Pre-Commitments to Purchase New Vaccines: Design Issues

Michael Kremer
Professor of Economics, Harvard University and Senior Fellow, Brookings Institution

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** Department of Economics, Littauer 207, Harvard University, Cambridge, MA 02138; mkremer@fas.harvard.edu.
Executive Summary

Malaria, tuberculosis, and AIDS kill approximately 5 million people each year. The overwhelming majority of deaths occur in poor countries. Despite recent scientific advances, research on vaccines for malaria, tuberculosis, and African strains of HIV remains minimal. This is in large part because potential vaccine developers fear that they could not sell enough vaccine at a sufficient price to recoup their research expenditures.

A vaccine purchase fund that pledged to purchase new vaccines could both create incentives for vaccine research and ensure that any vaccines developed would reach those who need them. The rationale for such a fund is discussed in a companion paper, “Pre-Commitments to Purchase New Vaccines: Rationale.”

This paper explores the design of vaccine purchase pre-commitments. Comprehensively specifying vaccine eligibility and pricing in advance is likely to be impossible. Administrators of a vaccine purchase fund will therefore need to use some discretion in determining vaccine eligibility and pricing after candidate vaccines have been developed. For the fund to stimulate research, vaccine developers must trust it not to abuse this discretion. The credibility of purchase pre-commitments can be enhanced by including industry representatives on committees making eligibility and pricing decisions, insulating committee members from political pressure through long terms, decentralizing decisions, and pre-specifying fund procedures.

I propose the following three-step process: 1) Candidate vaccines would have to be approved by some regulatory agency, such as the U.S. FDA; 2) Candidate vaccines would also have to meet a market test – developing countries wishing to purchase vaccines using fund resources would be required to contribute a co-payment and draw down an account that they would hold within the fund; 3) In addition to the base price, bonus payments for vaccines should be linked to vaccine effectiveness, perhaps as measured by the estimated number of lives or Disability Adjusted Life Years saved by the vaccine.

Since vaccine research is expensive, but manufacturing additional doses is usually cheap, research incentives depend primarily on the total market for vaccines rather than on the price per dose. Trying to reduce the cost of a vaccine purchase fund by reducing the number of people immunized is therefore a false economy. To maximize research incentives while ensuring that vaccines reach those who need them, countries receiving vaccines should provide co-payments close to their conservatively estimated willingness to pay for vaccines.

To avoid offering either too low a vaccine price to spur adequate research or an unnecessarily high price, the fund should specify both an initial price and a schedule according to which the vaccine price would rise over time until a vaccine had been developed. This procedure mimics auctions, which are often efficient procurement methods when costs are unknown. To avoid creating incentives for vaccine developers to withhold vaccines from the market while waiting for the price to rise, the price should not rise at a rate substantially greater than the interest rate.

As an illustrative example, a vaccine purchase fund capitalized with $100 per life potentially saved by a vaccine over twenty-five years would require $2.4 billion in pledges for malaria, $4.8 billion for HIV, or $3.1 billion for tuberculosis. A private foundation could pledge to use part of its principal to purchase malaria, HIV, or tuberculosis vaccines, should they be developed, while spending its interest income on grants for existing vaccines and research on new vaccines. No funds would be spent or pledges called unless a vaccine were developed.
Malaria, tuberculosis, and AIDS kill an estimated 5 million people each year. In the past fifty years, these diseases have claimed six times as many lives as all wars [WHO, 1999b]. Virtually all malaria cases, and more than 95% of new HIV and tuberculosis cases, are in developing countries [UNAIDS, 1998; WHO, 1998], although the spread of drug resistance threatens increased infection and death in developed countries as well. Almost 90% of malaria cases and 70% of new HIV infections occur in sub-Saharan Africa [WHO, 1999a; UNAIDS, 1998].

Recent scientific advances have increased the potential for development of effective vaccines. Yet, despite the huge toll of these diseases, very little vaccine research is directed towards malaria, tuberculosis, and African strains of HIV. Potential vaccine developers fear that they would not be able to sell enough vaccine at a high enough price to recoup their research investments. This is both because these diseases primarily affect poor countries, and because vaccine markets are severely distorted. A companion paper, “Purchase Pre-Commitments for New Vaccines: Rationale,” discusses the rationale for a vaccine purchase fund which would pre-commit to purchase vaccines and provide them to developing countries at an affordable price. Such a fund would both create incentives for vaccine research and ensure that if vaccines were developed, they would reach people in developing countries.

