

## **Creating Markets for New Vaccines**

### **Part I: Rationale**<sup>\*</sup>

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## Abstract

Malaria, tuberculosis, and the strains of HIV common in Africa kill approximately 5 million people each year. Yet research on vaccines for these diseases remains minimal—largely because potential vaccine developers fear that they would not be able to sell enough vaccine at a sufficient price to recoup their research expenditures.

Enhancing markets for new vaccines could create incentives for vaccine research and increase accessibility of any vaccines developed. For example, the World Bank has proposed establishing a fund to help developing countries finance purchases of specified vaccines if they are invented. The U.S. administration's budget proposal includes a tax credit for new vaccines that would match each dollar of vaccine sales with a dollar of tax credits. This paper examines the rationale for such proposals.

Private firms currently conduct little research on vaccines against malaria, tuberculosis, and the strains of HIV common in Africa. This is not only because these diseases primarily affect poor countries, but also because vaccines are subject to severe market failures. Once vaccine developers have invested in developing vaccines, governments are tempted to use their powers as regulators, major purchasers, and arbiters of intellectual property rights to force prices to levels that do not cover research costs. Research on vaccines is an international public good, and none of the many small countries that would benefit from a malaria, tuberculosis, or HIV vaccine has an incentive to encourage research by unilaterally offering to pay higher prices. In fact, most vaccines sold in developing countries are priced at pennies per dose, a tiny fraction of their social value. More expensive, on-patent vaccines are typically not purchased by the poorest countries. Hence, private developers lack incentives to pursue socially valuable research opportunities. Large public purchases could potentially enlarge the market for vaccines, benefiting both vaccine producers and the public at large.

Government-directed research programs may be well-suited for basic research, but for the later, more applied stages of research, committing to compensate successful private vaccine developers has important advantages. Under such programs, the public pays only if a successful vaccine is actually developed. This gives pharmaceutical firms and scientists strong incentives to self-select research projects that have a reasonable chance of leading to a vaccine, and to focus on developing a viable vaccine rather than pursuing other goals.

Committing to purchase vaccines and make them available to poor countries may be attractive relative to other ways of rewarding vaccine developers. Extending patents on other pharmaceuticals to reward developers of new vaccines would place the entire burden of financing vaccines on those needing these other pharmaceuticals. Increasing prices for current vaccines without explicit incentives for development of new vaccines would be insufficient to spur new research.

Malaria, tuberculosis, and the strains of HIV prevalent in Africa kill almost five million people each year. Yet relative to this enormous burden, very little vaccine research is directed towards these diseases. Potential vaccine developers fear that they would not be able to sell enough vaccine at a high enough price to recoup their research investments. This is both because these diseases primarily affect poor countries, and because vaccine markets are severely distorted. This paper examines the economic rationale for committing in advance to purchase vaccines for these diseases. Such commitments could create incentives for vaccine research and help ensure that if vaccines were developed, poor countries could afford them. Because a vaccine purchase commitment would require no funds until a vaccine was available, it would not compete with budgets for current efforts to control diseases using existing technology.

These issues are particularly timely. The U.S. administration's budget proposal [<http://www.treas.gov taxpolicy/library/grnbk00.pdf>] includes \$1 billion in tax credits over the 2002-2010 period for vaccine sales. The program would match every dollar of qualifying vaccine sales with a dollar of tax credit, effectively doubling the incentive to develop vaccines for neglected diseases. Qualifying vaccines would have to cover infectious diseases which kill at least one million people each year, would have to be approved by the U.S. Food and Drug Administration (FDA), and would have to be certified by the Secretary of the Treasury after advice from the U.S. Agency for International Development. To qualify for the tax credit, sales would have to be made to approved purchasing institutions, such as the United Nations Children's Fund (UNICEF). Although the administration's proposal is structured as a tax credit, it would have effects similar to an expenditure program that matched private funds spent on vaccines.

The World Bank president, James Wolfensohn, recently said that the institution plans to create a \$1 billion fund to help countries purchase specified vaccines if and when they are developed [Financial Times, 2000]. Wolfensohn's proposal is being discussed within the Bank and would have to be approved by the Bank's board. One option under consideration is a more general program to combat communicable diseases of the poor. For a general program to stimulate research, it must include an explicit commitment to help finance the purchase of new vaccines if and when they are developed. Without an explicit commitment along the lines proposed by Wolfensohn, it is unlikely that the large scale investments needed to develop vaccines will be undertaken.

The concept of a vaccine purchase fund has also received support from European political leaders [<http://www.auswartiges.amt.de>, 1999].

Section 1 of this paper provides background information on malaria, HIV, and tuberculosis; discusses the prospects for vaccines for these diseases; and reviews the current state of scientific progress towards vaccine development.

Section 2 discusses distortions in the market for vaccines and for vaccine research. People tend to underconsume vaccines for a number of reasons. First, individuals have inadequate incentives to take vaccines, since those who take vaccines not only benefit themselves, but also benefit others by breaking the cycle of infection. Second, the chief beneficiaries of vaccination are often children, who cannot contract to pay vaccine sellers the future earnings they will reap if they take vaccines and stay healthy. Third, consumers are often more willing to pay for treatment than prevention, perhaps because it takes time for them to learn about the effectiveness of vaccines. Monopoly pricing further limits access to patented vaccines. Perhaps because of these factors, most countries purchase vaccines in bulk and distribute them at

subsidized rates. At appropriate prices, these large public purchases could potentially make both vaccine producers and the population at large better off than they would be under monopoly pricing by reducing the cost per dose and expanding the market.

Distortions in the market for vaccine research are even greater than those for vaccines themselves. Rough calculations suggest that the social benefits of malaria, tuberculosis, or HIV vaccines may easily exceed the returns to a private developer by a factor of ten or more, so vaccine developers will lack incentives to pursue socially valuable research opportunities. Research incentives are too small in many fields, but the situation is particularly problematic for vaccines and is dire for vaccines against diseases which primarily affect poor countries. It is often possible to design around vaccine patents, and since vaccines are primarily sold to governments, brand loyalty provides minimal benefit to the original developer. Once developers have sunk resources into developing vaccines, governments are often tempted to use their powers as regulators, major purchasers, and arbiters of intellectual property rights to obtain vaccines at prices which cover only manufacturing costs, not research costs. Since research and development on vaccines for malaria, tuberculosis, and HIV is a global public good that benefits many small countries, no single country has an incentive to encourage research by offering higher prices, and hence many countries have historically provided little or no intellectual property rights protection to vaccines. Most vaccines sold in developing countries sell for pennies per dose, and newer, on-patent, vaccines, which sell for a dollar or two per dose, do not reach the poorest countries. Crude calculations suggest that a malaria vaccine would be cost-effective relative to other developing country health programs at \$41 per person immunized. The gap between the \$41 at which a vaccine would be cost-effective and the \$2 which the historical record suggests a vaccine developer would be likely to obtain for a vaccine implies that

under current institutions, potential vaccine developers would not have incentives to pursue socially valuable research opportunities.

Section 3 examines the appropriate roles of “push” and “pull” programs in encouraging vaccine research and improving access to vaccines once they are developed. “Push” programs pay for research inputs, for example through grants to researchers, while “pull” programs pay for an actual vaccine. Push programs are well suited to financing basic research, because it is important that the results of basic research are quickly communicated to other scientists. Grant-funded researchers have incentives to publish quickly, while researchers with strong financial incentives to develop a vaccine might wish to withhold information from competitors.

Historically, however, governments have relied heavily on push programs to encourage even the later, more applied stages of vaccine development, in part because it was thought necessary to finance research expenditures in advance of the development of a vaccine. With the development of the biotech industry and the increased availability of finance from venture capitalists and large pharmaceutical firms, it is now much easier for scientists to attract investors to finance research, as long as a substantial market is expected for the product.

Pull programs can provide such a market, and they have several attractive features relative to traditional push programs for encouraging the later stages of vaccine development. Under pull programs, the public pays nothing unless a viable vaccine is developed. This gives researchers incentives to self-select projects with a reasonable chance of yielding a viable vaccine, rather than to oversell their research prospects to research administrators and the public. It allows politicians and the public to be confident that they are paying for an actual vaccine, rather than supporting a vaccine-development effort that might not be warranted scientifically. Pull programs also provide strong financial incentives for researchers to focus on developing a

marketable vaccine, rather than pursuing other goals, such as publishing academic articles.

