commitments for vaccines for diseases concentrated in poor countries have considerable appeal across the ideological spectrum as a market-oriented mechanism that brings the resources of the private sector to address the health needs of the world's poorest countries. To move forward, institutional donors would need to launch a legally binding commitment program.

Such advance purchase commitments could be undertaken by a number of sponsors—including rich country governments, international organizations like the World Bank, and private foundations such as the Bill and Melinda Gates Foundation. As discussed in the introduction, the U.K. government has committed to work in cooperation with other donors to enter into such purchase commitments for malaria and HIV vaccines. The G-7 finance ministers have announced an agreement to work with others on developing a pilot advance purchase commitment during the 2006 calendar year.<sup>39</sup>

If a commitment to purchase a vaccine needed primarily in poor countries failed to produce an effective vaccine, no donor funds would be spent; if it succeeded, tens of millions of lives would be saved at remarkably low cost.

*We invite reader comments. Please send an email to <editors@innovationsjournal.net>.*

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24. Amy Finkelstein, "Static and Dynamic Effects of Health Policy: Evidence from the Vaccine Industry," *Quarterly Journal of Economics* 119 (2004): 527-564.
25. Kremer and Glennerster (, 2004), op cit.
26. Barder et al., op cit.
27. Kremer and Glennerster, 2004, op cit.
28. Barder et al.
29. Ibid. For those readers who may be unfamiliar, the Vaccine Fund is the financing arm to the Global Alliance for Vaccines and Immunization (GAVI). The Vaccine Fund offers support to qualifying governments of the world's poorest countries for: (1) new and under-used vaccines; (2) funding to help government strengthen their basic immunization services; and (3) safe injection equipment in the form of auto-disable syringes and safe disposal boxes. More information is available online at <http://www.vaccinealliance.org>.
30. World Bank. *Disease Control Priorities in Developing Countries* (New York: Oxford Medical Publications, Oxford University Press for the World Bank, 1993).
31. Global Alliance for Vaccines and Immunization, "Health, Immunization, and Economic Growth—Research briefing #2, Vaccines are Cost-Effective: A Summary of Recent Research," available: [http://www.vaccinealliance.org/General\\_information/Immunization\\_informa/Economic\\_Impact/vacc\\_cost.php](http://www.vaccinealliance.org/General_information/Immunization_informa/Economic_Impact/vacc_cost.php) AND World Health Organization, "Less-Used Vaccines Against Major Diseases are Cost-Effective, Researchers Conclude," *Bulletin for the World Health Organization* 78 (2000): 274.
32. Peter Neumann, et al., "Are Pharmaceuticals Cost-Effective? A Review of the Evidence," *Health Affairs* 19 (2000): 92-109.
33. Berndt, et al.
34. A particularly interesting precedent was set in the 1960s, when the U. S. Government used a contract offering to purchase manganese ore to stimulate domestic production. As part of the Domestic Manganese Purchase Program, the General Services Administration (GSA), a U.S. federal executive agency, issued regulations offering to purchase, at guaranteed minimum prices, "...manganese ores that met the specifications detailed in the applicable regulations." In *Himfar v. U.S.* (355 F.2d 606, Ct. Cl. 209; 1966), the Federal Court of Claims enforced a uni-

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lateral contract under which the federal government agreed to purchase at the predetermined price all domestic manganese ore that met certain criteria specified in its contract. Morantz and Sloane (2001) note that this decision provides compelling evidence that a vaccine commitment would be readily enforced, even against the government. Morantz and Sloane. *See also* Kremer and Glennerster, (2004).

35. Kremer et al. (2005) discuss this point in more detail, but it is worth giving a brief comment on the current model of private R&D for pharmaceuticals. In existing markets, large pharmaceutical firms tend to have an “integrator” role in the drug discovery process—playing the central (although not exclusive) role in coordinating discovery activities and in bring products through development and to the market (Kettler and Towse 2002, op cit). Smaller biotechnology companies usually focus on early stage research; if initial tests at these biotech companies are promising, their work is then usually either licensed to, or purchased by, larger pharmaceutical companies for later stages of development, marketing, and manufacturing. Most biotechnology companies are wholly dependent on external sources of finance, such as venture capital funding. The R&D market place varies by therapeutic class and by product, leading to more short-term, project-specific contracting between biotechs and large pharmaceutical firms.

36. Barder, Owen, Ruth Levine, Michael Kremer, and the Advanced Market Commitment Working Group (2005) *Making Markets for Vaccines*, Washington DC: Center for Global Development. Barder et al.

37. Hannah Kettler, 2000 “The biotechnology industry and orphan drug incentive: A win-win strategy for Europe?” *Journal of Commercial Biotechnology*, 7(1): 62-69.

38. William Muraskin, *The War Against Hepatitis B: A History of the International Task Force on Hepatitis B Immunization* (Philadelphia: University of Pennsylvania Press, 1995); AND and Louis Galambos, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1985-1995* (Cambridge, U.K.: Cambridge University Press, 1995).

39. HM Treasury, op cit.