This paper discusses the design of pre-commitments to purchase vaccines. In particular, it proposes methods for setting a purchase price and establishing criteria for eligibility of candidate vaccines for purchase under the fund.

Section 1 argues that it is impossible to pre-commit to a comprehensive set of eligibility and payment rules for vaccines that have not yet been developed, and that a vaccine purchase fund will therefore need some discretion to rule on eligibility and appropriate pricing once
candidate vaccines have been developed and tested. The vaccine purchasing process should be structured so as to convince potential vaccine developers that the fund will not abuse this discretion by insisting on low prices once developers have already sunk millions of dollars into research. If potential vaccine developers do not expect to cover their risk-adjusted research costs, they will not invest at all. Credibility can be enhanced by including representatives of industry as well as the scientific and public health communities on the committee making eligibility and pricing decisions; by insulating committee members from political pressure through long terms; decentralizing decisions; and outlining procedures for a vaccine purchase fund in advance.

Section 2 outlines a system in which potential vaccines would first have to receive regulatory approval and meet some other minimal eligibility requirements. They would then be subject to a market test: nations wishing to purchase vaccines would need to provide a modest co-payment and spend down an account assigned to them within the fund. Since these requirements are fairly minimal, an important part of compensation for vaccine developers should take the form of bonus payments tied to vaccine effectiveness.

Section 3 discusses vaccine pricing and the number of doses that would be purchased. Given that research and development on vaccines is typically very expensive, but manufacturing additional doses is usually cheap, research incentives are likely to depend primarily on the size of the total market for vaccines rather than on the price per dose. This suggests that trying to reduce the cost of a vaccine purchase fund by reducing the number of people immunized would be a false economy.

One way to avoid paying either too little or too much for a vaccine would be to specify a schedule according to which the price will increase over time until an appropriate vaccine is
invented. This procedure mimics auctions, which are efficient procurement methods in many situations in which the purchaser does not have full information about the cost of the product and there is insufficient competition to simply observe a market price. The price should not increase at a rate substantially greater than the interest rate, in order to deter vaccine developers from withholding vaccines from the market in order to obtain a greater price.

Section 4 argues that in order to maximize incentives for vaccine research, while still ensuring that vaccines will reach those who need them, countries receiving vaccine should provide co-payments somewhat under their estimated willingness-to-pay for vaccines. This implies that co-payments should rise with per capita income.

Section 5 reviews a number of other design issues that would arise with vaccine purchase pre-commitments.

The conclusion briefly considers the politics of such a program and the role that could be played by private foundations in helping to establish a vaccine purchase fund.

Appendix 1 puts forth some very rough estimates of the potential cost of a vaccine purchase fund, along with a sketch of how such a fund could be structured. A vaccine purchase fund capitalized with $100 per life potentially saved by a vaccine over a twenty-five year period would require $2.8 billion for malaria, $3.7 billion for tuberculosis, and $5.7 billion for HIV. Perhaps 15% of this could be covered by co-payments from developing countries, with the remaining $2.4 billion for malaria, $3.1 billion for tuberculosis, and $4.8 billion for HIV pledged by high-income countries and private foundations. No funds would be spent, or pledges called, unless a vaccine were developed.

Appendix 2 uses techniques from the economic theory of auctions to examine how vaccine prices should be determined.
The idea of an HIV Vaccine Purchase Fund was proposed 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 Vaccine Task Force [World Bank, 1999]. Kremer and Sachs [1999] and Sachs [1999] have advocated the establishment of a fund in the popular press. This paper draws on a number of earlier papers, including the vaccine work of Batson [1999], Mercer Management Consulting [1998], and Milstien and Batson [1994], and the broader academic literature on research incentives, including Dupuy and Freidel [1990], Guell and Fischbaum [1995], Johnston and Zeckhauser [1991], Lanjouw and Cockburn [1999], Lichtmann [1997], Russell [1998], Scotchmer [1997], Shavell and van Ypserle [1998], and Wright [1983]. This paper examines how a vaccine purchase fund could be structured, and proposes procedures for determining vaccine eligibility and pricing.