Finally, pull programs can help ensure that if vaccines are developed, they will reach those who need them.

Section 4 compares a vaccine purchase commitment program to other pull programs designed to increase incentives for vaccine research. Rewarding vaccine developers with extensions of patents on other pharmaceuticals would inefficiently and inequitably place the entire burden of financing vaccine development on patients who need these other pharmaceuticals. Cash prizes for research are economically similar to a vaccine purchase program, but provide a somewhat weaker link between vaccine quality and the compensation paid to vaccine developers. They are also likely to be politically less attractive and therefore less credible to potential vaccine developers. Encouraging vaccine development through research tournaments is likely to be difficult, since there is no guarantee that a vaccine could be developed within a fixed time period. While expanded purchases and deliveries of currently underutilized vaccines would be highly cost-effective health interventions in their own right, such purchases are unlikely on their own to convince potential developers of vaccines for malaria, tuberculosis, or clades of HIV common in Africa that historically fickle international aid donors will provide funds to purchase vaccines for these diseases ten or fifteen years from now. Explicit purchase commitments would also be needed.

A companion paper, “Creating Markets for New Vaccines: Part II: Design Issues,” discusses how commitments to purchase vaccines could be structured.

This paper builds on previous literature. The idea of committing to purchase vaccines was discussed in WHO [1996] and was advocated by a coalition of organizations coordinated by the International AIDS Vaccine Initiative at the 1997 Denver G8 summit. Since then, the idea

has been explored by the World Bank AIDS Vaccine Task Force [World Bank, 1999 and 2000]. Kremer and Sachs [1999] and Sachs [1999] have advocated the establishment of a program in the popular press. This paper also draws on earlier work on vaccines, including Batson [1999], Dupuy and Freidel [1990], Mercer Management Consulting [1998], and Milstien and Batson [1994], and on the broader academic literature on research incentives, including Guell and Fischbaum [1995], Johnston and Zeckhauser [1991], Lanjouw and Cockburn [1999], Lichtmann [1997], Russell [1998], Scotchmer [1997], Shavell and van Ypserle [1998], and Wright [1983].

This paper differs from some of the earlier work mentioned in examining the case for commitments to purchase vaccines in light of the underlying economic principles of asymmetric information and time consistency. In particular, this paper argues that information asymmetries between funders and researchers may hamper programs which fund researchers in advance. The time-inconsistent preferences of governments imply that in the absence of specific commitments general statements of intent to purchase vaccines will not be credible. This paper also differs from earlier work in comparing commitments to purchase vaccines to other pull programs.

## **1. Background on Malaria, HIV, and Tuberculosis**

This section reviews the burden of the major infectious diseases, discusses scientific prospects for vaccines, and argues that current research efforts are paltry relative to the burden these diseases impose.

### **1.1. The Burden of Malaria, HIV/AIDS, and Tuberculosis**

Estimates of the burden of infectious disease vary widely, but it is clear that the burden is huge. The World Health Organization estimates that each year there are 300 million clinical cases of malaria and 1.1 million deaths from malaria. Almost all cases are in developing countries, and almost 90% are in Africa [WHO, 1999a]. Malaria is particularly likely to kill children and pregnant women. Resistance is spreading to the major drugs used for treating malaria and for providing short-term protection to travelers [Cowman, 1995].

Each year, approximately 1.9 million people die from tuberculosis. More than 98 percent of these deaths occur in developing countries [WHO, 1999a]. However, with up to 17 percent of tuberculosis infections resistant to all five major anti-tubercular drugs, the spread of resistance poses a threat to developed as well as developing countries [WHO, 1997]. The existing BCG vaccine, which is distributed widely, provides short-run, imperfect protection against tuberculosis, but a more effective vaccine, providing longer-term protection, is lacking.<sup>1</sup>

More than 33 million people are infected with HIV worldwide, over 95% of whom live in developing countries. In 1998, about 2.3 million people died of AIDS, 80% of whom lived in sub-Saharan Africa. Approximately 5.8 million people were newly infected, 70% of whom were in sub-Saharan Africa [WHO, 1999a; UNAIDS, 1998]. New life-extending HIV treatments are far too expensive for most individuals and governments in low-income countries. Since people with compromised immune systems are especially vulnerable to tuberculosis, the spread of HIV is contributing to the spread of tuberculosis. Indeed, of the 1.9 million people who die annually from tuberculosis, 400,000 are infected with HIV.

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<sup>1</sup> The vaccine has been much more effective in some trials than others: trials in Britain suggest effectiveness up to 80%, while those in the southern United States and southern India suggest close to zero effectiveness.

## 1.2. The Potential for Vaccines

Vaccines have proved effective against many other infectious diseases, and in the long run, they are likely to be the most effective and sustainable way to fight malaria, tuberculosis, and HIV/AIDS. The potential of vaccines is illustrated most vividly by the success of the smallpox vaccination program, which led to the eradication of the disease in the 1970s. About three-quarters of the world's children receive a standard package of cheap, off-patent vaccines through WHO's Expanded Program on Immunization (EPI), and these vaccines are estimated to save 3 million lives per year [Kim-Farley, 1990].<sup>2</sup> However, only a small fraction of children in poor countries receive newer vaccines, such as the *Haemophilus influenzae b* (Hib) vaccine, which are still on patent and hence more expensive.

The Global Alliance for Vaccines and Immunization (GAVI), with major financing from the Gates Foundation, is undertaking a large-scale effort to improve utilization of existing vaccines. This effort is likely to raise coverage rates and save millions of lives. Coverage rates would likely be further increased if effective vaccines were available against malaria, tuberculosis, or HIV/AIDS, since governments would then have greater incentives to maintain their immunization infrastructure, and parents would have more incentive to bring their children in for vaccination. Even if malaria, tuberculosis, or HIV vaccines only achieved the same coverage rates as the inexpensive EPI vaccines, they would still save millions of lives.

The question of whether vaccines can be developed against malaria, tuberculosis, and HIV remains open, but there is reason to be optimistic. A recent National Academy of Sciences report [1996] concludes that the development of a malaria vaccine is scientifically feasible.

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<sup>2</sup> Vaccination rates are uneven around the world, but the 74% worldwide vaccination rate does not just reflect rich country experience: of the 118 million children born each year, 107 million are born in developing countries.

Candidate vaccines have been shown to protect against malaria in several rodent and primate models. Moreover, the human immune system can be primed against natural malaria infection. People who survive beyond childhood in malaria endemic areas obtain limited immunity which protects them against severe malaria, although not against parasitemia and milder illness. Since vaccines prime the immune system by mimicking natural infection, vaccines may similarly provide protection against severe disease. Recently, candidate vaccines have been shown to induce protection against tuberculosis infection in animal models. The example of the existing BCG vaccine suggests that the human immune system can be primed against tuberculosis infection. A number of candidate HIV vaccines protect monkeys against infection and induce immune responses in humans.

Nonetheless, formidable scientific and technological obstacles remain in the way of development of malaria, tuberculosis, and HIV vaccines. All three diseases have many variants and evolve rapidly, making it difficult to design vaccines which are effective against all variants of the disease and which remain effective over time.

Recent advances in immunology, biochemistry, and cloning have given scientists new tools to understand the immune response to these diseases, find correlates of protection useful in testing whether candidate vaccines are likely to succeed, and develop better animal models. Genetic sequencing of the organisms causing tuberculosis, AIDS, and malaria is either complete or far advanced. This may help scientists create vaccines which target many different antigens, and thus are more effective in the face of genetic diversity.

### **1.3. Current Vaccine Research**

Despite the increasing scientific potential, current research on vaccines for malaria, tuberculosis, and HIV is paltry relative to the burden of these diseases. According to a Wellcome Trust study, public and non-profit malaria research amounted to about \$84 million in 1993, with vaccine research making up only a small fraction of the total [Wellcome Trust, 1996]. The amount of private sector spending on malaria is unknown, but is generally considered to be far lower than public spending. Less is known about total expenditures on tuberculosis research, but the United States National Institutes of Health, one of the world's leading funders of basic research, spends around \$65 million per year on tuberculosis research, compared with \$2.7 billion on cancer research [NIH, 1999].

