CMH Working Paper Series
Paper No. **WG2:7**

Title
Public Policies to Stimulate the Development of Vaccines and Drugs for the Neglected Diseases

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Abstract

The World Health Organization [2001] estimates that malaria, tuberculosis, and the strains of HIV common in Africa kill over 5 million people each year, overwhelmingly in developing countries. Vaccines offer the best hope for a sustainable solution to this problem. Yet research on vaccines or appropriate drugs for these diseases remains minimal—largely because potential developers fear that they would not be able to sell enough of their product at a sufficient price to recoup their research expenditures.

This is not only because these diseases primarily affect poor countries, but also because of severe market failures limiting research on these diseases- particularly on vaccines. Once developers have invested in developing vaccines and drugs, government 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. Thus, intellectual property rights for pharmaceuticals have historically been weak in developing countries. 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 on diseases primarily affecting poor countries.

Programs to encourage development of new products can be classified in two broad categories: push programs, which subsidize research inputs; and pull programs, which reward developers for actually producing the desired product. Government-directed research programs may be well suited for basic research, but for the later, more applied stages of research, pull programs have important advantages. Under such programs, the public pays only if a successful product 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 useful product, and to focus on developing a viable vaccine or drug rather than pursuing other goals. Finally, appropriately designed pull programs can help ensure that if new products are developed, they will reach those who need them.

Committing to purchase vaccines and drugs and make them available to poor countries may be the most attractive form of pull program. Extending patents on other pharmaceuticals to reward developers of new products would place the entire burden of financing new products on those needing these other pharmaceuticals. Increasing prices for current vaccines without explicit incentives for development of new vaccines would be an expensive and potentially ineffective way to spur new research.

For purchase commitments to spur research, potential developers must believe that the sponsor will not renege on the commitment once desired products have been developed and research costs sunk. Courts have ruled that similar commitments are legally binding contracts. Given appropriate legal language, the key determinant of credibility will therefore be eligibility and pricing rules, rather than whether funds are physically set aside in separate accounts. The

credibility of purchase commitments can be enhanced by specifying rules governing eligibility and pricing of vaccines in advance and insulating those interpreting these rules from political pressure.

Requiring candidate products to meet basic technical requirements, normally including approval by some regulatory agency, such as the U.S. FDA, would help ensure that funds were spent only on effective vaccines. Requiring developing to contribute co-payments would help ensure that they felt that the products were useful given the conditions in the field.

A commitment to purchase new vaccines at an average price of about $3 per person immunized, for example, would require about $285 million annually from donors, plus another $50 million annually from developing countries themselves. Markets of this size have proven sufficient to motivate research in the past. Such a program would be one of the world's most cost effective health interventions, costing around $4 per year of life saved. If a commitment to purchase vaccines fails to induce vaccine development, no funds would be spent; if it succeeds, tens of millions of lives would be saved.

Introduction

The World Health Organization [2001] estimates that malaria, tuberculosis, and the strains of HIV prevalent in Africa kill over five million people each year, overwhelmingly in poor countries. Yet relative to this enormous burden, very little research is directed towards these diseases. Potential developers of vaccines and drugs appropriate for poor countries fear that they would not be able to sell enough of their product at a sufficient price to recoup their research investments. This is both because these diseases primarily affect poor countries, and because vaccine and drug markets are severely distorted. This report examines the reasons for underinvestment in R&D and the potential of various public policies to address the problem.

Many developing countries have historically provided little or no intellectual property rights protection for pharmaceuticals. This is in part because once developers have sunk resources into developing vaccines and drugs, governments find it attractive to use their powers as regulators, major purchasers, and arbiters of intellectual property rights to obtain products at prices which cover only manufacturing costs, not research costs. Moreover, 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. Consequently, there is a huge gap between private and social returns. 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 even at $40 per person immunized. However, the gap between the $40 at which a vaccine would be cost-effective and the $1 or $2 that 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.

In addition, once new products are developed, they tend to be underconsumed. Pricing above marginal manufacturing cost limits consumption. Moreover, people tend to underconsume vaccines for a number of additional 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. Third, consumers are often more willing to pay for treatment than prevention.

Programs to encourage vaccine and drug development take on two broad forms. "Push" programs subsidize research inputs, for example through R & D tax credits or grants to researchers, while "pull" programs reward the development of an actual vaccine. Push programs are well suited to financing basic research, but have a much more mixed record at the later, more applied stages of product development, as illustrated by the U.S. Agency for International Development's (USAID) unsuccessful and scandal-prone efforts to develop a malaria vaccine were disastrous, for example. Researchers requested funding for unpromising research, and administrators complied. Tax credits to subsidize R&D are difficult to target. Historically, however, governments have relied heavily on push programs, in part because it was thought necessary to finance research expenditures in advance of the development of a desired product. 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 product is developed. This gives researchers incentives to self-select projects with a reasonable chance of yielding a viable product, 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 product, rather than supporting a development effort that might not be warranted scientifically. Pull programs also provide strong financial incentives for researchers to focus on developing a marketable product, rather than pursuing other goals, such as publishing academic articles. Finally, appropriately designed pull programs can help ensure that if new products are developed, they will reach those who need them.

A commitment to purchase vaccines or drugs if they are developed is probably the most attractive way of designing a pull program. Rewarding developers with extensions of patents on other pharmaceuticals would inefficiently and inequitably place the entire burden of financing development on patients who need these other pharmaceuticals. Patent buyouts are economically similar to purchase commitments, but provide a somewhat weaker link between product quality and the compensation paid to developers. Encouraging product development through research tournaments is likely to be difficult, since there is no guarantee that a desired product 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 or drugs for malaria, tuberculosis, or African clades of HIV 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.

The design of a purchase commitment will be a critical determinant of its effectiveness. If potential developers are to invest in research, they must believe that once they have sunk funds into developing a desired product, the sponsors of a purchase program will not renege on their commitments by paying a price that covers only the cost of manufacturing, and not research. 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. For example, the U.S. government was forced to honor a commitment to purchase manganese in the 1960's. This suggests that if programs contain appropriate legal language, the key determinant of their credibility will not be whether funds are physically set aside in a separate account, but the rules determining eligibility and pricing, and the procedures for adjudicating decisions under these rules. If potential vaccine developers are to invest in research, they must be confident that the adjudicators will not abuse their power. The credibility of a purchase commitment can be enhanced by clearly specifying eligibility and pricing rules, insulating decision makers from political pressure through long terms of service, and including former industry officials on the adjudication committee.

Eligibility conditions for candidate products would likely include some minimal technical requirements, which would ordinarily include clearance by a regulatory agency, such as the U.S. Food and Drug Administration (FDA). They could then be subject to a market test: nations wishing to purchase products would need to provide a modest co-payment tied to their per capita income and spend down an account assigned to them within the program. Requiring countries that receive vaccines or drugs to provide co-payments in exchange for these products would give countries incentives to carefully investigate whether candidate products are appropriate for their

local conditions. Moreover, for any fixed level of donor contributions, requiring co-payments gives potential developers greater incentives to conduct research. Any product meeting the technical requirements and attracting requests from developing countries would be eligible for purchase at some base price. Products exceeding these minimum requirements could potentially receive bonus payments tied to vaccine effectiveness.

Rewards should be greatest for the first developer. For example, the developer of the first effective malaria vaccine against a disease creates enormous social benefits. Developers of subsequent vaccines create benefits only to the extent that their vaccines are superior or serve populations that are not served by the first vaccine. The U.S. Orphan Drug Act specifies that the first developer has market exclusivity unless a subsequent product is clinically superior. This provision is generally believed to account for the Act's success in increasing research on orphan drugs. An analogous provision could grant market exclusivity for purchases under the program to the first product developed unless subsequent products were clinically superior.

Research and development on vaccines and drugs is typically very expensive, but manufacturing additional doses is usually reasonably cheap. Given total revenue from a product, research incentives are likely to be fairly similar if few doses are sold at a high price, or many doses are sold at a lower price. This suggests that in the case of vaccines it is efficient to pay per immunized child, rather than per dose, and to include countries and demographic groups in the program as long as vaccination is cost effective at the incremental cost of delivering additional doses (rather than at the average price per person immunized paid under the program). The total market promised by the program should be large enough to induce substantial effort by vaccine developers, but less than the social value of the vaccine. A rough rule of thumb is that a $250 million real annual market is needed to motivate substantial research. The nominal size of a

purchase commitment should be larger, perhaps around $330 million per year, given that vaccines may not be developed for some time. It is unlikely that vaccines for all three diseases would be developed simultaneously, but if donors wished to limit their potential liability, they could cap their committed annual expenditure. A program in which donors provide approximately $285 million in average annual contributions and co-payments from developing countries average another $51 million annually would be extremely cost effective, costing approximately $4 per year of life saved. The vaccine price per person immunized in the first 10 years would be about $3 and over this period about 1.7 billion discounted DALYs could be saved (or around 63 million lives of thirty-year olds). This would be a highly cost-effective intervention. For reference, in the 1993 World Development Report, the World Bank treats health interventions in developing countries that cost less than $100 per DALY as cost effective [World Bank 1993, page 64]. In comparison, anti-retroviral treatment of AIDS is estimated to cost $1100 per person per year and, since treatment would not be perfectly effective, the cost per life saved is likely to be considerably greater.

One way to avoid either paying more than necessary for a product or offering too little to stimulate research would be to offer a relatively modest price initially, and if this price proved insufficient, to raise the promised price gradually until it proved sufficient to spur vaccine development. As long as the price did not increase at a rate substantially greater than the interest rate, vaccine developers would not have incentives to withhold vaccines from the market in hopes of obtaining a higher price. Purchase pre-commitments are most needed and would be easiest to implement for vaccines, but the approach could also be adapted for drugs for malaria and tuberculosis. A sufficient market exists in rich countries for HIV drugs that this would not be an appropriate intervention for that case.

The purchase commitment approach has attracted interest from policymakers and the UK's Chancellor of the Exchequer Gordon Brown and the Development Minister Clare Short have supported the idea of an advanced purchase fund [Elliott and Atkinson 2001; DFID 2000]. In a speech at the International Conference Against Child Poverty in London, Gordon Brown stated, "a purchase fund—providing a credible commitment to create a market for current and future treatments in developing countries—would surely serve as a strong incentive to develop and deliver affordable treatments. That is why, in a joint effort with Italy, the President of the G-7, the UK proposes that a new global purchase fund for drugs and vaccines be created. Both for treatments that do not yet exist but could be developed in time—for AIDS and malaria, for example—as well as for those that already exist and need to be purchased now" [Brown 2001]. The UK Cabinet Office recently published a report providing more details about the advance purchase commitment that the UK is proposing to the international community as part of a package of measures to fight disease [PIU, 2001]. The concept of a vaccine purchase commitment has also received support from other European political leaders, including the German foreign minister and the Dutch development minister.

In the U.S., Senators Frist and Kerry and Representatives Pelosi and Dunn have proposed encouraging R&D on vaccines for AIDS, tuberculosis, and malaria using both enhanced R&D tax credits and a tax credit for sales of vaccines to nonprofit and international organizations. 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 this proposal is structured as a tax credit, it would have effects similar to an expenditure program that matched private funds spent on vaccines The Clinton administration's 2000-1 budget proposal included a proposal along these lines.

The World Bank president, James Wolfensohn, has 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]. However, the World Bank has yet to act on this commitment. Some within the Bank have advocated a more general program to combat communicable diseases of the poor. However, 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.

This report 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 report 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 report 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 report 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 at prices that cover R&D cost will not be credible. This report also differs from earlier work in comparing commitments to purchase vaccines to other pull programs and in discussing the design issues that would need to be addressed in creating such programs.

Section 1 of this report 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. Section 3 examines the appropriate roles of push and pull programs in encouraging research and improving access to vaccines and drugs once they are developed. Section 4 compares alternative pull programs. Section 5 of this report discusses how a purchase commitment could be made credible. Section 6 outlines a possible process for determining vaccine eligibility and pricing and section 7 discuss copayments from developing country governments. Section 8 discusses procedures if multiple vaccines are developed for a single disease. Section 9 discusses the appropriate size of the commitment and the cost effectiveness of the program. Section 10 argues that purchase commitments are most needed, and would be easiest to implement, for vaccines, but that the approach could also be adapted for drugs. Section 11 briefly considers the politics of programs to improve vaccine markets. It then

discusses the proposed UK, US, and World Bank programs and how a private foundation could participate in a purchase commitment program.

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 1.7 million people die from tuberculosis. More than 98 percent of these deaths occur in developing countries [WHO, 2000]. 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.[1]

[1] 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.

More than 36 million people are infected with HIV worldwide, over 95% of who live in developing countries. In 2000, about 2.7 million people died of AIDS, 80% of whom lived in sub-Saharan Africa. Approximately 5.3 million people were newly infected, 70% of who were in sub-Saharan Africa [UNAIDS, 2000]. Since people with compromised immune systems are especially vulnerable to tuberculosis, the spread of HIV is contributing to the spread of tuberculosis. Indeed, over 20 percent of the people who die annually from tuberculosis are also infected with HIV [WHO, 1999a; UNAIDS, 1998]. While reductions in the price of antiretrovirals can help some people, these products offer little relief to the vast majority in low-income countries. Widespread effective use will be difficult in the poorest countries, given weak health infrastructure, poor education, and the need to adhere to onerous treatment regimens in order to maintain efficacy and prevent the spread of resistance. Even advocates estimate that purchasing and delivering antiretrovirals will cost $1100 per person, per year. Limited health budgets will therefore save many more lives if devoted to other interventions, such as expanded coverage of childhood vaccinations, which can save a year of life for as little as $20.

The international community has set a series of international development goals (IDGs), also known as the “Okinawa targets,” that it has pledged to achieve by 2010. These include a 25 per cent reduction in HIV/AIDS among people aged 25 years or younger; a 50 per cent reduction in prevalence and deaths from TB; and a 50 per cent reduction in the burden of disease associated with malaria. There is little prospect of meeting these targets using existing technologies alone. New drugs can help, but because resistance develops quickly to drugs, truly sustainable reductions in the disease burden associated with malaria, tuberculosis and HIV/AIDS will come only with vaccines.

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].[2] 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. 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 Research for Malaria, Tuberculosis and HIV/AIDS

[2] 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.

Despite the increasing scientific potential, current research on vaccines for malaria and tuberculosis is paltry relative to the burden of these diseases. HIV research is oriented to the problems of developed countries. 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 that would be appropriate for people with AIDS in rich countries, rather than towards vaccines appropriate for poorer countries. 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.)

The private sector in particular performs little research on diseases of poor, tropical countries. According to WHO [1996], while 50 percent of global health research and development in 1992 was undertaken by private industry, less than 5 percent of that was spent on diseases specific to less 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 research market destroy incentives for private firms to conduct 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. Moreover, distortions in the markets for vaccines lead them to be underconsumed even relative to the incomes of the poor.