1. Flexibility vs. Commitment in Determining Vaccine Eligibility and Pricing

Some discretion would be needed to determine vaccine eligibility and payments for vaccines after vaccines have been developed and tested. Important steps to prevent a vaccine purchase fund from abusing this discretion include choosing credible decision-makers, insulating them from political pressure, adopting transparent rules, and decentralizing authority.

1.1 The Need for Discretion in Determining Vaccine Eligibility and Pricing

Decision-makers at a vaccine purchase fund will need discretion to determine eligibility and payments for vaccines after candidate vaccines have been developed. This is because before candidate vaccines had been developed, fully specifying all the requirements for eligible
vaccines and a complete system of prices linked to the vaccine’s characteristics is likely to prove impossible. The characteristics which would need to be specified in advance include:

- the required number of boosters and the ages at which the boosters must be taken. This is important because if too many boosters are required, fewer people will bring their children in to receive the full course of immunization.
- whether the vaccine can be given along with vaccines that are already widely administered, making delivery much cheaper, or whether a separate schedule would be necessary;
- the storability of the vaccine under various temperatures. Heat stable vaccines are easier to distribute in rural areas of developing countries.
- the extent of antigenic diversity against which the vaccine is effective. This will determine the areas of the world where the vaccine is effective.
- vaccine side effects on different sub-populations;
- the length of time for which the vaccine would provide protection;
- the effect of the vaccine on people who do not comply perfectly with the delivery protocol. For example, taking an initial dose of a malaria vaccine without a booster could potentially interfere with the development of natural limited immunity, reducing survival prospects.
- the percent reduction in disease incidence among those receiving the vaccine;
- in the case of malaria, the effect of the vaccine on the mosquitoes which spread malaria;
• whether the vaccine is “altruistic”, blocking further transmission but not protecting the individual who takes it. It may be difficult to encourage people to take such vaccines.

• whether the vaccine protects against morbidity, as well as mortality, and if so, how to assess the vaccine’s impact on morbidity;

• what level of rigor would be required from 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 likely extent to which resistance to the vaccine would develop;

Mis-specifying eligibility and pricing rules could misdirect research incentives away from appropriate vaccines, or vitiate research incentives altogether. For example, if the committee failed to specify otherwise, it might be obligated to purchase a malaria vaccine that interfered with the development of natural immunity and provided only temporary protection. Such a vaccine might merely postpone malaria deaths from childhood to young adulthood. If such a vaccine were eligible, researchers might pursue it, rather than devoting their efforts to more useful lines of research. On the other hand, a committee developing specifications might set standards for an ideal vaccine that was difficult to develop in practice, which would discourage pharmaceutical firms from following promising leads. For example, if the specifications required a 90% reduction in mortality in all localities, potential vaccine developers might not pursue a candidate vaccine that would be likely to yield 99% protection in most regions, but only 85% protection in others. If it were difficult to create a vaccine delivering 90% protection in all regions, no vaccine at all might be developed.
Aside from specifying eligibility rules, the fund would have to specify pricing rules. In order to provide appropriate incentives for researchers, the fund should pay more for superior vaccines; a vaccine with 90% efficiency is worth more than one with 80% efficiency, and a vaccine that requires no booster is worth more than one requiring boosters every five years. However, specifying a full schedule of prices based on characteristics of hypothetical vaccines is likely to prove impossible.

1.2 Preventing the Abuse of Discretion

Given the difficulty of fully specifying eligibility and pricing rules in advance, the vaccine fund will have to exercise discretion after vaccines have been developed and tested. However, once the vaccine developer has invested hundreds of millions of dollars in research and developed a vaccine, the committee might be tempted to use this discretion to insist on product improvements or offer a price that covered only manufacturing costs. Some indication that this is a significant problem is given by the experience of the prize the British government established in the 18th century for a method of determining longitude at sea. Sobel [1995] outlines the travails the inventor of the chronometer went through in trying to obtain the reward. She argues that the prize committee was biased towards an astronomical solution, and insisted on improvements and multiple trials, creating repeated delays, until the king intervened on behalf of the chronometer's inventor. Note that once a vaccine had already been developed, even a well-meaning committee, concerned with public health, would be tempted to insist on vaccine improvements and to conserve the fund’s resources so they could be spent on other worthy
health objectives. However, if pharmaceutical executives suspect that the committee will succumb to this temptation, they will be reluctant to invest in a vaccine.