Applied AIDS research is overwhelmingly oriented towards treatments which would be appropriate for people with AIDS in rich countries, rather than towards vaccines appropriate for poorer countries. The multi-drug treatments for HIV are not feasible for poor countries, since they cost \$10,000-16,000 a year [PhRMA, 1999], require ongoing immune monitoring, and need to be taken in perpetuity according to a precise protocol. To the extent that vaccine research is conducted, it is primarily oriented towards the HIV strains common in rich countries. Most candidate HIV vaccines tested worldwide are based on clade E, the strain of the virus most widespread in the United States, Europe, Australia, and Latin America, rather than the clades most common in Africa, where two-thirds of new infections occur. It is uncertain whether a vaccine developed for one clade would protect against other clades.

More generally, little research is oriented toward tropical diseases. Pecoul et al. [1999] report that of the 1,233 drugs licensed worldwide between 1975 and 1997, only 13 were for tropical diseases. Two of these were modifications of existing medicines, two were produced for the U.S. military, and five came from veterinary research. Only four were developed by

commercial pharmaceutical firms specifically for tropical diseases of humans. (Note, however, that the definition of tropical disease used in their assessment was narrow, and that many of the other drugs licensed in this period were useful in both developing and developed countries.)

## **2. Failures in the Markets for Vaccines and Vaccine Research**

One reason for the paucity of research on vaccines for malaria, tuberculosis, and clades of HIV common in Africa is simply that the countries affected by these diseases are poor, and cannot afford to pay much for vaccines. If this were the only reason, however, there would be no particular reason to target aid expenditures to vaccines or vaccine research, rather than to other goods needed in poor countries, such as food and shelter. In fact, however, distortions in the markets for vaccines lead them to be underconsumed even relative to the incomes of the poor. Even more severe distortions in the research market eliminate incentives for private firms to conduct vaccine research that would be cost-effective for society as a whole, even by the stringent cost-effectiveness standards used to evaluate health interventions in poor countries.

Sub-section 2.1 argues that vaccines are underconsumed and that large public purchases can potentially make both vaccine producers and consumers better off than they would be under monopoly pricing. Sub-section 2.2 argues that under current institutions, private returns to research are limited by the ease of designing around patents and by temptations for governments to hold down vaccine prices once vaccines have been developed. Sub-section 2.3 reports a rough calculation suggesting that vaccines would be cost-effective health interventions for poor countries at prices ten or twenty times as much as vaccine developers could hope to realize from

their work. Thus, under current institutional arrangements, private developers will lack incentives to pursue socially valuable research opportunities.

### **2.1. Failures in the Market for Vaccines**

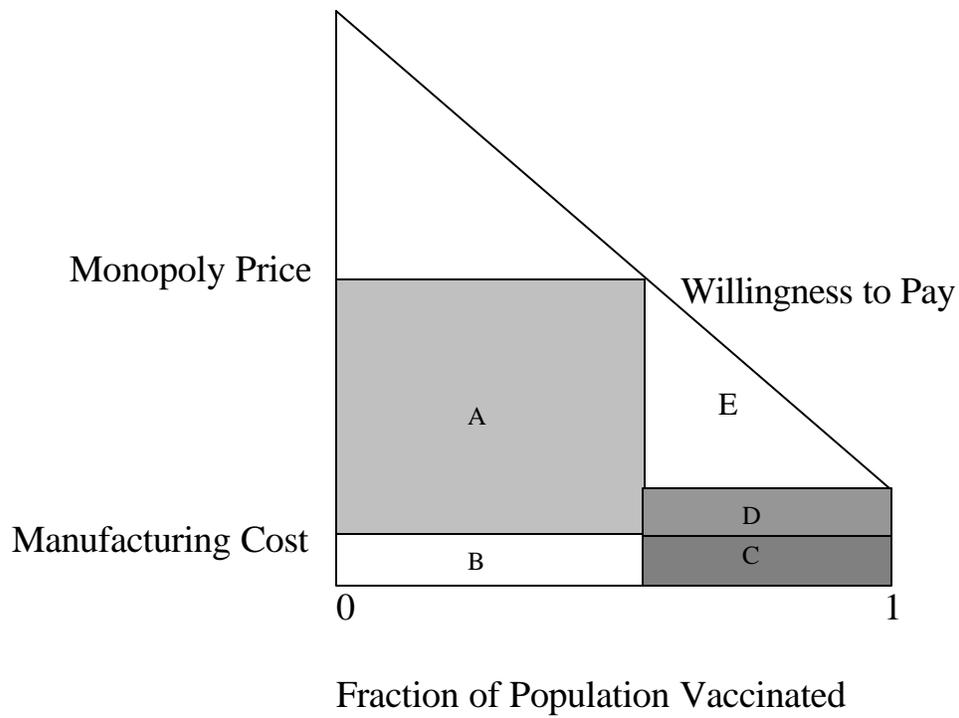
Vaccines are underconsumed for a variety of reasons. First, individuals who take vaccines not only benefit themselves, but also help break the chain of disease transmission, thus benefiting the rest of the population. Individuals have no incentive to take these external benefits into account in deciding whether to be vaccinated. Second, the chief beneficiaries of vaccines are often children. Even if the cost of vaccination is trivial relative to the extra future wages children will earn if they stay healthy, children cannot contract to pay for vaccination out of those future wages. Third, consumers seem much more willing to pay for treatment than prevention. Many potential consumers in developing countries are illiterate and place limited credence in official pronouncements about the benefits of vaccination. They may wait to see these benefits by observing what happens to neighbors who take vaccines. However, the benefits of vaccines, unlike those of drugs for treating diseases, are difficult to see, since the benefits of vaccines are not evident until considerably after vaccines are taken, and many people who do not take vaccines never get sick.

Monopoly pricing of vaccines would exacerbate underconsumption of vaccines. This may explain why governments in the vast majority of countries purchase vaccines and distribute them to the population either free or at a highly subsidized price. Because vaccine development is expensive, but manufacturing additional doses of vaccine is typically cheap, large government purchases can potentially make both vaccine producers and the general public better off than

they would be under monopoly pricing to individuals. This can be achieved by purchasing a large quantity of the vaccine at a lower price per dose than under monopoly pricing to individuals. The vaccine developer can be made better off if the total value of their sales (price times quantity) is higher than it would be under sales to individuals. Those consumers who would have been willing to pay the monopoly price are better off, as long as the taxes they would have to pay to finance government vaccine purchases are less than the monopoly price. The consumers who valued the vaccine at more than the production cost but less than the monopoly price can also be made better off, as long as the value they place on the vaccine is greater than the increase in taxes necessary to finance government purchases.

Figure 1 shows a situation in which government purchases can potentially make everyone better off than under monopoly pricing. The downward-sloping line shows the willingness to pay of different potential consumers for the vaccine, which depends on their income. The lower horizontal line represents the cost of producing an additional dose of the vaccine once the research costs have been incurred and the factory has been built. A monopolist will choose a price to maximize profits. Area A represents the surplus of revenue over marginal manufacturing costs under monopoly pricing. These funds can be used to cover the costs of research and development on the vaccine, the costs of building the factory, and any profits. Note that many people who are not willing to buy the vaccine at the monopoly price would be willing to pay more than the amount it costs to produce an additional dose of vaccine.

**Figure 1: Vaccine Pricing and Usage Under Monopoly Pricing and Government Purchases**



To see why large government purchases that expand the market and bring down the average cost per dose may potentially be able to make everybody better off, suppose that the government agrees to pay the vaccine manufacturer an amount equal to the sum of areas A, B, C, and D in exchange for enough vaccines for the entire population. If these purchases are funded by taxing people based on their income, with all people who would have paid the monopoly price paying just under that price, and all other people paying just over the actual production cost<sup>3</sup>, vaccine producers and the general public will both be better off than under monopoly pricing.<sup>45</sup> Areas D and E represent the social benefit of the vaccine purchase program.

Note that while large government purchases could *potentially* make both consumers and producers better off, if governments force prices too low, they risk making vaccine developers worse off than under a private market system, thus discouraging research.

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<sup>3</sup> Pharmaceutical manufacturers may try to sell the vaccine to different customers at different prices. However, the ability of pharmaceutical manufacturers to discriminate between customers in this way is limited, because all customers will try to obtain the vaccine at the lower price. The government has the power to tax higher income earners at a higher rate. Pharmaceutical manufacturers may come up with crude income indicators, for example by selling at a discount to groups of hospitals, but they have less scope to vary prices with income than the government does to vary taxes with income.