Sub-section 2.1 argues that under current institutions, private returns to research are on developing country diseases are limited because research is a global public good, and because once vaccine and drug developers have undergone the risk and expense of research governments have incentives to try to obtain products at prices that cover only manufacturing costs. Sub-section 2.2 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 2.3 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 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. The problem is particularly acute for vaccines and drugs for diseases that primarily affect developing countries, because once firms have sunk their research investments and developed a vaccine or drug, developing country governments have little motivation to pay prices that cover the risk and expense of research. Moreover, since this research is a global public good benefiting many small countries, no single country has an incentive to pay higher prices to encourage research.

Vaccine and drug research is subject to what economists call a "time consistency" problem. The research is very expensive, but once pharmaceuticals have been invented, they can usually be manufactured at low cost.[3] At this point governments have every incentive to try to

[3] Note, however, that new vaccines, particularly those based on conjugate technology, are likely to have somewhat greater manufacturing costs than traditional vaccines.

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 acting on their behalf therefore bargain for very low prices. Since potential researchers anticipate this redistribution, they invest less in research than they otherwise would. The recent activism that was intended to pressure pharmaceuticals to lower the price of antiretroviral HIV drugs is an example of this dynamic in action. Of course, antiretrovirals have a developed country market, so firms were willing to invest in their development. The same would not be true for a malaria vaccine or a clade C HIV vaccine.

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. 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.[4]

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 and recent events suggest that this skepticism is well placed. The South African government has 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. This controversy illustrates the need for new institutions that both create incentives for the development of new products and provide access for the poor to these products upon their development.

Research on vaccines for diseases prevalent in both developed and developing countries has been stimulated by demand in developed countries. However, the limited intellectual property rights available in many poor countries deter research on vaccines against diseases such as malaria, which would have little market in developed countries.[5]

Even if property rights were available, incentives for research would still be suboptimal, particularly for vaccines. In part this is because it is often possible to design around patents, and this may make it difficult for the original developers of new products to recoup their research

[4] 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.

[5] 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.

expenditures. Once they have invested millions in a risky effort to develop new drugs or vaccines, competitors may be able to slightly alter their approach so as to develop a competing product, 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 drugs and almost all vaccines, and these institutions are not particularly subject to brand loyalty.

2.2 Failures in the Market for Vaccines

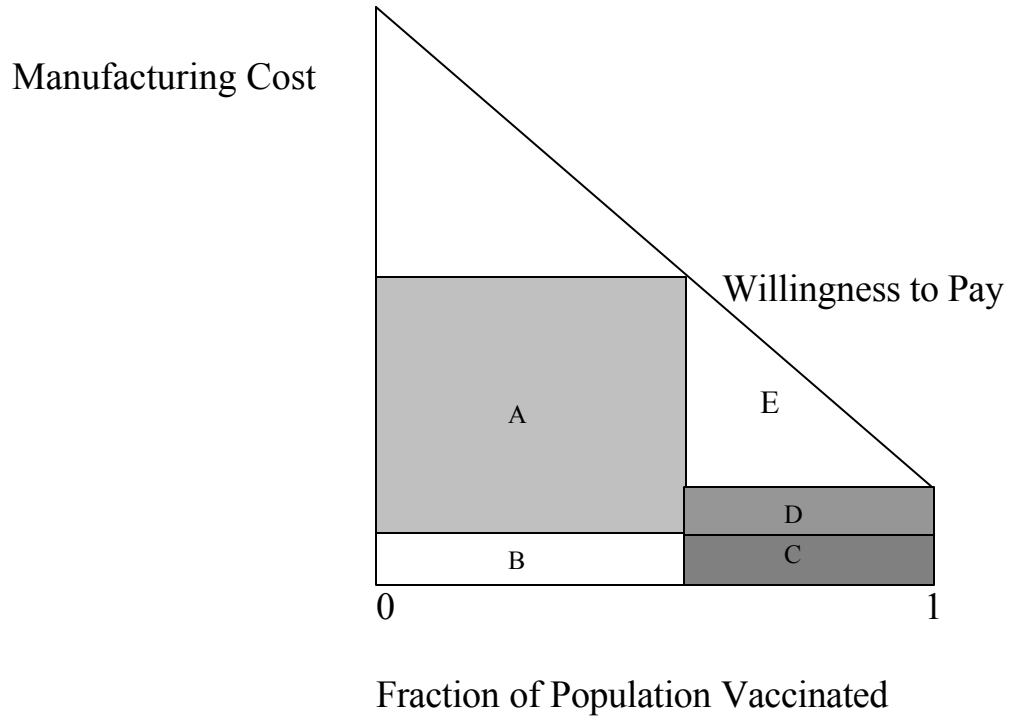
Even once vaccines have been developed, they tend to be underconsumed. First, individuals who take vaccines not only benefit themselves, but also help break the chain of disease transmission, thus benefiting the rest of the population. Individuals have no incentive to take these external benefits into 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

Pricing vaccines above the incremental cost of manufacturing an additional dose further exacerbate underconsumption of on-patent 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[6], vaccine producers and the general public will both be better off than under monopoly pricing.[7][8] Areas D and E represent the social benefit of the vaccine purchase program.

The same arguments which suggest that national vaccine purchases are potentially more efficient than individual purchases 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

[6] 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 to 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.

[7] 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.

[8] As discussed below, 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.

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. 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.

In any case, 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.

In addition, in practice, 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 that benefit more concentrated and politically organized groups, such as salaries for health workers.

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.[9]

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.

However, tiered pricing would not provide an incentive for research on diseases that affect only developing countries such as malaria, tuberculosis, and clade C HIV. Moreover, given that research is a global public good it is unclear how to motivate countries to accept a policy that requires them to pay more that they might for pharmaceuticals.

2.3 Social vs. Private Return: Some Quantitative Estimates

The market failures outlined above create a huge gap between the private return to developers and the social benefit of new vaccines and drugs. A crude estimate suggests that the social benefits of vaccines may be ten to twenty times the private benefits appropriated by

[9] When former 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].

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.

To illustrate the gap between the social value of a vaccine and the amount that could be appropriated by a private developer, consider the case of a hypothetical perfectly effective one-dose malaria vaccine. The cost-effectiveness of such a vaccine is modeled in (Glennerster and Kremer, 2001) and a summary of their results is presented here. .

A standard way to assess the cost-effectiveness of a health intervention is the cost per Disability Adjusted Life Year (DALY) saved. A standard cost effectiveness threshold for health interventions in the poorest countries is $100 per DALY. For example, in the 1993 *World Development Report*, the World Bank treats health interventions as 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. Approximately 97 million children are born annually in low-income and lower-middle-income countries with high enough malaria prevalence to make vaccination cost-effective, and approximately 24 million women become pregnant each year with their first child in countries with high enough prevalence to make vaccination of this group cost effective.[10] Assuming that 75% of targeted children and 50% of targeted first-time mothers are reached, so that 85 million people are immunized annually, that the incremental delivery costs for adding a

[10] Fewer children would be vaccinated if a tighter cost effectiveness standard were used [Glennerster and Kremer, 2001]. Existing cohorts of children younger than five might also be vaccinated, but since this is a one-time

vaccine to the EPI package are $0.40 per dose,[11] and that the marginal cost of delivery for pregnant women is $2.00 per woman vaccinated; delivery of such a vaccine would save 34.3 million DALYs each year and would cost $53.1 million annually, for a delivery cost of about $1.55 per DALY saved. At a cost-effectiveness threshold of $100 per DALY, immunizing these 85 million people with the malaria vaccine would be cost-effective even at a price of $40 per immunized person.[12] Note 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.[13] (See Glennerster and Kremer, [2001] for more detailed calculations of vaccine cost effectiveness including sensitivity analysis to vaccine characteristics.[14])

These calculations imply that from the standpoint of society as a whole, it would be cost-effective to conduct research leading to a malaria vaccine even if the research were risky and expensive enough that it would take $40 per immunized person, or $3.4 billion annually, in perpetuity, to recoup the research costs given the risk of failure. However, such a research investment would lose money for a private developer and hence would not be pursued. 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

occurrence, it is ignored in this calculation.

[11] The addition of both the three-dose hepatitis B and the one-dose 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.

[12] This is the vaccine price such that (delivery costs + the number of vaccinations * vaccine price)/ the number of DALYs saved equals $100, the cost effectiveness threshold.

[13] 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 that is causal.

[14] These calculations are similar to those in Kremer [2001] but the basic data underlying the calculations--including the regional burden of disease, age distribution, fertility distribution, GNP per capita, life expectancy, births, and

[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].[15] 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 $40 per immunized person at which vaccines would be cost effective. The huge disparity between private incentives to invest in research and the social benefits of a vaccine suggests that there will be far too little research investment 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.

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population--have all been updated.

[15] Even if the entire pharmaceutical budget in many African countries went to malaria vaccines, the benefit to a

3 The Roles of Push and Pull Programs in Encouraging Vaccine and Drug Research

The literature on research incentives distinguishes between "push" and "pull" programs. Push programs subsidize research inputs, for example through grants to academics, public equity investments in product development, research and development tax credits, or work in government laboratories. Pull programs increase rewards for development of a particular product, 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 discusses push programs. It first reviews the history USAID's push program to develop a malaria vaccine. It then discusses the underlying reasons for the program's failure, and discusses implications for government financed research, public equity investments, and targeted R&D tax credits. Sub-section 3.2 argues that pull programs are well-suited to the later stages of the vaccine development process and sub-section 3.3 reviews the limitations of pull programs.

3.1 Push Programs

While push programs are critical for stimulating basic research, their record in stimulating actual product development is decidedly mixed.

vaccine developer would be far less than the social benefit.

USAID's 1980s push program to develop a malaria vaccine, as chronicled by Desowitz [1991], provides as dramatic illustration of the potential problems with push programs. USAID's funding efforts focused on three research teams. Tests of a candidate vaccine developed by the first team found that only two of nine volunteers were protected from malaria, and suggested that the vaccine created side effects. These results, mixed at best, led USAID to claim 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."[16] That was in 1984. 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 pursing 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."[17] Once the grant came through, the principal investigator transferred grant funds to his personal account. He was later indicted for theft.

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

[16] All quotations are taken from Desowitz [1991], p. 255.
[17] From Desowitz [1991], p.258.

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.

USAID had arranged for independent oversight to be provided by the American Institute of Biological Science (AIBS). This proved ineffective – unsurprisingly – as Erickson and the AIBS-assigned project manager were having an affair.

The USAID case is extreme, and many push programs are quite successful. But more generally, researchers funded for promises rather than for delivering a product have incentives to report overoptimistic assessments to their superiors, and even to divert resources away from the search for the desired product, (although this does not usually take such a dramatic, criminal, form). These incentive problems occur whether research is publicly funded, governments make equity investments in private research, or governments award targeted R&D tax credits. The next subsections consider the particular problems associated with each of these policy interventions.

3.1.1 Publicly Funded Research

One of the problems with USAID's malaria vaccine research was that even after it became clear that research was not going well, researchers kept requesting funding and administrators kept approving it. Researchers have a natural tendency to exaggerate the promise

of their own lines of work. Scientific administrators may have trouble deciding which diseases are worth working on, and which scientific approaches, if any, are worth pursuing. They also have incentives to expand their empires.

Even if government-directed research programs manage to initially select appropriate research projects, they are likely to fail to revise these judgments 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 on the other hand may acquire its own bureaucratic momentum, which can lead 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 product are most promising, but also at the level of deciding which diseases and products should be targeted. 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 from the standpoint of society as a whole. This does not prove that such opportunities exist. Under a system of grant-financed research, advocates for particular diseases and scientists working on these diseases have an interest in exaggerating the research opportunities. 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 and drugs. Decision makers may therefore wind up financing ideas with only a minute probability of success, or worse, failing to fund promising research because they do not have confidence that its backers are presenting objective information on its prospects. In contrast, under a system in which developers are rewarded only if they successfully produce the desired product, there is a strong incentive for firms considering

research investments to realistically assess the prospects for success. Thus, if a tuberculosis vaccine is feasible, but a malaria vaccine in not, developers will pursue the tuberculosis vaccine.

The other, more spectacular, problem with USAID's malaria program was that researchers spent funds on themselves, rather than on the desired activity. The criminal activity in this case was unusual. More typically, under a system of grant-financed research, researchers may have incentives to devote effort to preparing the next grant application, or publishing articles that will advance their academic careers, perhaps on unrelated projects, rather than to focus on development of the desired product.

When governments directly allocate research spending up front, they may also sometimes base decisions partly 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 in particular. With pull programs, in contrast, the sponsors promise to pay for a viable vaccine wherever it is developed.

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. Surveys suggest that while both government and private R & D have strong positive returns, the rate of return on private R & D is substantially greater [Nadiri, 1993; Nadiri and Mamuneas, 1994; and Bernstein and Nadiri, 1988, 1991].

One variant on direct government research financing is investing government funds in private firms conducting desired research.[18] By combining public funds with private resources, the intention is to inject market discipline into the research process. However, public-sector

[18] These are sometimes called public-private partnerships, but actually pull funding is a public-private partnership as well.

equity investments in product-development projects are subject to the same fundamental problems as directly government-financed research. Indeed, the problem of firms misrepresenting their chances for success is in some ways exacerbated. Firms that 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.

Another danger with having public money going towards deals with private firms is that access to funds may be easier for those with connections to the individuals or organizations administering the grants. Grant administrators for their part may feel most comfortable funding researchers whose work they are previously familiar with. For example, the International Aids Vaccine Initiative (IAVI) has provided support for clinical trials to Alphavax, a small biotech company staffed in part by former employees of IAVI. (Washington Post, 11/26/98).

Grant administrators may feel political pressure when investing public funds in private firms just as they do when directly funding research. For example, existing programs often fund partnerships that involve a developed country and a developing country element. The stated justification is the technical merit of the proposal and claims that local firms understand the epidemiological and political environment better than international firms, but given the overwhelming concentration of scientists in developed countries, it also seems possible that the tendency to fund developing country teams reflects political considerations as well as the technical merit their proposals.

Public-sector investments in private sector research can also turn into a give-away that subsidizes a private sector firm. One indicator that a firm that has been awarded a government contract is being paid more than it will cost them to do the work is that the firm's stock price

jumps on the day the award in announced. The announcement that IAVI would support the clinical trials of an HIV vaccine under development by the firm Targeted Genetics caused that firm's share price to increase by 57% (Seattle Times 2/16/2000).

3.1.2 Targeted R&D tax credits

Similar problems arise when private research is subsidized through targeted R & D tax credits. Some have proposed special R&D tax credits targeted to research for drugs and vaccines for malaria, tuberculosis and HIV/AIDS. There are a number of problems with such tax credits.

1. R&D tax credits do not improve access to products once they are developed. Patent rights for a malaria or HIV vaccine developed by a company that received the credit would remain with the company for the usual period of market exclusivity. If intellectual property rights are respected, the vast majority of citizens of developing countries would not have access to the vaccine during this period.
2. R&D tax credits may not create incentives for the development of products appropriate for developing countries because markets in rich countries may be more lucrative. For example, in the case of an HIV vaccine, the vast majority of new infections occur in Africa, where clade C is most common. However, commercial development is focused on clade B, which is common in the U.S. and Europe. It is unknown whether a vaccine incorporating only antigens from clade B would be effective against clade C. However, under an enhanced R&D tax credit for AIDS vaccine research, firms might focus on a vaccine appropriate for only the commercial market.