It is therefore important to design the fund so as to make its commitments credible to vaccine developers. Credibility can be enhanced by appointing appropriate decision-makers and insulating them from political pressures through long terms, creating incentives for the fund to develop a reputation for fair dealing by having the fund pre-commit to purchase vaccines against several diseases, decentralizing purchase decisions as much as possible, and placing limits on the discretion used by the fund board by laying out reasonably transparent rules for determining eligibility and pricing.¹

The first step would be to appoint decision-makers who are insulated from political pressures by long terms and whom potential developers would trust not to renege on the fund’s commitments once a vaccine had been developed. This problem is similar to that faced by central banks which need to head off inflationary expectations by credibly promising to take tough action if inflation starts to increase, even though this tough action would be costly to the economy. This problem is solved by appointing people to the central bank with particularly strong anti-inflation preferences. Existing international vaccine purchasers such as the Pan American Health Organization (PAHO) and UNICEF have a culture of trying to purchase

¹ Note that the problem of inducing firms to conduct R&D 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 more than cover manufacturing costs, which in turn provides an incentive for firms to invest in R&D to produce attractive products that allow them to win procurement contracts. Rogerson [1994] 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. Unfortunately, the long-term future of a vaccine purchase fund is less certain.
vaccines at the minimum possible price, and as a result there is a history of antagonism between these institutions and the pharmaceutical industry. These institutions, therefore, might not be best suited to administer a program designed to increase private-sector incentives for vaccine development. If such an institution does administer the fund, it might be appropriate to delegate decisions regarding eligibility and pricing to a committee which would include some members appointed by the fund, some by industry, and some mutually-agreed on neutral members.

Commitments from the vaccine purchase fund might be more credible if the fund had an incentive to build a reputation for fulfilling its commitments. This suggests that perhaps the fund should not be limited to purchasing vaccines for a single disease, but instead should be able to receive new pledges to purchase vaccines for other diseases after vaccines were developed for the disease covered in the fund’s original mandate. In this case, the fund would have incentives to develop a reputation for treating vaccine developers fairly, so as to convince future developers that it would not renege on its promises. Nonetheless, it may be difficult to establish a reputation quickly, since a program of pre-commitments to purchase vaccines would be new, and the resolve of the sponsoring countries to maintain the program would be uncertain.

One way to prevent the vaccine purchase fund from insisting on a low price that did not fully cover the risk-adjusted cost of vaccine development would be to structure the fund so as to give its decision-makers a take-it-or-leave-it choice: either they buy the vaccine at a set price per dose, or they do not buy it at all. This helps solve the time-consistency problem, but at the cost of creating two other problems. First, if the price is fixed, then pharmaceutical firms will not

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2 Pledges for vaccines against different diseases should not be commingled, but kept in separate accounts. If the fund maintained a single account 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 fund would try to pay a very low price for the vaccine, hoping to save its resources to purchase vaccines for other diseases.

3 This addresses the most likely way that the fund could take advantage of vaccine developers. The fund will have limited incentives to insist on further trials, for example, because it will presumably want to get an effective vaccine
have an incentive to develop better vaccines, but simply to aim for a minimally acceptable vaccine. This problem can be at least partially addressed by requiring that at least a minimum price be paid for vaccine, but allowing upward flexibility if a high-quality vaccine is produced.

The other problem is that a vaccine which is useful, but not useful enough to warrant purchase at the minimum guaranteed price, might be rejected.\(^4\) Note, however, that if a vaccine turns out to be socially useful, but not good enough to qualify for purchase under the vaccine purchase fund, this would not preclude individual countries from purchasing the vaccine or other donors from purchasing it. This suggests that in order to convince potential vaccine developers to invest, any vaccine judged acceptable should be guaranteed some minimum price.

\[\text{2. A Three-Step Process to Balance the Needs for Commitment and Flexibility}\]

A vaccine purchase fund should be designed so that potential vaccine developers find the commitment to purchase vaccines at remunerative prices credible, but with enough flexibility that appropriate purchasing decisions can be made and that vaccine prices can vary with vaccine quality.

