Michael Kremer

*on how to improve world health*

Malaria, tuberculosis, and the strains of HIV common in Africa kill 5 million people each year, almost all of them in low-income countries. Effective vaccines against these diseases are desperately needed.

Yet there is a striking dearth of research and development (R&D) on vaccines and treatments for diseases primarily affecting poor countries. Of the 1,233 drugs licensed worldwide between 1975 and 1997, only 13 were for tropical diseases, and only 4 of these were specifically developed by commercial pharmaceutical firms to treat tropical diseases in humans. Half of all global health R&D in 1992 was undertaken by private industry, but of that, less than 5 percent was spent on diseases specific to poor countries.

The scientific challenges of developing vaccines for diseases such as malaria are formidable, but biotech and pharmaceutical firms often take on difficult scientific challenges. So what explains this underinvestment in R&D?

A key factor is that expected markets for these products are small, with most vaccines sold in poor countries currently priced at pennies per dose. The small expected market size is partly due to the poverty of these countries – but it also reflects severe distortions in markets for such vaccines. Typically, once pharmaceutical companies have invested in the R&D necessary to develop products, governments have often used their powers as regulators, dominant purchasers, and arbiters of intellectual property rights to keep prices low. In addition, because R&D on vaccines is an international public good, with the benefits of R&D advances spilling over to other countries, no country has the incentive to unilaterally offer to pay higher prices. Because firms anticipate low prices for products aimed at developing countries, they have limited incentives to invest in R&D.

In a forthcoming book, *Strong Medicine: Designing Pharmaceutical Markets to Treat Neglected Diseases,* Rachel Glennerster and I argue that foreign-aid donors should issue advance contracts committing to finance purchases of needed products such as malaria vaccines. This would provide vaccine developers with an incentive to invest in R&D and would help ensure that once vaccines were

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developed they would reach those who need them.

Programs to encourage the provision of R&D can take two broad forms. 'Push' programs subsidize research inputs, for example, through grants to researchers or R&D tax credits. 'Pull' programs reward research outputs, for example, by committing in advance to purchase a desired product at a specified price.

For pharmaceutical products needed in developed countries, R&D is spurred by a combination of both approaches: funding from institutions such as the U.S. National Institutes of Health covers the cost of most basic research, and the prospect of a market provides incentives for firms to turn their discoveries into marketable products. For products needed in developing countries, a number of push programs have been put in place, including the International AIDS Vaccine Initiative and the Malaria Vaccine Initiative – but policies have not yet been implemented that would guarantee a market to developers of new vaccines.

Push programs have led to some tremendous successes and are an essential part of any overall R&D strategy. However, these programs are also subject to several weaknesses. First, since funders cannot perfectly monitor the actions of grant recipients, researchers may be tempted to divert their effort away from developing the desired product toward other goals, such as researching problems of theoretical interest or working on their next grant application. In contrast, under pull programs money changes hands only when a usable product is delivered, so researchers' and funders' incentives are aligned.

A second problem is that researchers writing grant applications have incentives to make the case for funding appear as strong as possible. Decisionmakers must rely on the researchers for much of their information and they may therefore end up financing projects that have only a slight chance of success, or, worse, may be overcautious and fail to fund promising research. In contrast, under a pull program in which developers are rewarded once they produce the desired product there is a strong incentive for firms considering R&D investments to use all the information available to them in assessing their prospects for success.

A third concern with push programs is that when funds are allocated in advance of results, decisions may be based on political rather than scientific considerations. Domestically there may be pressure to allocate funds to specific states or congressional districts; internationally there may be pressure to allocate funds to specific countries. In contrast, under pull programs sponsors promise to pay for a viable vaccine no matter who develops it.

A dramatic illustration of the risks of push programs can be seen in the failure of U.S. Agency for International Development (USAID) efforts to develop a malaria vaccine in the 1980s. In 1984, the agency claimed that there had been a "major breakthrough in the development of a vaccine against the most deadly form of malaria in human beings," and that "the vaccine should be ready for use around the world, especially in developing countries, within five years." USAID spent $60 million on this program, only to discover that some of its grant money had been diverted and that the project director had received kickbacks. In the end, the research program yielded few results. Although there are of course many examples of successful push programs, the USAID example illustrates the vulnerability of such programs to general overoptimism and monitoring problems.

*Note by Michael Kremer*

Under pull programs the public pays only once a viable product is developed. How might a viable pull program be designed? The most attractive way to design a pull program is through an advance contract, in which sponsors commit to fully or partially cover the cost of purchasing products meeting certain prespecified technical requirements. For example, a sponsor could commit to guarantee a price of $15 (adjusted for inflation) for each of the first 200 million people immunized with a malaria vaccine, subject to a 10 percent co-payment from developing countries or other donors.

The credibility and design of the purchase commitment will obviously be a critical determinant of its effectiveness. Potential developers of a vaccine or drug must believe that once they have sunk funds into developing a product the sponsors will not renege on their commitments by paying a price that covers only the cost of manufacturing and not risk-adjusted R&D costs. Courts have held that similar public commitments to reward contest winners or to purchase specified goods constitute legally binding contracts, and that the decisions of independent parties appointed in advance to adjudicate such programs are binding. The credibility of a purchase commitment will therefore depend on clearly specifying product eligibility and pricing rules and on establishing a credible process for adjudicating any disputes.

A program could require that vaccines not only satisfy technical eligibility requirements, but also be subject to a market test. Nations wishing to purchase products or donors acting on their behalf might be required to provide a modest co-payment. This would help ensure that only useful products were rewarded and would give countries incentives to avoid wasting vaccines. Finally, force-majeure provisions should also be incorporated into the purchase agreement so that obligations would end if the disease environment changed radically and the product was no longer needed.

Given the enormous burden of diseases like malaria, commitments to purchase vaccines would be extremely cost effective. A price of $15 for the first 200 million people immunized, plus revenues from modest sales outside the program, would give a potential vaccine developer a net present value of revenues that would be comparable to the revenues from products developed for commercial purposes. A commitment at this level to purchase vaccines for malaria would be extremely cost effective, costing nothing if a usable product were not developed, and less than $20 per year of life saved if a vaccine were developed.

A wide range of policy leaders and organizations has endorsed the concept of purchase commitments. The Clinton administration proposed a pull program for HIV, tuberculosis, and malaria vaccines, and the Bush administration's Project Bioshield includes a pull-like mechanism for certain drugs and vaccines protecting against bioterrorism. Reports from the World Health Organization's Commission on Macroeconomics and Health and from the U.K. Cabinet Office have endorsed creating pull programs for vaccines. The president of the World Bank and leading members of the U.S. Congress, including Senators Frist and Kerry, have proposed pull programs. The Bill & Melinda Gates Foundation recently asked the Center for Global Development to establish a working group to examine the feasibility of a purchase commitment.

A number of organizations – including the World Bank, national governments, and private foundations like the Gates

Foundation – have the resources to enter into advance contracts to purchase needed vaccines. Such commitments may require changes in standard operating procedures, but they are certainly in the realm of feasibility. If purchase commitments fail to induce the development of new products, no money will have been spent. But if they succeed, millions of lives will be saved each year.