Similar issues are likely to arise in the case of a malaria vaccine. A vaccine for the commercially important markets of travelers and military personnel would likely focus on

the sporozoite-stage of malaria, but a vaccine focusing only on sporozoites might or might not be useful for long-term residents of malarious regions. It could potentially even be counter-productive, weakening the limited natural immunity built by those long-term residents who survive childhood. Underan R&D tax credit, firms might focus their research only on sporozoite-based travelers' vaccines.

Note that restricting an R&D tax credit to research specifically on clade C HIV vaccines or merozoite-stage malaria vaccines would be a blunt instrument, because it is possible that a vaccine designed for one HIV clade would prove cross-reactive against other clades, or that research on the sporozoite stage of malaria would prove useful in developing a malaria vaccine useful in developing countries. Rather than prejudge the scientific issues, it would be more effective to create rewards linked to the efficacy of a vaccine in the developing countries where the disease burden is greatest. Efficacy, of course, can only be assessed once a vaccine has been developed and so an R&D credit cannot be linked to efficacy.

Restricting an enhanced R&D credit to the clinical stages of research would help in targeting the tax credit, but would provide a very limited incentive, since only about 35 percent of the capitalized cost of R&D is incurred in the clinical phase [PhRMA, 2000].

3. Firms would no doubt use creative accounting to claim the credit for inappropriate expenses. Determining which expenses made by firms should qualify for a targeted R&D tax credit would be administratively complex. Expenses in vaccine research may be common to a number of research projects, not all of which would qualify for a targeted R&D tax credit. For example, modern vaccines typically include both antigens specific to a particular organism and adjuvants that potentially boost the effectiveness of several different vaccines.

Firms would have every incentive to claim that an adjuvant intended for an ineligible vaccine was actually for a malaria vaccine, so as to claim the credit. To take another example, biofermentation facilities can be used in several different projects, and firms would no doubt find ways to assign a high proportion of the costs to projects that qualify for the credit.

4. Even a tax credit that could be administered effectively would be an incentive only for those firms that have tax liabilities. Most biotechnology firms have no current profits or tax liability and thus would not benefit from an enhanced R&D tax credit, unless they were able to pass their tax credits through to their investors, which would be problematic.

In summary, push programs in general are vulnerable to overoptimism and monitoring problems. Sub-section 3.2 discusses the means by which pull programs may be more effective at aligning the incentives of scientists and funding agencies.

3.2 The Potential Role of Pull Programs

Historically, programs designed to encourage vaccine research have financed research inputs ahead of time rather than offering to pay for a desired product.[19] 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

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

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 is that they help in selecting projects, and in concentrating research where scientific prospects for vaccine and drug development are best. While the gap between private and social incentives for vaccine and drug development does not prove that socially useful research opportunities exist, it does suggest a case for aligning private and social incentives, so that private developers will have incentives to pursue any socially desirable research investments that do exist. A purchase commitment can do this. Since taxpayers pay nothing unless and until an effective product such as a vaccine is produced, elected officials and the public do not have to worry that they are investing millions to develop a technically infeasible vaccine. For example government officials do not have to decide whether a malaria vaccine or a tuberculosis vaccine, is more feasible scientifically. Instead, individual firms make their own judgments about which research opportunities to pursue. It is precisely when the scientific potential is difficult for outsiders to assess that purchase commitments have the greatest advantage over research grants or equity investments.

In addition to allowing researchers to self-select promising projects, pull programs encourage researchers to focus intently on developing a marketable product, 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

product 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. Product trials in the field must be conducted. Nobody wins a Nobel Prize for these important steps in product development. By linking payment to results, pull programs provide strong incentives to researchers to concentrate their efforts on development of workable, technology suitable for commercialization.[20]

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 if the government funds only worthwhile research projects and researchers focus all their energies on developing a particular technology, the expected discounted cost of developing a product is likely to be similar in net present value terms whether research is financed at the front end, through government grants, or through payments, at the back end, for a successful product.[21] In the more likely case, when research organizations are more careful in selecting projects and more focused on developing products if they are only paid if they succeed, private research will be more cost-effective than government programs.

The USAID example discussed in section 3.1 illustrates the dangers of trying to estimate the costs of push and pull approaches by asking grant-funded researchers how much it will cost them to develop a product and asking private developers how big a market they need to justify

[20] 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].

[21] The cost of capital may be lower for the government than for pharmaceutical firms, but the difference is not that large. All the major pharmaceutical companies are rated Aaa by Moody's (Moody's Industrial Manual, 2001). The bonds issued by these firms in dollars (at varying lengths of maturity) have an annual average nominal rate of interest of 7.65%. This rate is very close to the standard number that the US treasury department uses to discount both private and government projects, 8%.

investment. Grant-funded 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.[1] 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. Those that are too optimistic go bankrupt, while rivals outstrip those that are too pessimistic. If anything, pharmaceutical executives have an interest in overestimating the inducement they need for research, as discussed in section 9. It is therefore misleading to compare the amounts government scientists claim they would need to develop a particular technology with the market size pharmaceutical executives claim they would need to justify research investments.

3.3 Limitations of Pull Programs

One limitation of most pull programs is that they require specifying the output ahead of time.[22] A pull program could not have been used to encourage the development of the Post-It Note® 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, especially as existing institutions, such as the U.S. FDA, are already charged with making these determinations. (As discussed below, even for vaccines, however, defining eligibility standards is far from trivial).

[22] This is not always the case, as shown by the Wolfskehl Prize for proving Fermat's Last Theorem, discussed in more detail in section 5.1.

It is typically difficult to specify the output of basic research in advance and this makes it difficult to stimulate this sort of research through pull programs. Simply rewarding development of applied products is not a good way to stimulate basic research since the main objective of basic research 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.

To the extent that intermediate steps in the 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 the development of the desired technology, and hence might stimulate wasteful investments in research lines that were unlikely to lead to a viable product. For example, researchers might try to demonstrate efficacy in animal models for a product 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 product if they are given in the form of subsidies for future research on the candidate product.

Pull programs have some other disadvantages. 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. However, with the rise of the biotech and venture capital industries, both the research and financial markets have improved considerably, making it easier for investors to share risk, and so the need for governments to diversify risk has declined.

A number of theoretical models suggest that private firms competing for a patent may inefficiently duplicate each other's activities. A centralized push program may prevent this. However, in the case of research for malaria, tuberculosis and even HIV/AIDS vaccines, we seem far from a situation in which developers are overinvesting in R&D or inefficiently duplicating each other's work. (Moreover, 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.)

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

Even if one thinks that a mixture of push and pull programs are needed, current support for research is unbalanced. Several push programs are already in place to subsidize vaccine and drug research. For example, IAVI supports AIDS vaccine efforts and Medicines for Malaria Venture (MMV) supports malaria drug research. In contrast, there are currently no programs in place to reward developers of viable malaria, tuberculosis, or HIV vaccines. If the existing push programs were complemented with pull programs, researchers who slip though the cracks of the push system would still have an incentive to pursue promising research leads.

If vaccine and drug 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 drug and vaccine research could take several different forms; including commitments to purchase products, extensions of patent rights on other products, patent buyouts, and research tournaments. Governments could also try to simply signal willingness to pay more for future products such as vaccines by purchasing more existing vaccines at a higher price and by making non-binding statements about future intentions to purchase products. Given the huge disparities between private and social returns to research, it is likely that any program that committed to provide compensation to vaccine and drug developers would be an improvement on the status quo. However, this section argues purchase commitments are the most attractive option. While patent buyouts and commitments to purchase desired technologies are economically quite similar, purchase commitments more closely link payment to delivery of appropriate products and avoid the risk of buying out a patent only to discover that the original developer maintains effective monopoly rights because it possesses a trade secret. Extensions of patent rights on other pharmaceuticals inefficiently and inequitably place the entire burden of vaccine development on purchasers of those pharmaceuticals, 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 and other cost-effective technologies is certainly justified in its

own right, but on its own is unlikely to convince potential developers of vaccines and other appropriate products to treat malaria, tuberculosis, or strains of HIV common in Africa that the international community will be willing to pay for these products in ten or fifteen years. Vague public pronouncements without binding commitments may actually do more harm than good if they increase cynicism in the pharmaceutical industry regarding public policy towards R&D.

4.1 Patent Buyouts, and Purchase Commitments

Patent buyouts[23] and purchase commitments are economically similar. For example, instead of promising to pay $5 per dose for 50 million doses of a malaria vaccine per year for ten years, governments could simply offer to pay the present discounted value of this stream of payments, minus the manufacturing cost, in exchange for the patent rights to the malaria vaccine. The government could then put the patent in the public domain and allow free competition in manufacturing the vaccine. Both mechanisms tie rewards to the development of a desired product and improve access to products once they have been developed.

Patent buyouts 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 patent buyouts over purchase commitments 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

[23] 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, there is no need for such an auction.

decisions about screen size, color, style, reliability, and other issues best left to consumers. In contrast, governments purchase vaccines and regulate vaccine quality in any case

Moreover, in the case of vaccines, purchase commitments have significant advantages. Because biologicals are difficult to produce, a patent buyout might leave the developer with an effective monopoly due to trade secrets, even without the patent. In this case, the public would effectively pay twice: once for the patent and again for the product.

Compared to patent buyouts, product purchases also provide a closer link between payments and product quality. For example, suppose that a vaccine received regulatory approval, but was later found to have side effects. This was the case with the Wyeth-Ayerst rotavirus vaccine which was withdrawn from the U.S. market following evidence that it causes intususception in rare cases. If a patent buyout had been made at the date of regulatory approval, a long, uncertain, and wasteful legal fight might be needed to recover the money. Vaccine purchases, on the other hand, could be suspended as soon as evidence appeared of unacceptable side effects.

Moreover, purchase commitments are likely to be politically more attractive than patent buyouts, and thus more credible to potential product developers. Developers are vulnerable to expropriation, even if the terms of the compensation program legally obligate the government to provide compensation for any qualifying product: 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 50 million children each year at a few dollars a dose for ten years is likely to

be more politically appealing than awarding a multi-billion dollar windfall to a pharmaceutical manufacturer. Conversations with pharmaceutical executives suggest that they do not like anything that might have the appearance of a prize.

4.2 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 and drug development on patients in need of the drug for which the patent has been extended. For example, consider extending the patent on Prozac as compensation for developing an HIV vaccine. This 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.[24] An extension of the Prozac patent would prevent some people from getting needed treatment for depression.

[24] 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 are less likely to do so than HMOs, and so patent extensions are more attractive in countries with centralized health systems. Nonetheless, even under Britain's National Health Service, for example, decision makers face internal prices, and hence higher prices for particular drugs would lead to reduced purchases of those drugs.

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, 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 a malaria vaccine with the extension of a Prozac patent eliminates this link between the quality of the malaria vaccine and the magnitude of the compensation.

Another disadvantage of compensating product 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. This would amount a stronger incentive to perform the desired research.

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.

Tournaments have several limitations, however, and are therefore not well-suited to encouraging vaccine and drug 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 focus effort on the diseases with scientific prospects for success. 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 or drug purchase program, no public funds are spent unless the desired product is developed.

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 that had made the most progress toward the desired technology. Anticipating this, firms might invest in political correctness or scientific faddishness rather than in producing an effective product. Of course, a committee making purchase decisions for a vaccine or drug purchase program could also be subject to bias, but judgments about who has made the most progress developing a vaccine or drug are more subjective than judgments about whether a vaccine or drug with a particular set of results from phase III trials is satisfactory. Since there would be no clear-cut way to decide who was ahead in a tournament, awards might be subject to litigation and charges of favoritism.

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 product was developed.

Tournaments may lead researchers to put their efforts into looking good on the tournament completion date, rather than completing a product. Firms that 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 successful product 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.

4.4 Expanding the Market for Existing Vaccines and Drugs

Some argue that by purchasing more existing products, at higher prices, policy makers can signal their intention to provide a market for future products, and thus encourage research on desired technologies. Although the standard EPI package of vaccines is widely distributed, a number of effective vaccines that are already available are not fully used.[25] 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.

[25] 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.

However, by itself, paying more for currently available products may not make pharmaceutical firms confident that they will be rewarded for developing new products. For example, 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 pay for future vaccines fifteen years from now. Legally binding commitments to purchase future products would therefore still be needed to spur 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 products. 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 products at a remunerative price, there would be no reason to pay more for current products than had been implicitly or explicitly promised to developers. Paying high prices for both current and future products 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 or particular desired drugs, 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.

Thus, while increased purchases and delivery of existing drugs, and especially vaccines, are likely to be cost-effective ways of saving lives in their own right, in order to motivate R&D on future desired technologies, explicit commitments to reward developers of the desired future products would still be needed. Paying more for existing products than developers could have reasonably expected when they invested in research is likely to be an expensive way of encouraging research on future technologies.

In summary, among various possible pull programs, purchase commitments most closely reward the achievement of the desired goals and most cost effectively finance this reward. The effectiveness of a purchase commitment in encouraging firms to undertake research depends on its design. The next section takes up this issue.

5 The Credibility of Purchase Commitments

For a purchase commitment to be effective in spurring new research, potential developers must believe that once they have sunk money into producing a product, it will be purchased at a

price that covers their risk-adjusted costs of research, as well as their manufacturing costs. Sub-section 5.1 notes that courts have held purchase commitments to be legally binding contracts and argues that as long as the sponsor of a commitment has sufficient funds to fulfill the commitment, physically moving money to a separate account is unnecessary to provide legal commitment. It also discusses a number of precedents for a vaccine or drug purchase commitment, in which courts have upheld the legality of such contract. Sub-section 5.2 discusses some of the issues that would need to be addressed in specifying eligibility and pricing rules for a vaccine. Sub-section 5.3 argues that some discretion will be needed to interpret how general eligibility and pricing rules apply to any specific candidate vaccine, and discusses how the credibility of adjudicating institutions could be enhanced.

5.1 Legal Doctrine

This section, which draws heavily on Morantz and Sloane (2000), argues that a suitably designed commitment will be interpreted by the courts as a legally binding contract, and that hence the key credibility issue will not be outright default by the program sponsor, or whether money is physically set aside in a separate purchase fund, but rather questions over the interpretation of program rules.

Courts have ruled that publicly advertised contests are legally binding contracts. As summarized in Sullivan [1988], sponsors of contests are contractually obligated to pay the winners according to their public announcements. A contestant who performs the requested act has formed a valid and binding contract with the promoter. Attempts to escape liability by changing contest rules after a contestant has accepted the offer by performing the desired act are

generally treated as breach of contract. Advertisements with certain specifications (identification of good, definite quantity of good, etc.) for the purchase of goods at specified prices have also been found to be legally binding. (See Vaccaro [1972] for a summary and analysis of doctrine.)