\(^4\) The cost of this is the difference between the minimum price guaranteed under the program and the net social value of the vaccine. This could potentially be a large amount if the minimum payment were very high. However, in practice, the amount that could be raised from donors is likely to be such a small fraction of the social value of the vaccine that this potential loss would likely be small relative to the costs of failing to credibly commit to purchase vaccine, and thus deterring research.
In order to balance the need for commitment with that for flexibility, I propose the following process for selecting candidate vaccines. Candidate vaccines would first have to undergo the minimal test of approval by some regulatory agency (such as the U.S. FDA). They would then have to meet a market test – developing countries wishing to purchase vaccines using fund resources would be required to contribute a modest co-payment, and would be required to draw down an account they would have within the vaccine purchase fund. Any vaccines meeting these requirements would be eligible for purchase at some base price. However, a large portion of compensation for vaccine developers would be in the form of bonus payments linked to vaccine effectiveness, perhaps as measured by the estimated number of lives or DALYs saved by the vaccine.

**Step 1: Regulatory Approval**

To be eligible for purchase, vaccines would have to have been approved by a regulatory authority. This would ensure that the funds were spent for *bona fide* vaccines, rather than for quack remedies. One option would be to use existing regulatory authorities in developed countries, such as the U.S. Food and Drug Administration (FDA). It should be noted, however, that regulatory standards appropriate for one country might be inappropriate for others. 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. On the other hand, a malaria vaccine that interfered with the development of natural immunity might be appropriate for U.S. citizens traveling to areas with malaria, but not for long-term residents of these areas. Theoretically, some
international regulatory body might be appropriate. On the other hand, the FDA and similar institutions in Europe already exist, and potential vaccine developers have some sense of what to expect from them.

One possibility would be to rule that any donor’s fund could be used only for vaccines that were approved by that country’s regulatory authority. Another possibility would be to rule that if any of the regulatory authorities from major donors approved the vaccine, it would be acceptable. Since the main purpose of requiring regulatory approval in donor countries is to exclude quack vaccines, it might make sense to allow the fund, at its discretion, to waive the requirement of regulatory approval if the WHO or a scientific committee within the fund determined that the vaccine were appropriate for some countries, even if the vaccine were not cleared in any donor country. It seems unlikely that the committee would approve a vaccine that was not in fact useful.

Only minimal requirements beyond regulatory approval would be appropriate before vaccines were made eligible for the market test in step 2. For example, travelers’ vaccines for malaria, which protect people making short trips, should presumably be ineligible. However, eligibility requirements beyond regulatory approval should be minimal and should be clearly defined to reduce the potential for abuse of discretion by the fund, and thus enhance the credibility of purchase pre-commitments with potential vaccine developers. The basic judgement as to whether to purchase a particular vaccine should be decentralized to individual countries. Of course, these countries would be free to follow recommendations put out by the World Health Organization or some other body.
Vaccines could meet regulatory approval, but still be unsuitable for widespread use in developing countries. For example, consider a vaccine that was effective only if people received ten precisely timed boosters, but interfered with the development of limited natural immunity if people missed the boosters. Such a vaccine might be useful for some travelers, but not for most people in developing countries. To take another example, it might not make sense to purchase a vaccine if a better vaccine was expected to be available soon.

A fairly minimal market test is that the developing countries using the vaccine be willing to provide a modest co-payment, depending on their GNP per capita, and be willing to draw down an account within the vaccine purchase fund that would be established specifically for each country.

This market test allows purchasers the flexibility of making purchasing decisions after vaccines have been developed. Rather than pre-specifying complicated eligibility and pricing rules, the purchasers themselves could evaluate the usefulness of vaccines after they had been invented. Allocating accounts within the vaccine purchase fund to different countries gives each country an incentive to carefully consider its vaccine purchases. A country would know that if it spends its share of the fund resources on a marginally effective vaccine today, it will have fewer resources available tomorrow to buy a potentially superior vaccine.

In the absence of separate accounts, countries might agree to purchase even marginally effective vaccines. This is because countries would know that if they did not consume the resources of the fund, other countries would. If potential vaccine developers anticipated this, they would aim to create a vaccine that met only minimal eligibility requirements. If countries
are spending funds earmarked for their own vaccine purchases, they have more incentive to seek high-quality vaccines, thus providing incentives for potential vaccine developers to produce such vaccines.