<sup>4</sup> Note that if the willingness to pay for vaccines depends on factors other than income, then tax-financed government vaccine purchases may not make literally everyone better off, because some people may not want to take the vaccine at any price. To see this, it is useful to consider the cases of malaria and HIV. If a safe, cheap, and effective malaria vaccine were developed, almost everyone living in areas with malaria would presumably want to purchase it. On the other hand, some people might not want to take an AIDS vaccine, even if it were free, because they believe that they have a very low chance of contracting the disease. Since taxes would presumably fall equally on people with a low and a high risk of contracting AIDS, large government purchases of an AIDS vaccine might not literally make everyone better off. The willingness of people in low-risk groups to pay for the vaccine might be less than the increase in their taxes necessary to pay for vaccine purchases.

<sup>5</sup> As discussed in a companion paper, “Creating Markets for New Vaccines: Part II: Design Issues”, government purchase and distribution of products with large development costs but low manufacturing costs involves its own difficulties. Hence, governments do not purchase and distribute all such products. However, purchasing vaccines is likely to be much easier than purchasing other goods, such as CDs. It is difficult for the government to specify what characteristics a CD would need to be eligible for purchase, or how much to pay CD producers as a function of CD quality. Specifying eligibility and pricing rules for vaccines is easier, albeit far from trivial.

## 2.2. Failures in the Market for Vaccine Research

Economists have estimated that the social returns to research and development are typically twice the returns to private developers [Nadiri, 1993; Mansfield et al., 1977]. Private developers therefore lack incentives to pursue research on socially valuable projects. The gap between private and social returns to research is likely to be much greater for research on malaria, tuberculosis, and HIV vaccines than in many other research areas of applied research. This is because it is often possible to design around vaccine patents and because governments are often tempted to use their powers as regulators and large purchasers to hold down vaccine prices after firms have sunk their research investments and developed a vaccine. Because vaccine research is a global public good benefiting many small countries, no single country has an incentive to pay higher vaccine prices to encourage research.

It is often possible to design around vaccine patents, and this may make it difficult for the original developers of new vaccines to recoup their research expenditures. Once they have invested millions in a risky effort to develop new vaccines, competitors may be able to slightly alter their approach so as to develop a competing vaccine, driving down prices. In many industries, first-mover advantages are often as important as patents in spurring innovation. However, governments and international organizations purchase most vaccines, and these institutions are not particularly subject to brand loyalty.

Vaccine research is subject to what economists call a “time consistency” problem. Vaccine research is very expensive, but once vaccines have been invented, they can usually be manufactured at low cost.<sup>6</sup> Once a vaccine has been developed, even a public-spirited

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<sup>6</sup> Note, however, that new vaccines, particularly those based on conjugate technology, are likely to have somewhat greater manufacturing costs than traditional vaccines.

government may be tempted to try to obtain vaccines at a price that would cover manufacturing costs but not research costs. Governments are in a strong bargaining position at this point because they are major vaccine purchasers, they regulate vaccines, and they are arbiters of intellectual property rights. Governments and international organizations therefore can, and do, bargain for very low prices. Thus, while in theory government purchases of vaccines could make both vaccine producers and consumers better off, in practice they are often used as a vehicle to transfer wealth from vaccine producers to consumers.<sup>7</sup> Since potential researchers anticipate this redistribution, they invest less in research than they otherwise would.

The time-consistency problem that leads governments to pay low prices for vaccines is exacerbated by political problems in many developing countries that make vaccines a low political priority. In particular, since vaccines deliver a widely distributed benefit, they tend to receive less political support than expenditures which benefit more concentrated and politically organized groups, including salaries for health workers.

Moreover, vaccine research and development is a global public good, so each country has an incentive to free ride off research financed by other countries' governments or induced by their intellectual property rights protection. A large country, such as the United States, would know that if it did this, it would risk cutting off the flow of future research. Small countries, such as Uganda, can assume that individually their actions will have little effect on total research incentives. However, if all African countries act this way, there will be little incentive for development of a malaria vaccine.

This free-riding problem is particularly severe for countries that are only a small fraction of the world market and hence reap only a small fraction of the worldwide benefits of research.

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<sup>7</sup> Large liability awards can also be interpreted as a way that governments extract resources from vaccine developers.

Pharmaceutical prices are controlled at prices approximately one half of United States levels in the European Union, while in Japan, they are controlled at one quarter of U. S. levels [Robbins and Freeman, 1988]. The world's three leading infectious diseases affect many small developing countries, which have even less reason to internalize the benefits of drug development than the European Union or Japan.<sup>8</sup>

Historically, developing countries have not provided much protection for intellectual property rights for pharmaceuticals. Until recently, many developing countries did not grant patent protection for pharmaceuticals and thereby kept prices low [Siebeck, 1990]. Several developing countries, including India and Brazil, have recently agreed to enhance intellectual property rights for pharmaceuticals, but only under intense trade pressure from the United States. It remains to be seen whether the promised intellectual property rights policies will be enforced. Many pharmaceutical firms are skeptical. The South African government recently announced that it may attempt to force patent holders on AIDS drugs to license their patents to generic manufacturers. The United States initially opposed this, but abandoned its opposition in response to a storm of protest. Given the huge importance of an HIV or malaria vaccine to many developing countries, it is far from clear that the U.S. could induce developing countries to establish strong intellectual property rights for such vaccines, short of offering to pay for the additional costs this would impose on the countries.

Research on vaccines for diseases prevalent in both developed and developing countries has been stimulated by demand in developed countries. However, the limited intellectual

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<sup>8</sup> Data on the distribution of burden of disease by country is limited, but some rough calculations suggest that the share of the worldwide disease burden in the country with the greatest burden ranges from 14% and 18% for HIV and malaria respectively, which disproportionately affect Africa, to 25% for tuberculosis, which is a big problem in India. The share of burden borne by the top four countries is in the 40-50% range.

property rights available in many poor countries deter research on vaccines against diseases such as malaria, which would have little market in developed countries.

Note that even if intellectual property rights were enforced globally, the same arguments which suggest that national vaccine purchases are more efficient than individual purchases would also suggest that international purchases are potentially more efficient than national purchases. If vaccine developers charge a single monopoly price to governments, some countries will not be able to afford to purchase the vaccine. All countries could potentially be made better off, as long as the rich countries paid no more than the monopoly price they would have paid otherwise, and the poor countries pay less than the amount at which they value the vaccine, but more than the actual production cost. Note also that even if poor countries could somehow be induced to establish strong intellectual property rights for vaccine developers, they would still have market power as purchasers, and hence would still likely be able to negotiate a price below the full social value of vaccines. Hence research and development incentives would likely be too small even in this case.

The market could reach efficient size if vaccine developers charged each nation a separate price based on what they were willing to pay, through a system of tiered pricing. In fact, pharmaceutical firms do charge different prices to different countries. However, opportunities for tiered pricing are limited, partly by the possibility of resale, but primarily by fear of a political backlash in rich countries. Politically, it is difficult for pharmaceutical firms to justify charging much higher prices in one country than in another. For example, after a Congressional hearing in which Senator Paula Hawkins asked a major vaccine manufacturer how it could justify charging nearly three times as much to the United States government for vaccines

as to foreign countries, U.S. manufacturers stopped submitting bids to UNICEF to supply vaccines.<sup>9</sup>

One way to achieve some of the same objectives as tiered pricing would be to purchase vaccines internationally for a range of poor countries at a single price and then collect co-payments from these countries that would vary with their incomes. This approach would increase access to vaccines, while ensuring that richer countries, which have greater willingness to pay for vaccines, contribute more towards covering the costs of vaccine research and development. The embarrassment of charging many different prices to different countries would be avoided. This approach would, however, require outside funding to make up the difference between the price at which vaccines are purchased from manufacturers and the co-payments received from the poorest countries.

### **2.3. Social vs. Private Return: Some Quantitative Estimates**

A crude preliminary estimate suggests that the social benefits of vaccines may be ten to twenty times the private benefits appropriated by vaccine developers. Since potential vaccine developers will consider only private returns in setting their research budgets, incentives for vaccine research are almost certainly far too small.