Moreover, if the procedures in a contest stipulate who will judge the contest, decisions made by the stipulated judge of the contest are usually treated as conclusive. Contest judges' decisions are generally held to be conclusive as long as they are made in good faith, although some cases find that contracts giving one party the unilateral right to decide disputes are unenforceable. When the judge of the contest is an independent party, the courts almost universally hold the decision as final unless the decision was made in bad faith, or the judges exceeded the authority specified in contest rules.[26]

There are a number of precedent cases of purchase commitments and subsequent rewards. The Kremer prize for human-powered flight led to the historic flight of the Gossamer Albatross across the English Channel [Grosser, 1991]. In 1997 Andrew John Wiles received the Wolfskehl Prize for proving Fermat's Last Theorem. In the 1960's the U.S. government used a contract offering to purchase manganese ore in order to stimulate domestic production. As part of the "Domestic Manganese Purchase Program," a U.S. executive agency committed to purchase, at a minimum price, domestic manganese ore that complied with the conditions outlined in its contractual offer. Courts held that the commitment was legally binding. Given that legally binding contracts can be written, physically setting aside funds in an escrow account is not necessary for a commitment to be binding, as long as the sponsor of a purchase commitment has sufficient funds to fulfill the commitment. The key questions for credibility

[26] The credibility of the product purchase commitment can be increased by framing it as a unilateral contract (i.e., one not requiring a promise by others to become valid) and explicitly including a promise not to revoke. Some additional legal issues might arise if a purchase commitment were made by a national government or an international institution, and legal research would be needed to address these issues.

revolve around specifying eligibility and pricing rules and procedures for adjudicating disputes under these rules.

Depending on legal language, commitments could be made more or less binding. The options range from a simple announcement of an intention to purchase the desired product, to a legally binding announcement with details on eligibility and pricing. The more binding the commitment, the stronger the incentives for potential developers. In general, there is a tradeoff between flexibility and credibly committing to pay for a desired product. Imperfect commitment reduces both the expected revenue for developers and expected costs for the sponsor in the same proportion. It reduces efficiency only to the extent that the parties are risk averse.[27]

5.2 Issues to Consider in Determining Eligibility and Pricing

A program to increase the market for vaccines could offer to purchase vaccines meeting certain technical specifications, offer to match money spent on vaccine purchases by other institutions, or use some combination of these approaches. For example, the Kremer prize for human flight laid out detailed technical eligibility requirements. The Frist-Kerry-Pelosi-Dunn proposal does not specify detailed technical requirements, other than FDA approval, but merely states that a 100 percent tax credit will be given for sales of vaccines to non-profits and

[27] For example, consider a simple case in which potential vaccine developers seek to maximize expected profits and accurately interpret the degree of commitment entered into by potential donors. Suppose that in the absence of a particular piece of contractual language in the vaccine purchase commitment, there is a 90 percent chance the sponsor purchases the vaccine at the promised price and a 10 percent chance that they renege and renegotiate to a price of half the level originally promised. In this case, in the absence of a contractual arrangement, firms which seek to maximize expected profits will act as if the value of the program is not the promised annual revenue from the program, but rather 95 percent of the promised annual revenue. Note that while the expected incentive is only 95 percent of the promised level, so is the expected cost to the sponsor. To the extent that both vaccine developers and the sponsor are risk-averse, they would both prefer a perfectly credible commitment of $950 million to a 90 percent chance of $1 billion and a 10 percent chance of a $500 million payment. In this sense, imperfect credibility reduces the efficiency of purchase commitments.

international institutions, which would presumably make their own judgments as to whether candidate vaccines are acceptable.

The following are some of the key issues which would need to be considered in determining vaccine eligibility and pricing based on technical specifications. Similar issues would need to be considered if a purchase commitment were made for drugs.

- vaccine efficacy—the reduction in disease incidence among those receiving the vaccine.[28] Efficacy might vary in different circumstances. A vaccine could potentially be more efficacious against some strains of the disease than others, and thus be better suited to some geographic areas than others. It could work for some age groups, but not others. A vaccine might prevent severe symptoms of the disease, but not prevent milder cases.
- the number of doses required, the efficacy of the vaccine if an incomplete course is given, and the ages at which doses must be taken. If too many doses are required, fewer people will bring their children in to receive the full course of immunization. If the vaccine can be given along with vaccines that are already widely administered, delivery will be much cheaper.
- vaccine side effects. Side effects could differ for different sub-populations. Side effects would also need to be considered for people who do not comply perfectly with the delivery protocol. For example, taking a partial course of a malaria vaccine could potentially interfere with natural limited immunity.

[28] Some have speculated about the possibility of an "altruistic" malaria vaccine, which would block further transmission of the disease, without protecting the person who takes the vaccine. It is unclear how many people would be willing to take such a vaccine. Moreover, given the high intensity of malaria transmission in many parts of Africa, the epidemiological impact of an altruistic vaccine might be quite small unless the vaccination rate was very high. Committing in advance to purchase such a vaccine would be difficult.

- the time over which the vaccine provides protection, and whether booster shots could extend this period;
- what level of rigor would be required in the field trials. For example, how long would subjects have to be followed to determine the length of protection? How many separate studies in different regions would need to be conducted to assess efficacy against different varieties of the disease?
- the extent to which vaccines would lose their effectiveness over time. Presumably, some ongoing monitoring of vaccine effectiveness in the field would be required, and if it appears that resistance to the vaccine is spreading, vaccine purchases would have to be reassessed.

One possibility would be to design eligibility requirements based on rules using these criteria in such a way that vaccines would be considered eligible if they met a cost-effectiveness threshold. Eligibility and pricing rules could potentially be set so that vaccines meeting a certain cost-effectiveness threshold would be eligible for purchase and vaccines exceeding this threshold would receive higher prices.

Note, however, that care would be needed to minimize the possibility that mis-specified eligibility and pricing rules misdirect research incentives away from appropriate products. For example, it would be important to make clear that the commitment would not cover a hypothetical malaria vaccine that interfered with the development of natural immunity and provided only temporary protection. At the same time it is important not to set specifications so stringent that they would discourage pharmaceutical firms from following promising leads. For example, it would be a mistake to require a vaccine that achieved 90 percent efficacy against all strains of the disease, since in this case potential vaccine developers might not pursue a candidate

vaccine that would be likely to yield 99 percent protection against most strains, but only 85 percent protection against others, even if this were the best available research opportunity.

The program would have to specify pricing as well as eligibility rules. Paying more for superior products might create more appropriate incentives for researchers. A 90 percent efficacious vaccine is worth more than an 80 percent efficacious vaccine, and a vaccine that requires no booster is worth more than one requiring boosters every five years.

5.3 Procedures to Increase Credibility of a Vaccine Purchase Commitment

Credibility of vaccine purchase commitments to potential developers would be enhanced by appointing appropriate decision makers (such as a committee with some members who have worked in the pharmaceutical industry), insulating decision makers from political pressures through long terms of service, establishing a minimum purchase price, and placing limits on the discretion used by the program committee by laying out rules for determining eligibility and pricing. Another way to enhance the credibility of a commitment is to establish a program that covers a number of different diseases that primarily affect developing countries.[29] The program would then be able to build up a reputation for fair play and for fulfilling promises.[30]

[29] On the other hand, if the program maintained a single fund which could be used to purchase vaccines for any of several different diseases, then potential vaccine developers might fear that once they had invested money in developing a vaccine, the vaccine purchase program would try to pay a very low price for the vaccine, hoping to save its resources to purchase vaccines for other diseases. This problem could be addressed by maintaining separate funds (or making separate financial commitments) for different diseases.

[30] Note that the problem of inducing firms to conduct research and development on vaccines for which they expect the government to be the major purchaser is in some ways similar to the problem of inducing firms to conduct research and development on weapons for which they expect governments will be the major purchaser. In each case, the government must convince the firms contemplating undertaking research that it will not take advantage of them by insisting on low prices once they have already sunk their investments in research. Procurement rules for the U.S. Department of Defense do not instruct procurement officers to purchase orders at the lowest possible price, but instead to purchase at a price that covers suppliers' costs. The formulas used for calculating costs typically allow firms to cover more than manufacturing costs, which in turn provides an incentive for firms to invest in research and development to produce attractive products that allow them to win procurement contracts. Rogerson [1994]

Of course, while general eligibility and pricing rules could be set out, some degree of discretion in interpreting these rules would be needed once candidate products have been developed and tested.[31] Once the vaccine developer has sunk hundreds of millions of dollars in research, adjudicators might be tempted to offer a price that covered only manufacturing costs or to insist on excessive product testing and improvements. This temptation is an example of what was previously identified as a "time-consistency problem." In order to invest in research, pharmaceutical executives must be confident that adjudicators will not succumb to these temptations.

In particular, the reward should not be ex post estimates of "actual" R&D expenditures. Not only would this erode confidence among potential developers that they will be able to recover the cost of bearing the risk associated with research, but it would also lower incentives to perform research efficiently. Firms would have incentives to overstate the cost of research and to make wasteful expenditures.

The experience of central banks may offer some lessons for the design of an advance purchase program. Just as an advance purchase program would need to make a credible commitment to purchase an effective vaccine if one were developed, central banks need to head off inflationary expectations by credibly promising to take tough action if inflation starts to

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suggests that this serves as a reputational mechanism for encouraging research by defense contractors. The Defense Department has an advantage in that it is a long-standing institution, with a well-developed reputation about how it treats contractors, and contractors can count on the desire of the Defense Department to maintain a reputation for the future, because the continued existence of the Defense Department seems assured.

[31] Setting efficacy requirements for eligibility for an HIV vaccine is particularly difficult. Because of the key importance of a core group of high-risk people in influencing the spread of HIV, even a vaccine of low efficacy may prove useful in disrupting the chain of transmission if it is targeted to this group. On the other hand, at least theoretically, an imperfectly effective HIV vaccine could increase the spread of HIV, since people might adopt riskier behaviors if they felt they had reduced the chance of infection by taking an imperfect HIV vaccine. This outcome seems unlikely, however, since in steady state, an imperfectly effective vaccine could also potentially make the highest activity people more hopeful about their chances of being uninfected, and therefore less likely to adopt risky behavior. Delivery of an HIV vaccine may have to use very different channels than delivery of existing childhood vaccines, particularly if it is targeted to such a core group. Little is known about the costs of reaching such groups.

increase. Central banks insulate decision makers from political pressures by appointing them for long terms, and a vaccine purchase program could do the same. Appointing central bankers with strong anti-inflation credentials also helps build credibility for central banks. Similarly, delegating decisions regarding eligibility and pricing to a committee that included some members who had worked in industry could increase potential developers' confidence that the committee would not impose unreasonable conditions after they developed a vaccine.[32]

Credibility with potential vaccine developers would be significantly increased by a commitment to a minimum price and quantity in advance.[33] However, the benefits of this credibility device may come at some cost. Theoretically, a product that is useful, but not useful enough to warrant purchase at the minimum guaranteed price, would not be purchased at all.

In practice, however, this problem is not likely to be that serious. Most products that passed regulatory approval would be cost effective at even a high price per person immunized relative to the likely availability of funds [Glennerster and Kremer, 2001]. This is because vaccines falling far short of U.S. or European regulatory requirements have great difficulty winning wide approval in developing countries in any case.[34] Thus one can take as given that products will only be used if they meet a stringent risk-benefit ratio, meaning that it is quite unlikely that guaranteeing a minimum price *ex ante* would lead to rejection of an otherwise usable vaccine on cost-effectiveness grounds. If a product were not useful enough to warrant

[32] Unfortunately, there is a history of antagonism between the pharmaceutical industry and existing international vaccine purchasers such as the Pan American Health Organization (PAHO) and the United Nations' Children's Fund (UNICEF), which have a culture of trying to purchase vaccines at the minimum possible price. These institutions, therefore, might have difficulty administering a program designed to increase private-sector incentives for vaccine development.

[33] Setting low prices is the most likely way that the program could take advantage of developers. Program adjudicators concerned with public health will have limited incentives to insist on further trials, for example, because they will presumably want to get an effective product into the field.

[34] This is illustrated vividly by the apparently meager prospects of the Wyeth-Ayerst rotavirus vaccine in developing countries after it was withdrawn from the U.S. market following evidence that it causes intususception in rare cases. The benefits of the vaccine are likely to outweigh by far its risks in developing countries, where rotavirus kills three-

purchase at a few dollars per person immunized, the cost of failing to purchase it would not be that great. Moreover, if a product turned out to be socially useful, but not good enough to qualify for purchase under the program at the promised price, this would not preclude individual countries from purchasing the product or other donors from purchasing it. On balance, the potential costs of guaranteeing a minimum price seem small relative to the benefit of improving the credibility of commitments to reward vaccine developers, and thus spurring research.

6 Combining Technical Requirements and a Market Test

Technical eligibility requirements could potentially be combined with a market test. For example, candidate products could first be required to meet basic technical requirements, which would typically include clearance by some regulatory agency (such as the U.S. FDA). They could then be required to meet a market test—developing countries wishing to purchase products using program resources would be required to contribute a co-payment, and would be required to draw down an account they would have within the purchase program. Issues related to co-payments are discussed in detail in section 7 of this paper. Any products meeting the eligibility requirements would be eligible for purchase at some minimum price. Products exceeding these requirements could receive bonus payments linked to the effectiveness of the product. This would make commitments to purchase useful products at remunerative prices credible to potential developers, but would leave enough flexibility that appropriate purchasing decisions could be made after products had been tested and their characteristics became known.

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quarters of a million children each year. Nonetheless, it appears unlikely that the vaccine will ever be widely used.

6.1 Basic Technical Requirements

To be eligible for purchase, products would be required to fulfill basic technical requirements, which would normally include regulatory clearance by an established regulatory agency, such as the U.S. FDA or its European counterpart. This would ensure that the funds were spent for *bona fide* vaccines and drugs, rather than for quack remedies. However, a product may pass a risk-benefit assessment in one country, but not another. For example, a malaria or tuberculosis vaccine with significant but small side effects might not be appropriate for general use in low-prevalence countries, such as the United States, but might save millions of lives in high-prevalence areas.

It might make sense to allow the program, at its discretion, to waive the requirement of regulatory approval in donor countries if a country requested the product and a scientific committee established by the program concurred that it satisfied a risk-benefit assessment given the situation in the applicant country. More generally, it might be appropriate to guarantee that any candidate vaccine or drug satisfying certain high technical standards would receive automatic approval to go on to the market test. There could also be a gray area, in which candidate vaccines could be approved at the discretion of a scientific committee. This would provide assurance to potential developers that if they develop a high-quality product, they will have a market. It would also allow the committee the flexibility to consider purchasing vaccines or drugs that passed a risk-benefit analysis, but fell short of an ideal technology.