Note that decentralizing purchase decisions to individual countries reduces the chance that the fund will insist on further improvements or prices inadequate to cover risk-adjusted research costs once a vaccine has already been developed, and thus increases the credibility of commitment to potential vaccine developers. Under the proposed system, vaccine developers will not face a monopsonistic purchaser, and since the individual countries would not be able to use their accounts to purchase anything but 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 vaccine if one were available.5

There is some danger, however, that developing countries might purchase inappropriate vaccines, and further safeguards would be needed to prevent this. In particular, vaccine developers could try to induce developing countries to provide the co-payments necessary to purchase the vaccine through tied deals or outright bribes. Vaccine 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. This could potentially be an attractive arrangement for the developing country or its officials, since the country itself would contribute only a co-payment towards the cost of the vaccine, with the bulk of the financing coming from the vaccine purchase fund.

5 If interest were paid on accounts, countries would be under less time pressure to reach agreement with vaccine developers, and therefore might have such a strong bargaining position that they could prevent vaccine developers from recovering their research costs. Note that vaccine 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 fund could be used to fund grants for basic vaccine research, or allocated to countries where disease prevalence had increased since the Fund was established.
Outright corruption could probably be limited (although not eliminated) with provisions punishing firms found guilty of bribing officials and restricting the amount of travel, training, and other perks that vaccine 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. The developing-country vaccine market is a small part of overall business for most large pharmaceutical companies. They might be reluctant to risk bad publicity, the attention of regulators, and a legal sanction in order to make some extra money on vaccines.

Implicit tied dealings are much 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.²

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, NGO representatives, etc. Countries wishing to participate in the program could be required to set up such committees in advance, and to provide security of tenure to members. Some members of the committee could be appointed by the vaccine purchase fund. Of course, even if the committee included

² Payments by third parties also make corruption and tied deals 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 for their portion of the costs of the vaccine. With a modest co-payment, this would allow
members from outside government, the government would need to authorize public disbursements to cover co-payments. However, the committee could have authority to release resources from the country’s sub-account within the fund, opening the opportunity for non-governmental organizations or foreign donors to finance co-payments.

Whistle-blower procedures could be instituted to give committee members incentives to report any attempts at bribery by vaccine developers. Similarly vaccine developers could be given whistle-blower power to report 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.

Given the potential danger of tied deals and corruption, there should be some limit on the number of doses that the fund will purchase for any given country, and on the price it pays per dose. 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 children and adults would need to be vaccinated.

**Step 3: Bonus Payments Based on Vaccine Quality**

As noted above, given the potential problem of corruption or tied deals, any system with co-payments would require a cap on the price that the fund would be willing to pay per person immunized. Given that the requirement for co-payments merely establishes a minimal threshold for vaccine developers, and that it would be desirable for developers to have incentives to develop vaccines that exceed such a minimum threshold, the system of compensation for vaccine developers should include bonuses depending on the quality of the vaccine.
A committee with unlimited discretion to set vaccine prices could use that discretion to set prices inadequate to cover research costs. One way to preserve some flexibility, while at the same time creating some limits on the discretion of the committee, would be to guarantee a base price for any vaccine meeting the minimal requirements in steps 1 and 2, while also paying a bonus linked to indicators of the vaccine's success. Potential indicators include the number of lives (or DALYs) estimated to be saved by the vaccine, and the incidence and prevalence of the disease. The appropriate indicator depends in part on what reasonably transparent and objective procedures can be developed for measurement. It thus may vary among diseases.

Linking the bonus to an outcome measure, such as prevalence or DALYs or lives saved, rather than to a long list of characteristics like those in section 3.1, reduces the many dimensions required in drawing up specifications to a single dimension, and likely reduces the scope for arbitrary or opportunist action by the vaccine fund. A scientific committee would have a narrow mandate to estimate the number of lives or DALYs saved and the delivery costs, rather than to judge the broader questions of what vaccines would be eligible and how much should be paid for them. For example, the committee could not refuse to purchase vaccines that could not be taken by pregnant women; such vaccines would simply receive a smaller bonus, since they would save fewer lives and DALYs.