Consider the potential benefits from a hypothetical 80 percent effective one-dose malaria vaccine. A standard way to assess the cost-effectiveness of a health intervention is the cost per Disability Adjusted Life Year (DALY) saved. In its 1993 World Development Report, the

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<sup>9</sup> When President Clinton announced his childhood immunization initiative in 1993, he said, "I cannot believe that anyone seriously believes that America should manufacture vaccines for the world, sell them cheaper in foreign countries, and immunize fewer kids as a percentage of the population than any nation in this hemisphere but Bolivia and Haiti." [Mitchell, Philipose, and Sanford, 1993].

World Bank defined health interventions as “highly cost-effective” for poor countries if they cost less than \$100 per DALY saved. (In contrast, health interventions are considered cost-effective in the U.S. at up to 500 to 1000 times this amount – \$50,000-\$100,000 per year of life saved [Neumann et al., 2000].) The WHO recently estimated that malaria costs 39.3 million DALYs per year [WHO, 1999a].

Malaria is particularly deadly in children under five, who have not yet developed limited natural immunity, and women pregnant with their first child, whose immune systems are suppressed. The target population for a malaria vaccine would be the roughly 50 million children born annually in low-income and lower-middle-income countries with high enough prevalence to make vaccination cost-effective and approximately 10 million women pregnant with their first child living in countries with high enough prevalence to make vaccination of this group cost effective.<sup>10</sup> We assume that 75% of targeted children and 50% of targeted first-time mothers are reached, so that 42.1 million people are immunized annually. Incremental delivery costs for adding a single-dose childhood to the EPI package might be about \$1.00 per child vaccinated.<sup>11</sup> The marginal cost of delivery for pregnant women might be closer to \$3.00 per woman vaccinated. A rough calculation suggests that delivery of such a vaccine would save 17.6 million DALYs each year and would cost \$52.2 million annually for a delivery cost of about \$2.97 per DALY saved. This implies that at a cost-effectiveness threshold of \$100 per DALY, an 80% effective malaria vaccine would be cost-effective even at a price of \$41 per immunized person, or a total of \$.17 billion annually to immunize 42.1 million people.<sup>12</sup> Note

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<sup>10</sup> Existing cohorts of children younger than five might also be vaccinated, but since this is a one-time occurrence, it is ignored in this calculation.

<sup>11</sup> The addition of both the hepatitis B and the yellow fever vaccines (which are relatively expensive) to the WHO’s Expanded Program of Immunization increased the \$15 cost of the program by 15%, or \$2.25, including both manufacturing and distribution costs.

<sup>12</sup> To see this, note that  $17.6 \text{ million DALYs} \times \$100/\text{DALY} = \$1.76 \text{ billion} = \$52.2 \text{ million in delivery costs} + \$41 \text{ per dose} \times 42.1 \text{ million doses}$ .

that these figures do not take into account knock-on reductions in secondary infections or the potential economic benefits of reducing malaria prevalence beyond the impact on the individual suffering from the disease.<sup>13</sup> (See [Glennester and Kremer, 2000] for more detailed calculations of vaccine cost effectiveness.)

These calculations imply that from the standpoint of society as a whole, it would be cost-effective for private developers to conduct research leading to a malaria vaccine, even if the research were risky and expensive enough that the developer would have to charge \$41 per immunized person, or \$1.7 billion annually, in perpetuity, to recoup the research costs and the risk of failure. However, such a research investment would not be cost-effective from the standpoint of a private developer. To give some indication of this, the total developing country market for childhood vaccines is \$200 million annually [World Bank AIDS Vaccine Task Force, 2000]. The combined cost of the six vaccines in the standard Expanded Program on Immunization (EPI) package is about \$0.50 [Robbins and Freeman, 1988]. Of course, a vaccine under patent would likely generate greater revenues than off-patent vaccines. However, when the hepatitis B vaccine was first introduced and priced at \$30 per dose, it was used infrequently in developing countries [Muraskin 1995; Galambos 1995].<sup>14</sup> Even at a dollar or two per dose, hepatitis B and Haemophilus influenzae b vaccines do not reach most children in the poorest countries [General Accounting Office, 1999]. It seems likely that the developer of a malaria vaccine would receive payments worth less than one-tenth or one-twentieth of the \$41 per immunized person at which vaccines would be cost effective. The huge disparity between

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<sup>13</sup> Gallup and Sachs [2000] use a cross-country regression approach to estimate that countries with severe malaria grew 1.3% less per year than those without malaria. It is difficult to know the portion of this statistical relationship which is causal.

<sup>14</sup> Even if the entire pharmaceutical budget in many African countries went to malaria vaccines, the benefit to a vaccine developer would be far less than the social benefit.

private incentives to invest in research and the social benefits of a vaccine suggests that research investment will be far too little in the absence of public support.

To summarize, vaccine research is an international public good, since efforts by one country to develop a malaria vaccine will benefit others as well. Once vaccines are developed, governments may be tempted not to compensate vaccine developers for their research expenditures, so potential developers will not invest in research without credible commitments that they will be paid. A rough quantitative estimate suggests that vaccine developers will lack incentive to pursue malaria, tuberculosis, and HIV vaccine research, even if this research would be extremely cost-effective for society as a whole. These factors suggest that encouraging vaccine research may be very cost-effective relative to existing forms of development assistance which do not particularly target global public goods. The next two sections discuss alternative ways to promote vaccine research.

### **3. The Roles of Push and Pull Programs in Encouraging Vaccine Research**

The literature on vaccine research distinguishes between “push” and “pull” programs. Push programs provide funding for vaccine research, for example through grants to academics, public equity investments in vaccine development, research and development tax credits, or work in government laboratories. Pull programs increase rewards for development of a vaccine, for example by promising to purchase a vaccine if it is developed. Roughly, the distinction is between paying for research inputs and paying for research outputs. Sub-section 3.1 argues that pull programs are well-suited to the later stages of the vaccine development process, and discusses some of the problems with push programs, as illustrated by the history of USAID’s

push program to develop a malaria vaccine. Sub-section 3.2 argues that push programs are well-suited to financing basic research, and discusses how push and pull programs can be combined.

### **3.1. The Potential Role of Pull Programs**

Historically, programs designed to encourage vaccine research financed research inputs ahead of time rather than offering to pay for a vaccine.<sup>15</sup> This may have been in part because there were relatively few sources of finance for commercial pharmaceutical research outside a few major pharmaceutical companies. However, the rise of the biotech industry, the availability of venture capital, and the increased willingness and ability of large pharmaceutical firms to contract with smaller firms and universities have made it much easier for researchers with reasonable scientific prospects of developing a product to attract outside investors, as long as a sufficient market is expected for the product. Pull programs could create such a market. It is worth reevaluating methods of supporting research in light of this changed institutional environment.

Under pull programs the government pays nothing unless a vaccine is developed. This creates strong incentives for researchers to 1) carefully select research projects and 2) focus on developing viable vaccines, rather than pursuing other goals.

Perhaps the chief advantage of pull programs that provide strong financial incentives for production of a vaccine is that they help in selecting research projects. This is true both at the level of selecting individual research projects and at the level of determining whether a major

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<sup>15</sup> Several vaccines were therefore developed primarily in the public sector, and only later licensed out to the private sector for production. For example, the meningococcal meningitis vaccine was developed almost entirely at the Walter Reed Army Institute of Research, and a hepatitis B vaccine was designed by the Hepatitis B Task Force [Muraskin, 1995]. However, it is not clear that the development of these vaccines in the public sector reflects so

research effort on vaccines for malaria, tuberculosis, or AIDS is scientifically warranted at all. Researchers working on a particular line of research have an interest in exaggerating the promise of their own lines of research. Scientific administrators may have trouble deciding which diseases are worth working on, and which vaccine approaches, if any, are worth pursuing. They may wind up financing ideas with only a minute probability of success, or worse, failing to fund promising vaccine research because they do not have confidence that its backers are presenting objective information on its prospects.

Public-sector equity investments in vaccine-development projects are subject to a similar problem. Firms which believe that they have identified projects with very high expected net present value will be least inclined to seek public sector investments which would dilute their equity stake, while those who are least confident about their research prospects will be most inclined to seek outside equity investment.

Even if government-directed research programs manage to initially select appropriate research projects, they are likely to fail to revise these judgements in light of later evidence. If results on a particular research project that initially appear promising later turn out to be disappointing, a private firm is likely to shut the project down. A public entity may acquire its own bureaucratic momentum, leading governments to throw good money after bad. Public sector institutions are notoriously difficult to shut down.