Just as a product might satisfy a risk-benefit assessment in a high-prevalence developing country, but not in a low-prevalence developed country, is possible that a product could be appropriate in a developed country, but not elsewhere. For example, a malaria vaccine that interfered with natural immunity might be appropriate for travelers, who would not have built up

this immunity in any case, but not for long-term residents of malarious areas. A few minimal technical requirements beyond regulatory approval are therefore likely to be appropriate before products are made eligible for the market test described below. Travelers' vaccines for malaria, which protect people making short trips, would presumably be ineligible.[35] Other technical requirements might include a requirement that a product could only be purchased for a country if it had been shown effective for the strains of disease prevalent in that country. Vaccines requiring more than some cutoff number of doses to be effective might require a special waiver for eligibility. Some ongoing monitoring might be required, to ensure that resistance to a drug or vaccine had not developed and spread. However, keeping technical eligibility requirements beyond regulatory clearance minimal and clearly defined, to reduce the potential for abuse of discretion, would enhance the credibility of purchase commitments with potential developers. This would decentralize the basic purchasing decision to individual recipient countries. Of course, these countries would be free to consider recommendations put out by the World Health Organization or any other body.

6.2 The Market Test

As discussed above, products could meet regulatory approval, but still be unsuitable for widespread use in a particular developing country. For example, a vaccine that was effective only if people received ten precisely timed doses might be useful for the U.S. military, but not for most people in developing countries. Requiring products that satisfy the technical criteria to meet a market test would allow purchasers the flexibility to make decisions about whether a

[35] It might therefore, for example, be appropriate to specify that the program could require proof of efficacy over some extended period for sporozoite malaria vaccines.

particular product is appropriate for their needs. In particular, developing countries would have incentives to seriously consider the suitability of candidate vaccines if they had to provide a co-payment and draw down an account within the purchase program that would be established specifically for each country.

Co-payments, discussed in more detail in section 7, act as a market test to help ensure that after a particular product has been tested, it is actually considered worth purchasing. However, co-payments alone may not be sufficient to demonstrate country commitment, since donors might offer to help fund co-payments. It is not clear that it would be possible or desirable to prohibit this.

Countries could be further motivated to carefully consider their purchases by establishing sub-accounts within the program for each country. If a country decided to purchase a product, it would draw down the commitments allocated to it. This system would give countries an incentive to purchase a product only if they were confident that it could be effectively administered in their country and if they did not expect a superior product to come on the market shortly. Otherwise, they would be better off saving the funds in their sub-account.

Using separate sub-accounts avoids creating an incentive for countries to agree to purchase marginally effective products, thinking that if they did not consume the available funds, other countries would. If countries must spend funds earmarked for their own purchases, they will have more incentive to purchase only high-quality products, thus providing incentives for potential developers to focus on developing such vaccines. Since countries would not be able to use their accounts to purchase anything but drugs and vaccines, and would not receive interest on

their accounts if they remained unspent, they would have every incentive to use their accounts to purchase a good product if one were available.[36]

The purchase commitment could use a series of safeguards to help prevent purchase of inappropriate products due to bribery or tied deals. Such tied deals would be a potential danger if developers could offer to kick back some percentage of the purchase price to the developing country in the form of price reductions on other pharmaceuticals, or even bribes. The technical requirements for eligibility provide the first and most important line of defense. This would prevent a country from using program funds to purchase a quack product manufactured by a politically-connected firm. Outright corruption would be limited with provisions punishing firms found guilty of bribing officials and restricting the amount of travel, training, and other perks that sellers could provide to health ministry officials. Under the U.S. Foreign Corrupt Practices Act, firms and executives found guilty of bribing foreign governments are subject to criminal prosecution. Other nations are now adopting similar laws. Since the developing-country drug and vaccine market is a small part of overall business for most large pharmaceutical companies, they would likely be reluctant to risk bad publicity, the attention of regulators, and legal sanction in order to make some extra money on drugs and vaccines.

Whistle-blower procedures could be instituted to protect, or reward, committee members reporting attempts at bribery by developers. Similarly, developers could blow the whistle on committee members who tried to insist on kickbacks. Members of the committee who were proven to have asked for kickbacks could be removed from the committees.

[36] If interest were paid on accounts, countries would be under less time pressure to reach agreement with developers, and therefore might have such a strong bargaining position that they could prevent developers from recovering their research costs. Note that developers are automatically under time pressure to reach a deal with purchasers, because their patent is time-limited. Moreover, if interest is not paid on individual country accounts, then any interest accumulated on the program could be used to fund grants for basic research, or allocated to countries where disease prevalence had increased since the program was established.

Implicit tied dealings are more difficult to regulate. A pharmaceutical firm simultaneously negotiating with a health ministry over a malaria vaccine and an antibiotic might convey to the ministry that it would be willing to be flexible on the antibiotic price if the ministry would purchase the malaria vaccine. In the absence of further incentives, vaccine developers might therefore aim only at creating a vaccine that could pass minimal eligibility requirements, rather than a more widely useful vaccine.[37]

One way to limit corruption and tied deals, while still preserving a market test, would be to include civil society as well as governments in countries' decision-making processes. For example, the committee making purchase decisions for a country might include not only representatives of the Ministry of Health, but also respected physicians, non-governmental organization representatives, and scientists. Countries wishing to participate in the program could be required to set up such committees in advance, and members could have security of tenure. Some members of the committee could be appointed by the purchase program. The committee could have authority to release resources from the country's sub-account within the program. The government would need to authorize disbursements of public funds to cover co-payments, but donors could potentially fund co-payments.

In the case of vaccines, limiting the number of doses purchased for any one country would limit the potential loss from tied deals and corruption. The number of doses purchased for a country might be limited to the number needed for the annual birth cohort, with some adjustment for the initial years of the program when a backlog of unimmunized people would need to be vaccinated.

[37] Payments by third parties are also difficult to regulate. Suppose a Swiss firm invents a malaria vaccine which is not effective against the strains of malaria prevalent in some country, and therefore is not appropriate for that country. The government of Switzerland or a foundation supported by the firm could provide aid for purchasers to use towards their co-payments. With a 20 percent co-payment, this would allow the government of Switzerland or

6.3 Bonus Payments Based on Product Quality

Specifying a minimum price which would be paid for products meeting the first two steps – technical requirements and the market test -- would help provide potential developers with a credible commitment. However, it would be desirable for developers to have incentives to develop vaccines that exceed a minimum eligibility threshold. It might therefore be useful to consider providing bonus payments depending on product quality. One standard way to measure cost-effectiveness in health is the cost of saving a Disability-Adjusted Life Year, or DALY. DALYs take into account not only the years of life lost but also the years of disability caused by a disease. In order to create appropriate incentives for developers to develop high-quality vaccines, bonus payments could be set so as to tie the reward to the number of lives or DALYs saved and to the cost of delivery.

Bonuses could be provided for products believed to exceed a cost-effectiveness threshold, in dollars spent per DALY averted. If a product exceeded this threshold, some fraction of the resulting savings could be returned to the developer as a bonus above the base price.

Basing incentives on lives or DALYs saved would create good incentives for pharmaceutical firms to develop products that create positive externalities, such as a malaria vaccine with an altruistic component which kills gametocytes, and thus prevents other people from becoming infected. Any side effects of a vaccine or drug could be subtracted from the measure of lives or DALYs saved.[38]

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the foundation to spend one dollar to raise five dollars for the company.

[38] It is worth noting that currently, the medical profession and society as a whole seem to weight DALYs caused by side effects much more heavily than DALYs saved.

Bonuses could also be paid if the product was cheap to deliver. In the case of vaccines, this would create incentives for researchers to develop vaccines that are oral, rather than injectable, that do not require many doses, and that can be delivered along with the vaccines currently given as part of the Expanded Program on Immunization (EPI).

Bonus payments could potentially be set in two ways. A committee could be free to base bonus payments directly on its estimates of the number of lives or DALYs saved by a particular product, using any data it wished.[39] Alternatively, a schedule of bonus payments could be set in advance as a function of more easily measured product characteristics, such as efficacy in clinical trials, the number of doses needed, etc. An approach such as that used in Glennerster and Kremer [2001] could be extended to estimate the set of product characteristics associated with any particular cost-effectiveness threshold.

Directly estimating DALYs or lives saved after products are developed allows the program to consider a broad range of characteristics and to use up-to-date information, but it also creates more uncertainty for developers and raises the prospect of bias by the committee charged with estimating DALYs and costs.[40] The appropriate strategy depends in part on how

[39] Information about the number of lives or DALYs saved might become available only gradually, and therefore, if this approach were adopted, it might theoretically be best to condition payments on long-run outcomes. For example, it might initially be unclear whether a vaccine provides protection only temporarily, or indefinitely. The extent to which a vaccine prevents secondary infections might also be difficult to predict in advance. Initial bonus payments to developers could be based on conservative estimates of lives or DALYs saved and additional payments could be made later, depending on the realization of lives or DALYs saved. Of course, if payments were delayed, accumulated interest would have to be paid as well. Basing bonus payments to developers on realized DALYs or lives saved, rather than on the results of the clinical trials required for regulatory approval, creates better incentives to develop products that will work in the real world, rather than only in clinical trials, where it is easier to make sure that delivery protocols are followed exactly. Moreover, if bonus payments could be claimed after a product had already been used, it would be much more difficult for a price-setting committee within the vaccine purchase program to refuse to pay a remunerative price. Before a product is used in the field, the committee could argue that it deserves only a small bonus, citing potential problems with the product. However, if the product is used, and, for example, it reduces the burden of malaria by 90 percent, it will be very hard for the committee to argue that it is ineffective. (Exceptions to this are new diseases, such as HIV, for which predictions of prevalence in the absence of a vaccine are likely to be particularly inaccurate.)

[40] Basing incentives on mortality rather than DALYs might be attractive, since mortality is easier for the public to understand and perhaps less subjective and open to manipulation. On the other hand, it may be best to more closely tie incentives to objectives by rewarding DALYs saved. It is desirable to give researchers incentives to reduce

trustworthy the committee charged with these tasks is considered to be, and in part on what reasonably transparent and objective procedures can be developed for measuring vaccine efficacy. Thus, it may vary among diseases.[41]

Basing payments directly on the cost of delivery and on the number of lives or DALYs saved through the use of a product is also potentially problematic because these quantities depend not only on actions under the control of the vaccine developer, but also on actions by others. To the extent that health ministries cannot easily maintain cold chains or deliver vaccines to rural areas on a precise schedule, vaccinations that require cold chains and precisely timed deliveries will be expensive per life or DALY saved.

If the weaknesses of health ministries are not strategically aimed at extracting payments from the developer, this will create appropriate incentives for developers. Developers should try to design vaccines that are appropriate for actual health systems, not for some theoretical ideal health system. For example, if health ministries cannot maintain cold chains for vaccines, then vaccine developers should have incentives to develop heat stable vaccines.

However, to the extent that health ministries may behave strategically, it will be best to base bonus payments on preset indicators of the likely number of DALYs saved, rather than the actual number of DALYs. This is because if developers were paid based on realized DALYs saved, health ministries could potentially try to extract payments from the developer in exchange for agreeing to distribute the product efficiently. This would weaken incentives for product development.

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morbidity as well as mortality, and to guard against side effects that cause morbidity.

[41] For example, in Africa, HIV prevalence can be taken as a good indicator of future HIV deaths and disability, but prevalence of malaria may be a poor indicator of the total burden of malaria, since a vaccine might greatly reduce malaria mortality without preventing infection.

If the committee charged with estimating lives or DALYs saved simply makes honest mistakes in calculating these quantities, but those mistakes do not systematically tend to underestimate or overestimate the actual effects of the product, then the potential profit from developing a product could as easily be increased or decreased by the uncertainty in calculations of DALYs or lives saved. The attractiveness of investment in vaccines and drugs would be reduced, but only to the extent that developers are not willing to take gambles that could turn out to help them as easily as to hurt them.

Errors in estimation of DALYs or lives saved are particularly problematic if developers can influence these estimates through actions other than research. For example, if politically-connected pharmaceutical firms obtain more favorable DALY calculations, firms will divert effort towards developing political connections and away from developing good.

The scope for bias would be reduced by setting forth procedures as fully as possible ahead of time, working under a framework of establishing a bonus per life or DALY saved. The World Health Organization project on the burden of disease has developed detailed procedures for estimating DALY burdens. Epidemiological surveys could be conducted to assess the burden of various diseases prior to the development of vaccines or desired drugs.

6.4 Sunset Provisions

Sunset provisions could be incorporated into a purchase program. For example, a malaria vaccine fund could revert to the donors or be used for other health problems in developing countries if, after fifty years, no qualifying vaccine had been developed, or if at some earlier time, a scientific committee established by the program determined that the burden of malaria

had been sustainably cut more than 50 percent through other techniques, such as insecticides. Sunset provisions could be continuous, so that the purchase commitment would fall with the severity of the disease. Note that any bonus payment based on DALYs or lives saved would automatically fall with prevalence of the disease. A sunset provision would increase the risk borne by potential developers, but biotech and pharmaceutical firms routinely have to bear the risk that alternative technologies will render the projects they are working on superfluous. There is no reason why this should be any different for firms working on developing country diseases. It is efficient for researchers to consider the possibility that their work will be superseded by other technologies when choosing their research projects.

7 Co-Payments

Requiring countries receiving products to provide reasonable co-payments can boost incentives for vaccine developers given any fixed level of donor contributions. Co-payments also help ensure that the authorities in recipient countries feel that the product is suitable for use in their circumstances. This is important since conditions vary among countries. For example, a vaccine might be effective against the strains of malaria prevalent in some countries, but not against other strains. Finally, requiring co-payments is a useful test of a country's commitment to a program. If a country is prepared to make a co-payment, it is also more likely to be prepared to take the other steps necessary to ensure that the product is delivered to the people who need it.

Setting the level of co-payments involves a tradeoff between improving access once a product has been developed and creating incentives for product development. On the one hand, once a product has been developed, it will be produced at the efficient scale if the co-payment equals the marginal cost of producing an additional dose. On the other hand, given a fixed level

of donor contributions, incentives for product development will be greater if developing countries provide co-payments at their willingness to pay for the product.

Setting co-payments from countries receiving products just below their estimated willingness to pay for products will maximize incentives for product development while not reducing consumption of products below the optimal level. Since richer countries are likely to be willing to pay more for products than poorer countries, this implies that co-payments should rise with per capita income.[42] Willingness to pay may also be greater for diseases that create a particularly high health burden, such as HIV/AIDS. Given the uncertainty in estimating this willingness to pay and the need for a uniform co-payment policy across heterogeneous countries, it makes sense to estimate willingness to pay conservatively. Insisting on too great a co-payment would limit access to the product, and, by reducing take-up, would reduce incentives for product developers.

Note also that setting the required co-payments close to countries' willingness to pay reduces developers' temptation to try to extract supplemental payments from purchasing countries. It is not clear whether the purchase program should agree to be a party to purchases with supplemental co-payments greater than those required under the program, even if the recipient country agrees to this. Allowing supplemental payments broadens the scope for developers to demand prices greater than those offered under the purchase program, and these higher prices could potentially exclude some countries from access to products. For example, if the developer felt that most countries would be willing to supplement the required co-payment by $1 a dose, it might demand this from every country. Those countries unable to afford this supplemental payment would not be able to obtain the product.