Basing incentives on lives or DALYs saved would create good incentives for pharmaceutical firms to develop vaccines that create positive externalities, such as a malaria vaccine with an altruistic component which kills gametocytes, and thus prevents other people

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

8 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 prevent malaria mortality without preventing infection.
from becoming infected. Any side effects of a vaccine could be subtracted from the measure of lives or DALYs saved.\textsuperscript{9}

Ideally, the amount paid per DALY or life saved would be inclusive of delivery costs. Providing a set amount per DALY or life saved inclusive of delivery costs would create incentives for researchers to develop vaccines with low delivery costs, for example, by developing vaccines that are oral, rather than injectable, that do not require many boosters, and that can be delivered along with the vaccines currently given as part of the Expanded Program on Immunization. Payments to pharmaceutical firms would equal the quoted amount per DALY or life saved minus the delivery cost.\textsuperscript{10}

Information about the number of lives or DALYs saved might become available only gradually, and therefore it may be best to condition payments on long-run outcomes. For example, a vaccine that targeted only one antigen might protection only temporarily, because it might lead to the rapid spread of resistant strains of the disease. On the other hand, the long-run effects of an immunization program might be much larger than the short-run effects if the program reached enough people to significantly interfere with the chain of transmission of the disease. Initial bonus payments to vaccine 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. Basing bonus payments to vaccine developers on realized

\textsuperscript{9} 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.

\textsuperscript{10} The number of lives and DALYs saved through a vaccine, and the cost of delivery, 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 delivery will be expensive per life or DALY saved. Assuming the weaknesses of health ministries are not strategically aimed at extracting payments from the vaccine developer, this will create appropriate incentives for vaccine developers. Vaccine 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, strategic behavior by health ministries may distort incentives for vaccine development, as discussed below.
DALYs or lives saved, rather than on the results of the clinical trials required for regulatory approval, creates better incentives to develop vaccines 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 vaccine had already been used, it would be much more difficult for a price-setting committee within the vaccine purchase fund to refuse to pay a remunerative price. Before a vaccine is used in the field, the committee could argue that it deserves only a small bonus, citing potential problems with the vaccine. However, if the vaccine is used, and it reduces the burden of malaria by 90%, 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.)

Estimating the number of lives or DALYs saved by a specific vaccine would be difficult. There is great uncertainty about the number of deaths due to particular diseases, and even more uncertainty in projections of future deaths. Moreover, estimating DALYs involves judgements about discount rates, the relative severity of various disabilities, and how years of life at different ages should be weighted. Calculating DALYs is further complicated by interactions among diseases and the possibility that other treatments or vaccines will be developed in the future. However, the procedures for calculating DALYs, including the discount rates and age-weights used, can be set in advance, which provides transparency for potential developers. Moreover, since any vaccine meeting the minimal eligibility requirements will receive the base price,  

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11 It is theoretically possible, however, that the short-run effect of vaccines provides a better estimate of what economists call the welfare gain from the vaccine than does the long-run effect, because the long-run effect is likely to reflect behavioral change to a greater extent. For example, people might reduce use of mosquito nets in response to a partially effective malaria vaccine. By the envelope theorem, the welfare effect of a small change in DALYs can be measured directly, without taking into account behavioral change. The savings from reduced use of mosquito nets should offset the increased risk of malaria. This logic does not necessarily apply, however, if individual behavior creates externalities, as it plausibly could. Similar issues arise with regard to HIV.
potential vaccine developers need not worry that arbitrary or biased calculations will completely 
eliminate their reward for developing a vaccine.

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 vaccine, then the potential profit from 
developing a vaccine could as easily be increased or decreased by the uncertainty in calculations 
of DALYs or lives saved. The attractiveness of investment in vaccines would be reduced, but 
only to the extent that vaccine developers are not willing to take gambles that could as easily turn 
out to help or hurt them. As will become clear in the discussion of pricing in Appendix 2, 
systematic downward bias in estimation of DALYs or lives saved would lead pharmaceutical 
firms to insist on a greater announced price per DALY or life saved before investing, but it 
would not change the ultimate price paid for a given vaccine, assuming that firms anticipated this 
downward bias.

Errors in estimation of DALYs or lives saved are particularly problematic if vaccine 
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 vaccines.