The problem of selecting research projects exists not only on the level of deciding which research avenues toward a particular vaccine are most promising, but also at the level of deciding whether to expand vaccine research at all. Section 2.3 argued that since vaccines would be cost-effective at prices much greater than vaccines developers could hope to receive, private developers would have an incentive to pass up research opportunities that were cost-effective

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much the suitability of the public sector for this task as the barriers facing private-sector vaccine development.

from the standpoint of society as a whole. This does not prove that such opportunities exist. Elected officials and the public are likely to find it very difficult to assess the scientific opportunities for research on malaria, tuberculosis, and AIDS vaccines. Under a system of grant-financed research, advocates for particular diseases and scientists working on the disease have an interest in exaggerating the opportunities.

While the gap between private and social incentives for vaccine development does not prove that socially useful research opportunities exist, it does suggest a case for bringing private and social incentives into line, so that private developers will have incentives to pursue any socially desirable research investments that do exist. A vaccine purchase commitment can do this. Since taxpayers pay nothing unless and until an effective vaccine is produced, elected officials and the public do not have to worry that they are investing millions to develop a technically infeasible vaccine. Government officials do not have to decide between competing scientific approaches. Pharmaceutical firms contemplating pursuing a line of research and scientists contemplating joining biotech ventures in exchange for stock options will invest their money and time only if they believe the scientific prospects are promising. Purchase commitments have an advantage over research grants or equity investments precisely because the scientific potential for vaccines is difficult for outsiders to assess.

In addition to allowing researchers to self-select promising projects, pull programs encourage researchers to focus intently on developing a marketable vaccine, rather than on other goals. Many academic and government researchers have career incentives and intellectual interests that orient them to fundamental science. In contrast, the later, more applied stages of vaccine development include activities that are not particularly interesting intellectually, but are expensive. Techniques for manufacturing sufficient quantities of candidate vaccines in sufficient

purity for clinical trials must be developed. Animal models for the disease must be created. Vaccine trials in the field must be conducted. Nobody wins a Nobel Prize for these important steps in vaccine development. By linking payment to results, pull programs provide strong incentives to researchers to concentrate their efforts on development of a vaccine.<sup>16</sup> Under a system of grant-financed research it can be difficult to monitor that researchers are focusing on development of a vaccine rather than publishing articles or applying for the next grant.

A similar monitoring problem arises when private research is subsidized through R & D targeted tax credits. Currently, U.S. companies are eligible for a 20% research and development tax credit. A bill recently introduced in the United States Congress proposes increasing this credit to 30% for research on vaccines for diseases that kill more than one million people a year. One potential problem with such an approach is that firms doing research with only indirect implications for these diseases might try to claim eligibility for the credit, while focusing much of their effort on developing more lucrative products.<sup>17</sup> In contrast, a tax credit linked to the sale of a vaccine, such as that proposed in President Clinton's 2000 budget, does not face the same monitoring problems. This credit will only be awarded if a marketable vaccine is produced.

Another problem with push programs is that when governments directly allocate research spending up front, they sometimes base decisions on political, rather than scientific, considerations. For example, there may be pressure to spend funds in particular congressional districts. The analogue for internationally supported research on malaria, tuberculosis, and HIV is political pressure to allocate research expenditures to particular countries, developing countries

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<sup>16</sup> Of course to the extent that some of the work required to produce a vaccine is not so intellectually interesting, scientists will need to be paid more to conduct this work [See Stern, 2000].

<sup>17</sup> Another problem with the particular form of the research and development tax credit used in the United States is that it rewards incremental R&D spending, thus creating a ratchet effect which limits the rewards for sustained high R&D expenditures [Hall, 1993].

in particular. With pull programs, in contrast, the sponsors promise to pay for a viable vaccine wherever it is developed.

The risks that grant-funded scientists and research administrators competing for budgets will overestimate the chances of success and divert resources away from vaccine research are far from hypothetical. Desowitz [1991] chronicles the sad story of the U.S. Agency for International Development's (USAID) 1980s push program to develop a malaria vaccine. USAID's efforts focused on three teams. A candidate vaccine was developed by the first team. Tests with 9 volunteers found that only 2 were protected from malaria, and suggested that the vaccine created side effects. These results, mixed at best, did not prevent USAID from issuing wildly overoptimistic statements. 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. The vaccine should be ready for use around the world, especially in developing countries, within five years."<sup>18</sup> Fifteen years later, the world is still waiting for a malaria vaccine.

Early work by the second team yielded disappointing results, but not surprisingly, the principal investigator argued that his approach was still worth pursuing and requested an additional \$2.38 million from USAID. The expert consultants assigned to review the project recommended that the research not be funded. However, USAID's malaria vaccine project director told the USAID Office of Procurement that the expert panel "had endorsed the scientific methodology and the exceptional qualifications and experience of the researchers."<sup>19</sup> Once the grant came through, the principal investigator transferred grant funds to his personal account. He was later indicted for theft.

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<sup>18</sup> All quotations are taken from Desowitz [1991], p. 255.

<sup>19</sup> From Desowitz [1991], p.258.

The external evaluations of the third proposal called it mediocre and unrealistic. The USAID project director ignored the report and arranged for the project to be fully funded. The principal investigator and his administrative assistant were later indicted for theft and criminal conspiracy in diverting money from the grant to their personal accounts. Two months before his arrest, the Rockefeller Foundation had provided him with a \$750,000 research grant, and on the very day that he was arrested, USAID announced it was giving him an additional \$1.65 million for research.

By 1986, USAID had spent over \$60 million on its malaria vaccine efforts, with little progress. Since USAID believed that there would soon be many candidate malaria vaccines suitable for testing, it tried to obtain monkeys as test subjects for these vaccines. USAID's malaria vaccine project director, James Erickson, arranged for a contract to acquire monkeys to go to an associate who paid him a kickback. Erickson eventually pleaded guilty to accepting an illegal gratuity, filing false tax returns, and making false statements.

What about outside oversight? USAID had arranged for independent oversight to be provided by the American Institute of Biological Science (AIBS). Erickson and the AIBS-assigned project manager were lovers.

The USAID case is extreme, and many push programs are quite successful. But the general principle remains that researchers funded under push programs have incentives to be overoptimistic, and since they are paid before delivering a product, they may be tempted to divert resources away from the search for a vaccine.

The USAID example may shed light on why the administrators of push programs and the researchers financed by such programs often believe that push programs are somehow cheaper than pull programs.

As a first approximation, a biotech or pharmaceutical firm will find it profitable to take on a project if the probability of success times the net present value of profits if the project succeeds exceeds the cost of undertaking the project. This implies that even in the best case, if the government funds only worthwhile research projects and researchers focus all their energies on developing a vaccine, the expected discounted cost of developing a vaccine is likely to be similar in net present value terms whether research is financed at the front end, through government grants or induced by payments for a successful vaccine at the back end.<sup>20</sup> In the more likely case, when research organizations are more careful in selecting projects and more focused on developing vaccines if they are only paid if they succeed, private research is likely to be more cost-effective than government programs.

Why then do many government scientists argue that push programs are cheaper than pull programs? The USAID example illustrates that researchers are prone to underestimate their costs and overestimate their chance of success. Of course, scientists in pharmaceutical firms do the same. But pharmaceutical executives and biotech investors anticipate this overoptimism, and correct for it by requiring high projected hurdle rates before approving projects or investing funds.<sup>1</sup> The net effect is that pharmaceutical executives and biotech investors wind up approving projects that are likely to have positive net present value after correcting for the overoptimism of project proponents. It is misleading to compare the amounts government scientists claim they would need to develop vaccines with the markets pharmaceutical executives claim they would need to justify vaccine investments.

The analysis above is theoretical, but it is consistent with the empirical evidence, which suggests that both government and private R & D have strong positive returns, but that the rate of

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<sup>20</sup> The cost of capital may be lower for the government than for pharmaceutical firms, but the difference is not that large.

return on private R & D is substantially greater [Nadiri, 1993; Nadiri and Mamuneas, 1994; and Bernstein and Nadiri, 1988, 1991]. The empirical record of government efforts to pick winners in research and development of commercial products is littered with failures, from supersonic transport to the breeder reactor to the Carter oil shale program.