Note that tying co-payments to income achieves many of the benefits of tiered pricing. If co-payments are set appropriately, access to products is expanded so that products can be used

[42] Willingness to pay is also likely to be higher for countries with a greater burden of disease, but requiring a larger co-payment from countries with a greater disease burden seems inequitable and is likely to be politically infeasible.

wherever the social value of the product exceeds the marginal production cost. Incentives for product development can correspond to the aggregate willingness to pay for products. Yet developers need not take the politically damaging step of revealing their willingness to produce additional doses at low cost, thus risking generating enhanced political pressures for price regulation.

8 Procedures for Multiple Vaccines or Drugs

For purchase commitments to spur research, it is essential that intellectual property rights be respected. If the program purchases products from imitators, rather than respecting the intellectual property rights of the original developers, incentives for product development will be vitiated.[43]

Moreover, it may be worth supplementing patent enforcement with additional protection for product developers. Once a vaccine or drug for a particular disease has been developed, it becomes easier for competitors to develop alternative products. This is true even if the first product is protected by a patent, as it is often possible to design "me-too" copycat products that skirt around patents. Developers of the initial product, therefore, face a risk that a copycat drug or vaccine will be produced shortly after the initial one is developed and that this subsequent product will capture much of the market. This risk may deter research. In many industries, first-mover advantages due to network effects or to brand loyalty by customers help protect innovations, but governments are the main purchasers of vaccines, and are usually major

[43] If the vaccine purchase program were an international organization, it is not clear what court would have authority to rule on intellectual property rights questions. One option would be to spend funds from each donor in accordance with the intellectual property rights laws of that country. For example, U.S. funds would not be used to purchase vaccines that violate U.S. patents.

purchasers of drugs, and since governments are less likely to be influenced by brand loyalty than individual consumers, other forms of protection may be needed.

It will be important to preserve rewards for the initial developer. To see why, note that the world currently needs acceptable vaccines for malaria, tuberculosis, and HIV/AIDS, and incentives for a private developer are a small fraction of the social value. Once an adequate vaccine is developed, however, the world's need for a second vaccine will be much more limited. This suggests a smaller reward will be needed to bring private incentives for a second vaccine into line with the social value of a second vaccine.

To some extent, the initial developer will receive a larger share of vaccine purchases in any case, since the initial developer will sell vaccines used to immunize the backlog of unimmunized adults, while subsequent developers will be restricted to the market of new cohorts of children. Pricing a product in nominal terms will also disproportionately help the original developer, since real prices will fall over time. (It would even be possible to specify a falling time path of nominal prices.)

The developer of the first product could be further protected through an exclusivity clause similar to that in the Orphan Drug Act. This would require that the initial product be purchased if newer alternatives were not clinically superior. This provision is widely believed to have greatly increased research on orphan drugs [Shulman and Manocchia, 1997].

In the case of vaccines, the exception for clinically superior products may not weaken incentives for the first developer that much in practice. Since regulatory standards for approval of the first vaccine are likely to be high, it may be difficult to show that a subsequent vaccine is clinically superior.

Note that market exclusivity would apply only to the target population for which the original product was adequate. Thus, for example, if one firm develops an AIDS vaccine effective against a particular clade of the disease, it would have marketing exclusivity for that clade, but not for other clades.

One potential objection to the market exclusivity provision is that it could increase the risk borne by developers. In the absence of a market exclusivity clause, if several firms develop vaccines around the same time, they will share the market. Providing market exclusivity to the first vaccine developer could potentially increase risk. On the other hand, to the extent that prices fall if multiple vaccines are invented, or firms dissipate potential profits in marketing expenditures, the expected reward to investing in vaccine research and development is greater with a market exclusivity clause. The success of the Orphan Drug Act in increasing research and development on orphan drugs suggests that the increase in expected profits is the key issue for potential developers. If it were thought important to avoid increasing the risk borne by potential developers, purchases under the program could be limited to those products invented within some period (perhaps a year or two) following the licensing of the first acceptable product, unless a subsequent product was clinically superior. This would reduce risk for firms engaged in a tight race to develop a product, while also reducing the chance that "me too" products would greatly reduce sales for the initial developer and thus deter research.

The exception in the Orphan Drug Act's market exclusivity provision for clinically superior products could potentially be modified for application to a vaccine purchase commitment. Ideally, if a subsequent vaccine were clinically superior, the price paid would be related to the marginal improvement the subsequent vaccine represents over the original vaccine, and the original developers would continue to receive compensation in line with the social value

of their work. A bonus payment system provides a potential mechanism for doing this. One option would be to retain the exclusivity clause even if a superior vaccine were developed, but give the developer of the original vaccine incentives to buy out the technology of the second producer. The bonus payments that would go with supplying a superior vaccine would provide such an incentive. Alternatively, the newer vaccine could be purchased at a price based on its efficacy, but the developer of the newer vaccine could then be required to pay the original developer an amount equal to the price paid for the original vaccine, less an allowance related to the production cost of the new vaccine. While this approach matches private and social research incentives more closely than the blanket exception for superior products in the Orphan Drug Act, it would be difficult to administer.

9 Product Coverage and Pricing

This section first argues that the key determinant of research incentives will be the total revenue generated by a product, rather than, in the case of vaccines, the price per person immunized. Decisions about where it is cost effective to vaccinate or treat patients should be based on the incremental cost of manufacturing an additional unit of drug or vaccine, rather than the average price paid per person immunized or treated under the program. Given the desired market size and number of required vaccinations, the price per person immunized can be determined by dividing the desired market size by the number of people needing immunization. The tricky question is determining the appropriate market size. The total market promised should be large enough to stimulate research, but not so large that a purchase program would not be cost effective. Sub-sections 9.2 and 9.3 note that a rough rule of thumb in the industry is that a market of $250 million per year is necessary to spur significant research, and argue that a

purchase program would be highly cost effective even at a substantially larger scale. The sponsor of a purchase commitment could start with a modest program, which would not be too expensive, but retain the option to increase the value of the program if the original program proved too small to stimulate sufficient research. Sub-section 5.4 argues that as long as the product price is not expected to increase too quickly, this will not lead developers to withhold a product from the market in the hope of getting a better price.

9.1 Coverage

The key determinant of research incentives will be the total discounted revenue generated by a product. It is very expensive to conduct research, but once research is complete, it is typically fairly cheap to produce additional doses. For a fixed amount of total revenue, product developers will therefore be almost as happy to produce a high volume at a low price as a low volume at a high price.

This implies that, at least as a first approximation, prices should be set per person immunized or treated, not per dose. There is little reason to pay more per person immunized if more doses are required to provide immunity than if a single dose is required. In fact, the vaccine is more valuable if only a single dose is required to provide immunity, as this reduces delivery costs and is likely to increase patient compliance.

Moreover, the purchase program would not save money in the case of vaccines by excluding large countries from coverage, or excluding countries if vaccination or treatment is cost effective at the marginal cost of production, but not at the average price paid for vaccination or treatment under the program. This is a false economy, because potential developers will need a fixed amount of revenue to induce them to conduct research, and if fewer doses are purchased,

the price per person immunized or treated will need to be greater to induce the same amount of research.[44]

Given the quantity of product likely to be needed, the price per immunized person or treated person should be set so as to yield the desired market size. Market size should be large enough to stimulate research if scientifically warranted, but not so large that a desired product would not be cost effective.

9.2 What Size Market Is Needed to Spur Research?

There is no single answer to the question of how large a market is needed to spur research. The larger the market for a product, the more firms will enter the field, the more research leads each firm will pursue, and the faster a product will be developed. The more researchers entering the field, the smaller the chance that any particular firm will be the first to develop a product. Thus the cost of development to the firm, adjusted by the risk that a particular firm or research team will not win the development race, rises with the potential size of the market. This means that increasing the size of the purchase commitment does not increase developers' expected profit, because doing so lowers the probability that any one firm will be the first to successfully develop the desired product. This increases the risk and cost of performing R&D. Given the enormous burden of malaria, tuberculosis, and HIV/AIDS, it is important to provide sufficient incentive for many researchers to enter the field and to induce major pharmaceutical firms to pursue several potential leads simultaneously so that products can be developed quickly. Moreover, given the limited cost-effectiveness of current products for these

[44] Excluding countries that would have bought products in the absence of a program at prices greater than or equal to the price paid by the program would, however, increase incentives to develop products. A sliding scale of co-

diseases and the difficulty of achieving prevention through behavioral change, there is little risk that payments made as a result of a purchase commitment could exceed the cost of saving the equivalent number of lives using today's treatments or expanded prevention programs.

Because potential developers know that their research may fail, in order to have incentives to conduct this work, they must expect to more than cover their research expenses if they succeed. For example, if potential biotechnology investors expect that a candidate product has a 1 in 10 chance of succeeding, they would require at least a tenfold return on their investment in the case of success to make the investment worthwhile.[45]

There are several ways to get a sense of the minimum market size needed to motivate investors. Estimates of the average cost of product development are controversial, but in her review of the various studies on NCE costs, Kettler [1999] suggests that the costs per NCE launched today may approach $600 million. DiMasi et al [1991], who examined 93 randomly selected new chemical entities from a survey of twelve pharmaceutical firms and found that, taking into account the risk of failure at each stage in the drug development process, the average cost per approved New Chemical Entity (NCE) was $114 million 1987 dollars. Capitalizing this to the date of marketing approval at a (probably over-generous) 8 percent discount rate implies an average cost of $214 million 1987 dollars, or approximately $313 million 1999 dollars. While this figure is of some interest, there is wide variation in the cost of developing pharmaceuticals. DiMasi found that for most stages in the development process, the standard deviation of cost was greater than the mean cost. Vaccine and drug trials for diseases with low

payments could be used to gradually phase out the program.

[45] As discussed above, advocates for grant-funded research programs may have incentives to be over-optimistic about the prospects for easily developing vaccines. The Institute of Medicine estimated in 1986 that a malaria vaccine could be developed for $35 million. This estimate is far too low. From the limited description of their methodology, it seems that their cost estimate assumes success in every stage of the vaccine development process, while in fact, it is likely that many different candidate vaccines will have to be tried before a usable vaccine is developed. A further indication that the Institute of Medicine's estimates were over-optimistic lies in their 1986

incidence, such as HIV and tuberculosis, require very large samples, and are therefore expensive.[46]

The cost of developing malaria, tuberculosis, or HIV vaccines may be much higher than suggested by these estimates, since surveys of existing drugs and vaccines are disproportionately likely to focus on the low-hanging fruit of entities that are cheap to develop. Unfortunately, vaccines for malaria, tuberculosis, and HIV may not be such low-hanging fruit.

It is more useful to consider the revenue streams that seem sufficient to induce vaccine research in developed countries. Table 1 presents the sales revenues for vaccines of several major pharmaceutical companies. These figures come from the firms' annual reports, and represent their most important products. This means that they have some products that receive annual revenues that are lower than the figures presented here. These vaccines have a range of revenues, and average annual revenue in the sample is around $280 million. This figure is consistent with the range identified by Mercer Management Consulting [1998].

prediction that a malaria vaccine could be licensed within 5 to 10 years.

[46] Regulators may require large samples even for vaccines for diseases with higher incidence, because they believe it is especially important to detect potential side effects of vaccines, since they are administered to healthy people.

Table 1: Annual sales revenues for vaccines 1999 (selected companies)

Producer	Product	1999 Sales Revenue ($ million)
Merck + AventisPasteur	Hepatitis vaccines	159
	Viral vaccines (includes chickenpox)	69
	Other vaccines (includes travelers')	339
	Combination Hexavac (projected)	350
SmithKline Beecham	Total hepatitis vaccines	78
	Infanrix (pediatric combination vaccine)	196
	Lymerix (Lyme disease)	40

Source: Merck Annual Report (1999); SmithKline Beecham Annual Report (1999).

One approach to estimating the necessary size of a program is to ask pharmaceutical executives whether a purchase program could serve as an important incentive for research, and how big the program would need to be to do so. There are several reasons why this approach may give misleading results. First, the question is mis-specified. As discussed above, firms must decide not merely whether to invest in developing a particular product, but also at what level to invest. The more lucrative a market, the more leads they will pursue. Second, pharmaceutical executives may see the question as part of a price negotiation, and may therefore inflate their estimates, particularly if they expect that budgets are likely to be cut in a process of negotiation. Third, pharmaceutical firms may well request programs that increase their profits, without necessarily increasing their incentives to develop a new product. In particular, pharmaceutical executives may claim that the most useful motivator for HIV vaccine research would be higher prices on existing vaccines. Pharmaceutical executives clearly have an incentive to claim this, whether or not it is the case. Fourth, pharmaceutical firms have been

criticized for failing to invest in research on vaccines for diseases which kill millions of people, while investing in more commercially viable drugs [Silverstein, 1999]. This may make executives reluctant to admit that they are not investing in vaccines because they think such vaccines would not be profitable. It is more politically acceptable for executives to say that they are not investing because they see few scientific prospects for such a vaccine. Fifth, firms are heterogeneous. Most of the respondents to such surveys are from large pharmaceutical firms. These firms require larger markets to shift their corporate strategy. Biotech firms may be willing to enter at lower market sizes. Kettler (1999) shows, for example, the large response of biotech companies to the orphan drug incentives relative to large pharmaceutical companies. Even among pharmaceutical firms, some may do more work on vaccines, for example, than others. Firms that specialize in vaccines would be willing to enter the market at a lower size than those whose strategic focus is elsewhere. Averaging the responses of both of these types of firms does not give the correct answer to the question of the necessary market size to successfully encourage the development of a malaria vaccine. The relevant cost is rather the marginal cost of inducing each successive firm to enter the market. Finally, scientists working on vaccines or drugs appropriate for developing countries may not have even considered the possibility of starting biotech firms or seeking investors, but if a large market were expected for such products, they might start thinking about this. Given that they probably have not spent that much time thinking about these issues yet, their responses to questions may not be that informative.

The opinion of outsiders, familiar with the industry, but not part of it, may be somewhat more credible. A respected pharmaceutical consulting firm estimates that a $250 million annual market is needed to motivate pharmaceutical firms [Mercer Management Consulting, 1998]. As discussed in section 9.3, when this figure is adjusted to take into account likely inflation between now and the period when vaccines are sold, the corresponding nominal annual market size for a purchase pre-commitment would be $336 million. A ten-year purchase commitment would

likely be sufficient to motivate research, given that potential developers are likely to heavily discount sales after this period, and that competing products are likely to emerge after ten years in any case, and drive down prices to the point at which they could be more broadly affordable.[47] A condition of participation in the program could be agreement to license the products to producers in developing countries after ten years of purchases at an appropriate level.