In summary, while the case of USAID's malaria vaccine program is extreme, and many push programs are effective, push programs in general are vulnerable to overoptimism and monitoring problems. With pull programs, in contrast, biotech and pharmaceutical firms spend their own money on research, and the public pays only if a vaccine is produced.

### **3.2. Combining Push and Pull Programs**

Although pull programs have an advantage in the later stages of development, push programs are likely to be well-suited to financing basic research. The main objective of basic research, by definition, is to provide information to other researchers rather than to develop products. A program which ties incentives to the development of a product would encourage researchers to keep their research results private as long as possible in order to have an advantage in the next stage of research. In contrast, grant-funded academics and scientists in government laboratories have career incentives to publish their results quickly. (One way around this would be to link payment to research output, but it is difficult to measure the quality of basic research. It is not simply a matter of testing if a vaccine works, or a product sells.)

Push programs also have some attractive features even for later stages of research. To the extent that intermediate steps in the vaccine research and development process create spillovers for other researchers, it might be worth considering providing milestone payments tied to these

intermediate steps. For example, milestone payments could be paid if efficacy were demonstrated in animals. However, milestone payments do not target the ultimate objective of a vaccine, and hence might stimulate wasteful investments in research lines that were unlikely to lead to a viable vaccine. For example, researchers might try to demonstrate efficacy in animal models for a vaccine that was unlikely to be safe in humans. This problem is greater the larger the milestone payment; if a milestone payment is greater than the cost of performing the research, firms might find it profitable to reach the milestone even if they know they can go no further. Milestone payments will be less likely to stimulate wasteful research on candidates unlikely to yield a viable vaccine if they are given in the form of subsidies for future research on the candidate vaccine.

It is not clear whether the same body which administers a vaccine purchase commitment program should also award milestone payments. On the one hand, a track record of milestone payments could help build credibility for a vaccine purchase commitment. On the other hand, a committee that had supported, or not supported, a line of research through milestone payments might find it difficult to be objective in assessing eligibility and pricing for a vaccine purchase commitment.

Push programs have other advantages. Government programs that pay for research whether it succeeds or fails transfer the risk of failure from the research firms' shareholders to society at large, and to the extent that shareholders cannot diversify risk in the stock market, this risk-spreading is a potential advantage of push programs. A number of theoretical models suggest that private firms competing for a patent may inefficiently duplicate each other's activities. A centralized program may prevent this. (On the other hand, while decentralization

may lead to some duplication of effort, it also means that mistakes by a single decision-maker will not block progress towards a vaccine.)

One of the biggest advantages of push programs relative to pull programs (other than patents) is that they do not require specifying the output ahead of time. A pull program could not have been used to encourage the development of the Post-It Note<sup>®</sup> or the graphical user interface, because these products could not have been adequately described before they were invented. In contrast, it is comparatively easier to define what is meant by a safe and efficacious vaccine, and existing institutions, such as the U.S. FDA, are already charged with making these determinations. As discussed in the companion paper, “Creating Markets for New Vaccines: Design Issues,” even for vaccines, however, defining eligibility standards is far from trivial,

In general, society seems to prefer to use direct government support for basic research, while using the promise of an exclusive market, rather than centralized government programs, to stimulate the applied work of actual product development. Applying the same principle to vaccines would suggest using the promise of a market to encourage applied vaccine research.

Some push programs are already in place to spur vaccine research, although funding is modest. For example, the International AIDS Vaccine Initiative (IAVI) supports AIDS vaccine efforts. In contrast, there are currently no programs in place to fully reward developers of viable malaria, tuberculosis, or HIV vaccines. If the already existing push programs were complemented with pull programs, researchers would still have an incentive to pursue any promising research leads that slip through the cracks of the push system.

If vaccine research were supported through a mix of push and pull programs, push funders could insist on a share of revenues if a project they support leads to a vaccine that is

rewarded through a pull program, or could condition public financing on agreement to supply the vaccine to poor countries at a modest markup over manufacturing costs.

#### **4. Alternative Pull Programs**

Pull programs that reward successful vaccine research could take several different forms other than commitments to purchase vaccines, including extensions of patent rights on other products, cash prizes, research tournaments, and signaling willingness to pay more for future vaccines by purchasing more existing vaccines at a higher price.<sup>21</sup> Given the huge disparities between private and social returns to research, it is likely that any reasonable program to reward vaccine developers would be cost effective relative to the alternative of sticking with the status quo. However, this section argues that extensions of patent rights on other pharmaceuticals are not the most efficient way to reward vaccine developers; that while cash prizes and commitments to purchase vaccines are economically quite similar, purchase commitments are likely to be somewhat more attractive politically, and thus more credible to potential vaccine developers; and that research tournaments are inappropriate for situations like vaccine development, in which it is possible that no satisfactory product will be created by a given date. Purchasing and distributing currently underutilized vaccines is certainly justified in its own right, but on its own is unlikely to convince potential developers of vaccines for malaria, tuberculosis, or strains of HIV common

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<sup>21</sup> In a previous paper [Kremer, 1998], I discuss the possibility of buying out patents, using an auction to establish the patent's value. This can be seen as a method of determining the appropriate cash prize in lieu of a patent. One advantage of this approach is that it can be used even for inventions such as the Post-It® note, which could not be defined ahead of time and which would be very hard to create even a semi-objective procedure for valuing. On the other hand, the auction procedure for valuing patents described in that paper may be subject to collusion. For products such as vaccines, which are comparatively easier to define ahead of time and for which it is comparatively easy to evaluate effectiveness, advance purchase commitments may be just as effective as patent buyouts, and less subject to collusion.

in Africa that the international community will be willing to pay for these vaccines in ten or fifteen years.

#### **4.1 Patent Extensions**

Jonathan Mann, the late founding director of the WHO Global Program on AIDS, suggested compensating the developer of an HIV vaccine with a ten-year extension of patent rights on another pharmaceutical. With successful pharmaceuticals bringing in as much as \$3.6 billion in annual sales [CNNfn, 1998] such a patent extension would be very valuable. Patent extensions may be politically appealing to advocates, in that they need not go through the budget process. However, they inefficiently and inequitably place the entire burden of financing vaccine development on patients in need of the drug for which the patent has been extended. To see this, note that extending the patent on Prozac as compensation for developing an HIV vaccine is economically equivalent to imposing a high tax on Prozac and using the proceeds to finance cash compensation for the HIV vaccine developer. High taxes on narrow bases are typically an inefficient way of raising revenue, since they distort consumption away from the taxed good.<sup>22</sup> An extension of the Prozac patent would prevent some people from getting needed treatment for depression.

The potential countervailing advantage of patents is that when they are applied to the invented good, they closely link the inventor's compensation to the value of the invention, since inventors will be able to charge more for valuable inventions. If a vaccine is more effective,

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<sup>22</sup> As Michael Rothchild has pointed out to me, if governments and Health Maintenance Organizations (HMOs) purchase pharmaceuticals, patents may be equivalent to a broad-based tax. Nonetheless, patents may still be distortionary if HMOs and governments respond to pharmaceutical prices in their treatment decisions. Governments

causes fewer side effects, and is easier to administer, it will bring in more revenue. Patents therefore create appropriate incentives for potential inventors. However, rewarding the inventor of an HIV vaccine with the extension of a Prozac patent eliminates this link between the usefulness of the invention and the magnitude of the compensation.

Another disadvantage of compensating vaccine inventors with extensions of patents on unrelated pharmaceuticals is that the right to extend a patent would be worth the most to firms holding patents on commercially valuable pharmaceuticals, and these firms may not be those with the best opportunities for vaccine research. This problem would not be fully resolved by making patent extensions tradable, since firms holding patents on commercially valuable pharmaceuticals would presumably receive some profits in any such trades. If vaccine developers were compensated in cash, rather than patent extensions, they could receive the full value of the compensation without sharing it with the holders of patents on unrelated pharmaceuticals.

## 4.2 Cash Prizes

Cash prizes in lieu of patents are economically similar to purchase commitments. However, purchase commitments more closely link payments to vaccine quality and are more politically attractive, and hence more credible. The disadvantages of government purchases are likely to be minor for vaccines.