If politicians are unwilling to assume liability for more than a fixed amount of potential expenditure, coverage under the program could be capped. For example, suppose that a $250 million annual market per disease was deemed necessary to spur serious research on a vaccine for malaria HIV or TB, but that political leaders were unwilling to commit up to $750 million in potential annual expenditures on new vaccines. Suppose also that the chance that malaria, HIV, and tuberculosis vaccines were all developed simultaneously were judged to be less than 10 percent. Instead of only covering vaccines for two diseases, an alternative approach would be to pledge $350 million in annual purchases for vaccines for any of the diseases, subject to a $700 million cap on total committed annual expenditures. In the unlikely case that vaccines for three diseases were developed simultaneously, purchases for each would average one-third of $700 million, or $233 million. The expected market for a vaccine developer would be 0.9 * $350 million + 0.1 * $233 million, or $338.3 million.

9.3 Cost-Effectiveness

[47] The life of a patent is 20 years. However, a vaccine would only reach the market several years after the date of application for a patent. The effective life of a patent is the number of years of remaining on the patent from the time that it is first brought to market. Shulman, DiMasi, and Kaitin [1999] report that the average effective patent life for new drugs and biologicals is 11.2 years under the Waxman-Hatch Act, which granted extra protection to inventors to partially make up for loss of patent life during regulatory review. Without the Act, patent life would be 8.2 years. The Act covers the U.S. only, and there is no reason to believe that developing countries will offer similar patent protection. As noted above, a requirement to license vaccines after ten years could potentially be built into

While the need to motivate research sets a lower bound on the size of the purchase commitment, the need for the program to be cost effective when compared to alternative health interventions sets an upper bound on the size of a purchase commitment. Given the level of funding which is likely to be forthcoming, this is unlikely to prove a serious constraint. In the 1993 World Development Report, The World Bank treats health interventions that cost less than $100/DALY saved as cost effective [World Bank, 1993]. A program to purchase vaccines for malaria, tuberculosis, and HIV would be one of the most cost-effective health interventions in the world.

Glennerster and Kremer [2001] consider preliminary estimates of the cost-effectiveness of commitments to purchase vaccines for malaria, tuberculosis and HIV at various funding levels, vaccine efficacy levels, and required numbers of doses. [48]

The base case examined is based on a 100 percent effective one-dose vaccine and an average annual market of $336 million for each vaccine. This market size estimate is developed from the Mercer Management Consulting [1998] estimate that the annual market needed to motivate pharmaceutical firms is $250 million. Assuming that it will take about ten years to develop a vaccine and that the costs would have to be recouped over another ten years of sales, the relevant sales would be made between ten and twenty years from now. If the rate of inflation for the next 15 years is 2 percent, $336 million in nominal terms, at the midpoint of the vaccine sales, corresponds to $250 million now.

Donors would contribute approximately $285 million annually, co-payments providing the remainder. The incremental delivery cost per additional dose of vaccine added to the EPI

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the program.

[48] Note that the model presented here incorporates several refinements from that in Kremer [2001]. For example, this model uses updated data on GNP per capita, population, births, fertility, and age distribution. It also includes gains from targeting high-risk groups. While the results vary somewhat from those reported in Kremer [2001], the

package is assumed to be $0.40. This seems safe, given that the World Bank estimated that adding two new relatively expensive multiple dose vaccines to the EPI package would increase the cost of the package by 15 percent, or $2.25, including both the purchase price and the delivery cost [World Bank, 1993]. Co-payments per immunized person are assumed to be of 0.09 percent of per capita Gross National Product (GNP) for HIV/AIDS, 0.02 percent of per capita GNP for tuberculosis, and 0.03 percent of per capita GNP for malaria.[49]

The net present value of expenditures per discounted DALY saved over a ten-year horizon would be $10 for malaria, $12 for tuberculosis, and $44 for AIDS. However, the benefits of the program will continue beyond the 10-year life of the purchase commitment. We assume that after 10 years, the price of the vaccine falls to $0.50 per person immunized. This is a conservative estimate, as EPI vaccines currently sell for substantially less. The net present value of expenditures per discounted DALY saved would be $5 for malaria, $8 for tuberculosis, and $3 for AIDS. Overall, the cost would be about $4/DALY. The cost-effectiveness may be underestimated, as these calculations do not take into account the likely reduction in secondary infections due to vaccinations. The vaccine price per person immunized in the first 10 years would be $3.22 for malaria, $2.01 for tuberculosis, and $3.39 for HIV. This would be an extremely cost effective intervention relative to existing treatments for these diseases.

Purchase commitments would remain cost effective under a range of alternate assumptions about vaccine efficacy, the number of vaccine doses required, and the size of the fund.

qualitative implications remain the same.

[49] These percentages are chosen to be proportional to the DALY benefits of each vaccine per person immunized, since willingness to pay presumably increases with DALY benefits per person vaccinated.

9.4 Increasing the Promised Price over Time

The sponsor of a purchase commitment program could start with a relatively modest program. If additional incentives were judged necessary to spur vaccine research, the promised price could be increased until the desired product was developed or the price reached the social value of the desired product.[50] This procedure mimics auctions, which are typically efficient procurement mechanisms in situations in which production costs are unknown.[51]

As long as the price promised for a product does not increase at a rate greater than the interest rate, firms will not have an incentive to sit on a product they have developed while waiting for the price to rise. To see this, note that a firm which delays selling a product postpones its returns into the future, and therefore has to discount these returns at the interest rate. In addition, delay risks the possibility that a competitor will introduce an alternative product. Finally, if the developer has already taken out a patent, delay uses up the patent life.

If the price promised to developers was increased, this increase could potentially be restricted to products which were based on patents that had not yet been taken out. Greater incentives may not be needed to stimulate the final stages of research on a candidate product that is already promising. Moreover, restricting price increases to products based on new patents reduces the chance that firms will withhold a product from the market in the hope that prices will increase. Pharmaceutical firms are not likely to risk delaying patent applications for fear that a competitor will preempt them, especially since there are potentially many competing biotech firms that could patent products, whereas only a few large pharmaceutical firms actually conduct

[50] Since the quantity purchased would stay constant, total revenue would rise in proportion to price.

[51] Another option would be to pre-announce that if no vaccine had been developed by a certain date, the price would start growing automatically. However, it is probably better to let future decision makers choose whether or not to increase the price, since in some scenarios it would be optimal not to increase the price. For example, there would be no need to increase the price if general technological advances in biology reduced the expected cost of developing a vaccine sufficiently that many firms decided to pursue vaccines.

clinical trials and manufacture drugs and vaccines.[52] As discussed in the appendix for the case of vaccines, increasing the price over time may induce firms to delay starting research on a vaccine, or slow down the pace of this research, but this strategic delay will not be severe if many firms can potentially compete to develop a vaccine. Moreover, while product trials could not be conducted secretly, research towards patents could be, and this would make it much more difficult for potential developers to collude to increase the price by delay.

The appendix uses techniques from the economic theory of auctions to examine the effect of increases in price on vaccine development. The main results are as follows: If there are many competing firms, a system in which the price starts low and rises over time will generate a vaccine at close to the lowest possible cost. The fewer competing researchers, the longer each waits before beginning vaccine research. The greater the initial price, the more rapidly a vaccine will be developed. This implies that if society values a vaccine highly, it should choose a high initial price, and thus be willing to incur the risk of paying more than the minimum cost necessary to spur vaccine development. In the most realistic case, increasing the growth rate of the price will speed vaccine development unless very few firms could potentially compete to develop the vaccine.

10 The Scope of a Purchase Commitment

[52] One potential problem with this approach is that vaccine developers might incorporate unnecessary late-patented components in the vaccine to qualify for a higher price. However, a committee could rule on what were the key patents used in a given vaccine, so simply adding an extra useless patent would not lead to a higher vaccine price.

Potentially, advance purchase commitments could be used to encourage research not only on vaccines, but also on other techniques for fighting disease, including drugs, diagnostic devices, and insecticides against the mosquitoes which transmit malaria.

Covering a range of technologies would avoid biasing research effort towards vaccines, rather than other technologies to fight disease. The example of the British government's prize for a method of determining longitude suggests that prize terms should be set so as to admit a variety of solutions. Most of the scientific community believed that longitude could best be determined through astronomical observations, whereas the actual solution was through development of a sufficiently accurate clock. Pre-specifying an astronomical solution would have been a mistake.

On the other hand, opening up the program to any method of fighting disease would make defining eligibility and pricing decisions almost impossible. For example, developers of new HIV counseling techniques could seek to obtain payments for new techniques for promoting safe sex. Resources would be wasted in disputes over the impact of such programs. If only vaccines for malaria, tuberculosis, and HIV were eligible, the resources wasted on administration and on attempts to influence the committee would likely be fairly small relative to the cost of developing a vaccine, since only those who had actually developed a vaccine would have an entry ticket to begin trying to influence the disposition of program funds. One factor that militates toward restricting the program to vaccines and drugs is that existing institutions, such as the U.S. FDA, already have a reputation for adjudicating safety and efficacy of vaccines and drugs. A safe, environmentally appropriate insecticide might be an excellent way to fight malaria, but a whole set of procedures would need to be developed to determine eligibility

standards for insecticides. This suggests that research on insecticide might be better supported through push programs.

In principle, purchase commitments are appropriate for both drugs and vaccines, but if a choice has to be made for budgetary reasons, vaccines are probably a higher priority, since distortions in vaccine markets are more severe. Drugs are widely considered to be more profitable than vaccines. There is a relatively larger market for drugs than vaccines currently, particularly in the case of HIV/AIDS. In fact, a sufficient market exists in rich countries for HIV drugs that a purchase commitment for these drugs should not be a priority. Drugs also have more vocal interest groups to lobby for their development and funding because the benefits of drugs are more concentrated. Since drugs are much more susceptible than vaccines to the spread of resistance, individual decisions to take drugs may potentially create negative, as well as positive, externalities.

A number of technical considerations also make a purchase fund for drugs more difficult to create and operate than a purchase fund for vaccines. First, it is easier to specify the desired product and the number of doses needed in the case of vaccines than drugs. Regulators rarely, if ever, approve vaccines that have significant side-effects because vaccines are given to healthy people. This means that if a purchase commitment requires that a vaccine pass regulatory approval it need not specify in detail the side-effects that would be unacceptable. In contrast, since drugs are taken by sick people, regulators often willing to approve drugs with significant side-effects. A drug with strong side effects might not be worth taking against an ordinary case of malaria, but might be appropriate against drug-resistant cerebral malaria. As a result, a purchase commitment for drugs would have to specify the purchase price and quantity that would be associated with a particular level of side effects. For a vaccine, the number of doses

needed can be estimated from aggregate population data, whereas the number of drug doses needed depend on many decisions by individual patients and health care providers. Furthermore, because drugs are more subject to the development of resistance than vaccines, it may be appropriate to limit the use of a new drug for malaria or tuberculosis, for example, to only those patients who have strains of these diseases resistant to current treatments so as to postpone development of resistance to the new drug. Thus, a purchase commitment providing a subsidy for new products, but not for existing products could potentially cause a counterproductive shift towards new products. Finally, policy makers run the risk of creating an incentive for the development of a new drug that is only slightly better than the existing product (taking resistance into account), which would be wasteful. Since no vaccine currently exists for malaria or HIV, and the existing tuberculosis vaccine is of very limited use, this would be less of a problem for vaccines. These factors imply that targeted push programs, such as tax credits for clinical trials in developing countries linked to commitments to sell in these countries at reduced prices, may be useful for drugs, even if they are not particularly attractive for vaccines. Nonetheless, the fact that regulatory institutions such as the FDA approve drugs makes pull programs for drugs worth considering.

Table 2 shows the number of deaths caused annually by various diseases for which vaccines are needed. Given a sufficient budget, it might be appropriate to commit in advance to purchase vaccines developed against any of these diseases. However, if funding is tightly limited, it may be appropriate to target the most deadly diseases.

Table 2: Deaths from Diseases for which Vaccines Are Needed

Diseases	Deaths (000)[a]	%
AIDS	2285	27.47
Tuberculosis	1498	18.01
Malaria	1110	13.34
Pneumococcus[b]	1100	13.22
Rotavirus	800	9.62
Shigella	600	7.21
Enterotoxic *E. coli*	500	6.01
Respiratory syncytial virus[c]	160	1.92
Schistosomiasis[d]	150	1.80
Leishmaniasis	42	0.50
Trympanosomiasis	40	0.48
Chagas disease	17	0.20
Dengue	15	0.18
Leprosy	2	0.02
Total deaths	8319	100.00

[a] Estimated, World Health Report, WHO, 1999
[b] A pneumococcus vaccine was just approved for use in the United States, but it needs to be tested in developing countries, and perhaps modified accordingly.
[c] The Jordan Report, NIAID, 1998
[d] R. Bergquist, WHO, personal communication
Source: Children's Vaccine Initiative, CVI Forum 18, July 1999, p. 6.

An alternative option would be to start with some easier-to-develop vaccines and drugs as a way of building credibility. It also may be useful to first experiment with purchase commitments for a few vaccines or drugs and then consider modifying or extending the program based on the resulting experience.

11 Conclusion

For a purchase commitment to stimulate research investment, it must provide a credible promise that developers of good products will be rewarded. Eligibility requirements could include both minimal technical standards, and the market test that developing countries be willing to provide a co-payment for the product. To provide incentives for development of high-quality products, bonus payments for products could be tied, directly or indirectly, to the number

of lives or DALYs saved by the product, and to the delivery cost. The developer of the first viable product could have market exclusivity unless subsequent products are clinically superior. The price would be set on the basis of children immunized or disease episodes treated, rather than doses administered.

This conclusion briefly discusses the politics surrounding vaccine purchase programs. It then discusses the UK proposal for an advanced purchase commitment, the proposed U.S. tax credit for qualifying vaccine sales, and the proposed World Bank $1 billion commitment for financing vaccine purchases. Finally, it discusses how a private foundation could implement a vaccine purchase commitment.

11.1 The Politics of Creating Markets for Vaccines and Drugs

A key barrier to the development of political momentum for the financing of vaccine research is that there is no ready-made political constituency with a strong self-interest in lobbying for such a program. The development community obtains more jobs, budget, and influence from government programs than from programs which create open competition within the private sector. Government scientists similarly benefit from push programs. Pharmaceutical firms benefit from programs such as an R&D tax credit that allow them to claim the credit for work that they would have undertaken anyway. Activist groups obtain more publicity and funds by attacking pharmaceutical companies than by advocating better incentive systems. These groups are well placed to affect the political decision-making process.

Of course, a purchase commitment need not be a threat to any of these interest groups. Conflict between the need for incentives to develop new vaccines and existing prevention and

research efforts will be limited if a purchase commitment is financed from pledges rather than current budgets. When a vaccine became available, it might be seen as justifying increasing the total aid budget. Alternatively, once a vaccine became available, some existing prevention efforts may be less cost effective, and budget savings will be possible. The prospect of these future cuts will be politically easier than cutting existing programs, as future aid budgets do not have as much constituency among aid workers as current aid budgets. The people currently promoting condom use or researching HIV may have retired or gone on to other jobs by the time an HIV vaccine has been developed. It is worth noting that the budgetary conflict between research on new vaccines and efforts to control disease using existing technologies is sharper if research is financed out of current budgets, as it would be in push programs, than if it is financed through future vaccine purchases, which would come out of future budgets.

However, in the absence of extremely committed well-informed leadership, indifference by these constituencies, or even lukewarm support, will not be enough. At least some of these groups must be convinced to provide strong support. For example, if an advance purchase commitment is part of a larger fund, the package of policies can include prevention and treatment programs that are likely to be important to members of the development and activist communities.

Pharmaceutical firms will be interested in seeing some expenditure early in the program. This may be in part because such expenditures would enhance the credibility of the commitment, and in part because a program rewarding, say, a malaria vaccine, would not necessarily yield high expected profits, since much of the profit would be dissipated in competition to develop the vaccine. It may be easier to find champions for such programs in the pharmaceutical industry if some portion of the funds can be used to cover vaccines which are closer to development. In

particular, several new pneumococcus vaccines are expected to be developed soon. Additional work will be needed to test the suitability of these vaccines for developing countries, and perhaps to modify them to reflect the strains of pneumococcus prevalent there. As currently written the Frist-Kerry-Pelosi-Dunn proposal would cover new pneumococcus vaccines since the disease kills more that one million people per year. Note however that one vaccine for pneumococcus has been licensed recently, and this particular vaccine would not be eligible since it will have been developed prior to the passage of the legislation.

11.2 Potential Sponsors of New Markets for Vaccines and Drugs

Commitments to purchase vaccines could be undertaken by governments of industrialized countries, the World Bank, or private foundations. One institution could establish the basic infrastructure for a program and make an initial pledge and other organizations could later make pledges of their own. The initial pledge could cover particular diseases or countries, with later pledges broadening the program. Nations might not want to pledge to a vaccine purchase commitment program operated under another donor nation's control, so it might make sense to build in procedures for representation of multiple donors on decision-making bodies at the start, even if the program were initially supported by only one or two donors.

11.2.1 The UK initiative

The UK's Chancellor of the Exchequer Gordon Brown and Development Minister Clare Short have supported the idea of an advanced purchase commitment [Elliott and Atkinson 2001; DFID 2000]. In a speech at the International Conference Against Child Poverty in London,

Gordon Brown stated, "a purchase fund—providing a credible commitment to create a market for current and future treatments in developing countries—would surely serve as a strong incentive to develop and deliver affordable treatments. That is why, in a joint effort with Italy, the President of the G-7, the UK proposes that a new global purchase fund for drugs and vaccines be created. Both for treatments that do not yet exist but could be developed in time—for AIDS and malaria, for example—as well as for those that already exist and need to be purchased now" [Brown, 2001]. The UK Cabinet Office recently published a report that proposes to the international community an advance purchase commitment as part of a set of policy measures to fight communicable diseases [PIU, 2001].

11.2.2 The US tax credit proposal

In the U.S a tax credit for sales of vaccines for AIDS, tuberculosis, and malaria to nonprofit and international organizations has been proposed both by Senators Frist and Kerry and Representatives Pelosi and Dunn. This approach was also advocated by the Clinton Administration, but it is unclear what the position of the Bush Administration will be. 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 this proposal is structured as a tax credit, it would have effects similar to an expenditure program that matched private funds spent on vaccines.

The details of which vaccine sales would qualify would be worked out by the U.S. Agency for International Development (USAID) under the program, and the analysis in this report suggests that the details of their procedures will be quite important for the effect of the program. Biotech and pharmaceutical firms are more likely to find the commitment credible if, once the tax credit legislation is passed, USAID quickly specifies guidelines for how it will allocate credits. In particular, USAID would need to specify how it will address issues of vaccine pricing (presumably, it would not approve credit allocations for a small quantity of vaccine sold at tens of thousands of dollars per person immunized), how much of the fund could be spent on a vaccine that is currently far along in research, such as the pneumococcus vaccine; and what procedures would be used to allocate credits if multiple versions of a vaccine were available.

11.2.3 World Bank

The World Bank president, James Wolfensohn, has said that the institution plans to create a $1 billion loan fund to help countries purchase specified vaccines if and when they are developed [Financial Times, 2000]. Glennerster and Kremer [2000] discuss this proposal in more detail. The World Bank has yet to act on this proposal. Some health advocates in the Bank have argued for a more general program to combat communicable diseases of the poor. For a general program to stimulate research, however, 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. As discussed above, increased coverage of existing vaccines, while desirable in its own right, will by itself be inadequate to

convince potential vaccine developers that there will be a market for new vaccines when they are developed, given the long lead times for vaccines and the fickleness of donor interest.

Of course, an explicit commitment to help finance purchases of new vaccines will not interfere with other initiatives to tackle communicable diseases of the poor. This is because the commitment does not have to be financed unless and until a vaccine is developed. So, for example, the Bank could increase lending to promote the use of bednets against malaria, or increase coverage of existing vaccines, while committing that if and when new vaccines are developed, it will provide loans to countries purchasing these vaccines.

Some within the Bank and on the Bank's board have traditionally regarded earmarking future credits for a particular purpose as undesirable because it reduces the flexibility of the Bank to provide loans where they are most needed and would achieve the greatest benefit. Sacrificing flexibility is a mistake when it brings no compensating advantage. However, earmarking is necessary as a response to time-consistency problems. In particular, in the case of vaccines, earmarking can help resolve the time-consistency problem inherent in convincing potential vaccine developers that governments will compensate them adequately once they have sunk funds into developing vaccines. The loss of flexibility associated with earmarking does not seem like a major problem, since it would be hard to imagine a situation in which purchasing vaccines for malaria, tuberculosis, and AIDS would not be cost effective and a major development priority. In any case, a commitment could be structured so that it would be triggered only if a vaccine satisfied a particular cost-effectiveness threshold.

For countries to have an incentive to participate in the proposed World Bank program, loans will need to be at the concessional International Development Association (IDA) rates, and must not simply substitute for other concessional loans countries would have received. This is

because commitments by one country to purchase vaccines benefit other countries by encouraging vaccine research and development. No one country, therefore, has a sufficient incentive to make a commitment on its own (the global public good problem).

As the World Bank considers its policy towards research for vaccines to benefit the poor, it may consider partnerships with national governments or private foundations in which these institutions could work together to provide the markets necessary to encourage the development of vaccines against malaria, TB, and HIV/AIDS through IDA, the World Bank's concessional loan facility. Under this option, national governments would commit that if effective vaccines were developed, and that if IDA made loans to help developing countries purchase these vaccines, the UK would cover all or most of the repayments. Governments would deposit promissory notes with a World Bank trust fund now, but payments would not be made, or counted against national budgets, until appropriate vaccines were developed and IDA loans were extended for vaccine purchases.

This approach is effectively equivalent to a vaccine purchase commitment in that donors would finance purchase of vaccines and then make them available to developing countries. However, it has a number of advantages:

- Governments and the World Bank would share the burden of financing vaccines.
- The approach is generalizable: other countries could make similar World Bank trust fund contributions.
- Given the ten-year grace period on repayment of IDA loans, governments would not be hit with a sudden budgetary shock if vaccines were developed. For example, if a vaccine were developed in 2009, and IDA loans for vaccine purchase began in 2010, national government expenditure on repayments would not begin until 2020.
- At least in the UK, if budgetary procedures are followed, the commitment will not count towards the national budget until the funds are drawn, thus allowing the UK to continue

to spend current aid budgets on immediate priorities, while also inducing the R&D needed to develop vaccines by committing to spend a part of future budgets on vaccines.

This approach would not require IDA to commit in advance to particular loans to particular countries for vaccine purchases. If the World Bank does make a general commitment in advance to making IDA loans for vaccine purchases under this plan, this strengthens research incentives for pharmaceutical firms. A joint endorsement of this approach by the World Bank and a national government would be an incentive for other countries to make similar contributions. In addition, this approach also does not require the next IDA replenishment to go through. In the unlikely event that negotiations for IDA replenishment fall through, IDA could finance loans for vaccine purchases entirely out of reflows from payments of earlier loans. In order to provide incentives to developers, the World Bank could specify that these IDA loans would be available to purchase vaccines meeting eligibility conditions at a pre-specified minimum price.

11.2.3 Private Foundations

Private foundations could also play a major role in creating markets for new vaccines. Foundations may find it easier than governments to credibly commit to future vaccine purchases, given their greater continuity of leadership. In particular, the Gates Foundation has $22 billion in assets, and one of its main priorities is children's health in developing countries, and vaccines in particular. U.S. law requires private foundations to spend at least 5 percent of their assets annually. This suggests that a way that "push" and "pull" incentives for vaccine development could be combined. A U.S. foundation could spend 5 percent of its assets annually on grants to help expand use of existing vaccines and provide for vaccine research. Meanwhile, the

foundation could put its principal to use in encouraging vaccine research, simply by pledging that if a vaccine were actually developed, the foundation would purchase and distribute it in developing countries.

Appendix: The Effect of Increasing the Promised Price for Vaccines

This appendix analyzes the effects of increasing the price pledged for a vaccine under the simplest model of auctions, in which each firm has a private cost of developing a vaccine, and these costs are independent. Suppose that the cost of developing a vaccine for pharmaceutical firm i, denoted c_i, is independently drawn from a distribution F with upper support $\overline{p}$ and that there are N symmetrical pharmaceutical firms. Suppose the price p starts at some value $\underline{p} < \overline{p}$ and then grows, or is expected on average to grow, at a constant rate until a vaccine is invented, or until p reaches $\overline{p}$.

An equilibrium consists of a function $p_i(c_i)$ mapping each firm's cost into a price at which it will develop a vaccine. A necessary first-order condition for $p_i(c_i)$ to be privately optimal is that the growth rate of surplus, p_i-c_i, must equal the discount rate plus the hazard rate that a rival firm will develop the vaccine. In the simplest case, in which bidders are symmetric and the cost of developing a vaccine is not correlated among bidders, p_i increases monotonically with c_i. Given monotonicity, the hazard rate that a rival will enter depends on the probability that a rival firm has a cost slightly greater than c_i conditional on no firm having a cost less than c_i. As the number of firms grows, $p_i(c_i)$ declines, asymptotically approaching c_i, and the hazard rate that a rival enters grows without bound. Thus, if there were many symmetric pharmaceutical firms, this auction mechanism would lead a vaccine to be developed at a price very close to the cost of its development. Increasing the number of bidders not only reduces the expected price, but also reduces the expected time until a vaccine is developed given F and the growth rate of p.

At least over some range, increasing the growth rate of p, taking $\underline{p}$ as fixed, will speed the time until a vaccine is developed. This is despite the fact that the first-order condition implies that the faster the growth rate of p, or equivalently the lower the discount rate, the greater $p_i(c_i)$.

To see why increasing the growth rate of p speeds the auction, note that if the growth rate of p is infinite, then the auction concludes immediately because the price immediately attains its upper limit of $\overline{p}$. As the growth rate of p approaches zero, the expected time for the auction to conclude grows without bound. Moreover, reducing the growth rate of p must asymptotically increase the time until a vaccine is developed, since as $\dot{p}/p$ approaches zero, $p_i(c_i)$ approaches its lower bound of c_i, and hence as the growth rate slows, the reduction in p_i is bounded, whereas the time it takes for the auction to reach any particular price increases without bound as the auction slows.

It seems likely that the expected time until a vaccine is produced typically declines with the growth rate of p, given $\underline{p}$, but if there are few firms, it is possible to construct examples in which the expected time until a vaccine is produced increases with the growth rate of p. If there are many firms, then $p_i(c_i)$ will be very close to c_i, and hence reducing the growth rate of p will have little effect on $p_i(c_i)$, but will still lengthen the time required to reach any price. Hence, with many firms, a rapidly growing price, given $\underline{p}$, is likely to lead to a much faster vaccine discovery. On the other hand, if there are only a small number of firms, then $p_i(c_i)$ may be significantly greater than c_i, and reducing $p_i(c_i)$ may significantly shorten the auction. Consider the extreme case with only one firm. If p grows rapidly enough, the bidder will prefer to wait until the end of the auction, when the price reaches $\overline{p}$, before developing a vaccine. On the other hand, if the growth rate of the price is less than the interest rate, then once p/c_i is great enough, the vaccine will be developed. Thus, at least for some realizations of c_i, increases in the growth rate of p can lengthen the time until a vaccine is developed. If the distribution of the cost of development is such that most of the mass is at a low level, but there is a thin tail reaching up

to $\overline{p}$, then increases in the growth rate of p can lengthen the expected time until a vaccine is developed.

Holding constant $\overline{p}$ and the growth rate of the price, the higher $\underline{p}$, the shorter the time until a vaccine is developed. This suggests that the more a vaccine is valued, the greater $\underline{p}$ should be. In the extreme, if the social value of the vaccine is far greater than the upper support of c, then it would make sense to either have the price rise very quickly, or to choose $\underline{p}$ close to $\overline{p}$. Some may feel that the social value of vaccines is so great that it is better to spend more money than to risk delay, but this does not seem to be the revealed preference of rich country governments.

As long as the price does not grow that much faster than the interest rate, pharmaceutical firms will not actually sit on a vaccine they had already developed, waiting for the price to rise. Given discounting, it would be better for the firm to wait to begin research, rather than to first incur the cost of developing a vaccine, and then sit on the vaccine. Even if the firm got lucky and developed a vaccine faster than it expected, it would not sit on it if the growth rate of the program were equal to or less than the discount rate. Once a vaccine is developed, the opportunity cost of losing out to another bidder is not $p-c_i$, but rather p. The firm would only wait to develop the vaccine if the growth rate of p exceeded the discount rate plus the hazard rate that another firm would develop a vaccine.[53]

The optimal initial price depends on the expected cost of developing the vaccine, and therefore would generically differ between diseases. To see this, consider a hypothetical example in which each pharmaceutical firm faces its own cost of developing a vaccine, but it is common knowledge that the cost of developing a malaria vaccine is such that research would be

[53] I am considering the case in which there is only one potential patented vaccine, so the winner reaps the entire

profitable at between $5 and $6 per person immunized, while the cost of developing an HIV vaccine is such that research would be profitable at between $15 and $16 per person immunized. Starting the auc tion at more than $6 per person immunized would provide unnecessary rents to developers of a malaria vaccine. Starting the auction at less than $15 per person immunized would unnecessarily delay the development of an HIV vaccine.

The analysis above treats the cost of developing a vaccine as independently distributed across bidders, but in practice, there are almost certainly common components to this cost, and to the benefits of selling a vaccine to the program. This will create some tendency towards a winner's curse. Firms might try to publicize any leads in research in order to deter rivals. This is a general feature of patent races, and is not specific to this mechanism. Since developing a vaccine involves many stages of research, and promising vaccines can fail at any stage from laboratory tests to animal trials to Phase 4 human trials, potential rivals are unlikely to believe that the leader has a lock on becoming the first to develop a vaccine.[54]

reward.

[54] For example, rotavirus vaccine was recently withdrawn from the U.S. market, at least temporarily, following reports of side effects.

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