Compared to cash prizes in lieu of patents, vaccine purchases provide a closer link between payments and vaccine quality. For example, suppose that a vaccine received regulatory

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are less likely to do so than HMOs, and so patent extensions are more attractive in countries with centralized health systems.

approval, but was later found to have side effects. If a cash prize had been awarded at the date of regulatory approval, it might be difficult to get the money back. Vaccine purchases, on the other hand, could be suspended if countries wished to cease purchasing vaccines.

Moreover, purchase commitments are likely to be politically more attractive than cash prizes, and thus more credible to potential vaccine developers. Vaccine developers are vulnerable to expropriation, even if the terms of the compensation program legally obligate the government to provide compensation for any qualifying vaccine: the funds could be extracted from them in a supposedly separate, unrelated action. For example, a pharmaceutical firm that had just earned a windfall on a malaria vaccine might be subject to stiff price regulation on another product. This suggests that it is important to design a compensation program in ways that are as politically acceptable as possible, and that generate the minimum amount of resentment. Purchasing malaria vaccine for the 50 million children born in Africa each year at \$5 a dose for ten years is likely to be more politically appealing than awarding a \$2.5 billion prize to a pharmaceutical manufacturer. Conversations with pharmaceutical executives suggest that they do not like anything labeled as a prize.

Cash prizes in lieu of patents lead to free competition in manufacturing newly invented goods, whereas public purchases require the government to specify details of the goods purchased. This would represent a significant advantage of prizes over purchases for most goods, but it is less important for vaccines. For example, if the government committed to purchase high-definition television sets as a way of encouraging research, it would have to get involved in decisions about screen size, color, style, reliability, and other issues best left to consumers. In contrast, governments regulate vaccine quality in any case. Moreover, an

effective malaria vaccine would be easy to allocate, since a single course would presumably be taken by all children in malarious areas.<sup>23</sup>

### 4.3 Tournaments

In research tournaments, the sponsor promises a reward to whoever has progressed the farthest in research by a certain date. (See [Taylor, 1995] for a discussion of tournaments.) The design competitions often used to select architectural firms are examples of tournaments. In a vaccine tournament, a committee might be established with instructions to award a cash prize to whichever research team had made the most progress toward a vaccine as of a specific date. If no vaccine had been completed by that date, additional funds could be set aside for further rounds of the tournament.

Tournaments have several limitations, however, and may not be appropriate for encouraging vaccine research.

First, a payment must be made no matter what is developed. While tournaments provide incentives for researchers to devote effort to developing a product, they do not address the problem of determining whether research on a particular vaccine is worth pursuing at all. Advocates for a particular disease and scientists working on the disease will always want to encourage the establishment of tournaments for research on their disease, even if the prospects for ultimate success are low. With a vaccine purchase program, nothing is spent unless a vaccine is developed.

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<sup>23</sup> Note that many people are likely to live in areas where taking the vaccine is a borderline decision, and even in these areas, the appropriateness of vaccination depends primarily on technical issues rather than personal preferences.

Another problem with tournaments is that once research has been completed, the award committee might be tempted to allocate the reward on grounds other than progress in research. The committee might award the reward to a more politically correct firm, to a university team, or to whoever had done the most scientifically interesting work, rather than to the team which had made the most progress toward a vaccine. Anticipating this, firms might invest in political correctness or scientific faddishness rather than in producing an effective vaccine. Of course, a committee making purchase decisions for a vaccine purchase program could also be subject to bias, but judgments about who has made the most progress developing a vaccine are more subjective than judgements about whether a vaccine with a particular set of results from phase III trials are satisfactory.

Collusion among potential researchers may be particularly harmful in tournaments. If only a few pharmaceutical firms had done a significant amount of work, they could collude to exert low effort on doing further research, since the reward would be paid whether or not a vaccine was developed.

Tournaments may lead researchers to put their efforts into looking good on the tournament completion date, rather than completing a vaccine. Firms which discovered promising research leads that were unlikely to yield solid results before the deadline might ignore their leads, while firms that received information that the research line they were pursuing would not yield a vaccine might not reveal this information.

Tournaments are also politically unattractive. Governments may not find it politically attractive to pay large amounts for research that may have not progressed very far. Since there would be no clear-cut way to decide who was ahead in research, awards might be subject to litigation and charges of favoritism.

Finally, rewards in tournaments would have to be in cash, rather than in guaranteed sales, since no vaccine may have been developed by the end of the tournament. As noted earlier, however, cash rewards are less politically attractive than guaranteed markets.

#### **4.4 Expanding the Market for Existing Vaccines**

Some argue that by purchasing more existing vaccines at higher prices, policy makers can signal their intention to provide a market for future vaccines, and thus encourage research on new vaccines. Although the standard EPI package of vaccines is widely distributed, a number of effective vaccines that are already available are not fully used.<sup>24</sup> Purchasing and distributing existing vaccines which are not widely used in developing countries, such as *Haemophilus influenzae b* (Hib) vaccine, would be a cost-effective way to save many lives.

However, by itself, paying more for currently available vaccines may not make pharmaceutical firms confident that they will be rewarded for developing new vaccines. It could easily take ten years to develop malaria, tuberculosis, or HIV vaccines, and developers would need to recoup their investment through sales in the ten years following the vaccines' development. Since international interest in health in developing countries is fickle, pharmaceutical firms might well feel that the availability of funds to purchase Hib vaccine now at a remunerative price does not guarantee that the international community would be prepared to

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<sup>24</sup> For example, the hepatitis B vaccine is underused. An effective vaccine for malaria or one of the other major killers would likely be consumed much more widely than the hepatitis B vaccine, since the disease burden of hepatitis B is small relative to that of AIDS, tuberculosis, or malaria. Moreover, malaria kills young children very quickly after infection and the onset of symptoms, whereas hepatitis B infection can remain asymptomatic for decades, and many people may not understand its relation to the deaths it causes from primary hepatic cancer in middle age or beyond.

pay for future vaccines fifteen years from now. Legally binding commitments to purchase future vaccines would still play a critical role in spurring research.

Moreover, given that the Hib vaccine was developed without any expectation of realizing substantial profits in developing countries, paying more than pharmaceutical firms could reasonably have expected for these vaccines would provide extra profits to pharmaceutical firms. Providing these extra profits might be worthwhile if it were the only way to establish a reputation for paying remunerative prices for future vaccines. Not surprisingly, pharmaceutical manufacturers argue that the best way to persuade them that work on future vaccines would be rewarded would be to buy currently available vaccines at a high price. However, if it were possible to commit now to purchase future vaccines at a remunerative price, there would be no reason to pay more for current vaccines than had been implicitly or explicitly promised to vaccine developers. Paying high prices for both current and future vaccines as a way of encouraging future research amounts to paying twice.

Finally, some argue that increasing current vaccine sales will increase vaccine R&D budgets because pharmaceutical firms finance research on a division by division basis, as a percentage of current sales. It is possible that some firms might use such a rule of thumb to reduce unproductive competition for funds among divisions seeking to increase their R&D budgets. While some pharmaceutical firms may find this rough rule of thumb useful under the current environment, if the environment changes, they will have incentives to change these rules. In particular, if there is an explicit, credible commitment to purchase vaccines, there is reason to think that companies would change their R&D budgeting rules. Finally, note that even if some firms are particularly subject to wasteful internal budget battles and therefore impose draconian

internal budget rules, there will be even greater incentives for other firms to expand R&D and for new biotech firms to enter the field in response to increased markets.

In summary, increased purchases and delivery of existing vaccines are likely to be very cost-effective ways of saving lives in their own right. However, in order to motivate R&D on future vaccines, it is necessary to supplement increased purchases of existing vaccines with explicit commitments to reward developers of future vaccines. Paying more for existing vaccines than vaccine developers could have reasonably expected when they invested in research is likely to be an expensive way of encouraging research on future vaccines.

## 5. Conclusion

This paper has argued that private incentives for research on vaccines for malaria, tuberculosis, and strains of HIV common in Africa likely to be a small fraction of the social value of new vaccines, so that under current institutions, potential vaccine developers would have incentives to pass up socially valuable research opportunities. Moreover, if vaccines were developed, access to vaccines would be limited if they were sold at monopoly prices.

Commitments to purchase vaccines and make them available to developing countries for modest co-payments could both provide incentives for development of vaccines, and ensure that vaccines reach those who need them. Taxpayers would pay only if a vaccine were developed.

A companion paper, “Creating Markets for New Vaccines: Part II: Design Issues,” discusses the design of these vaccine purchase commitments.

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