In order to reduce the chances of bias, the fund could set forth its 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.
Another potential problem with paying vaccine developers a bonus based on realized DALYs saved is that health ministries could try to extract payments from the vaccine developer in exchange for agreeing to distribute the vaccine efficiently. This would weaken incentives for vaccine development. If payments to vaccine developers were inclusive of delivery costs, ministries could threaten to featherbed their staffs. However, perhaps it is too cynical to believe that health ministries would greatly interfere with distribution of vaccines to obtain payoffs.

3. Vaccine Pricing

Previous sections have dealt with the form of payments for vaccines, but not the absolute amount. If a vaccine purchase fund offered to pay too little, no vaccine would be developed. If the fund offered too high a price, the program would be unnecessarily expensive, and theoretically it is even possible that the fund could stimulate excessive vaccine research, drawing scientists from other important research topics into a wasteful and duplicative race to be the first to develop a vaccine. This section first argues that the key determinant of whether potential vaccine developers will invest in research is the total size of the vaccine market, rather than the price per dose, and that it therefore does not make sense to try to save money by buying only a small number of doses. It then discusses estimates of the cost of vaccine development and the social value of a vaccine, which should serve respectively as lower and upper bounds on the size of the market promised to vaccine developers. Finally, it proposes a procedure under which the price offered for a vaccine would rise over time until a vaccine was actually developed. This procedure will help avoid offering either too little or too much for a vaccine, and as long as the
price does not increase too quickly, it will not lead vaccine developers to sit on a vaccine without releasing it.

3.1 Price, Quantity, and Total Revenue

The key issue for potential vaccine developers deciding whether to invest in research will be the total size of the market, rather than the price per dose. This is because it is very expensive to conduct research, but once research is complete, and factories are built, it is typically cheap to produce additional doses. The chemicals used in producing vaccines are typically inexpensive.

This implies that prices should be set per immunized person, not per dose. Given that pharmaceutical manufacturers will be motivated primarily by the size of the total market, rather than the price per dose, there is no reason to pay more per immunized person 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 compliance by patients.

Moreover, the vaccine purchase fund should not try to save money by purchasing fewer doses. This is a false economy, because potential vaccine developers will need a fixed amount of revenue to induce them to conduct research, and if fewer doses are offered, the price per dose for the doses that are purchased will simply need to increase.

People should be immunized if the benefits of administering the vaccine exceed the marginal production cost of producing and distributing an additional dose. Assuming that new vaccines could be distributed along with the vaccines currently given as part of the Expanded Program on Immunization, a generous estimate of the cost of production of distribution would be
$1.50 per dose. This would imply that a vaccine should be purchased as long as the benefits of inoculating someone are greater than $1.50. Assuming a 5% discount rate, and a disease that is equally likely to strike at any age, this implies that newborns should receive the vaccine if the DALY burden per capita is greater than 0.008. Given the quantity of vaccines purchased, the price per immunized person should be set so as to make the total market an appropriate size. A lower bound on the size of the total market should be the market necessary to induce substantial effort by vaccine developers. An upper bound should be the social value of the vaccine.

### 3.2 The Cost of Vaccine Development

There is no single “cost” of vaccine development. The larger the market for a vaccine, the more biotech firms will enter the field, the more research leads each pharmaceutical firm will pursue, and the greater the risk-adjusted cost of developing a vaccine. The total cost of the research conducted by the biotech and pharmaceutical industries will increase with the size of the potential market. The goal should not just be to induce each pharmaceutical firm to pursue one potential lead for an HIV vaccine but to convince each firm to pursue several leads. That said, it is useful to discuss estimates of the minimum cost of producing a vaccine.

Estimates of the cost of vaccine development vary widely. As discussed in section 2.2, 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 dollars. This estimate seems 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.\footnote{An additional indication that the Institute of Medicine’s estimates were over-optimistic lies in their 1986 prediction that a malaria vaccine could be licensed within 5 to 10 years.} Because potential vaccine developers know that their research may fail, in order to have incentives to conduct this work, they must expect more than cover their research expenses if they succeed. For example, if potential biotechnology investors expect that a candidate vaccine 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.

Another set of estimates come from 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\% discount rate implies an average cost of $214 million 1987 dollars, or approximately $313 million 1999 dollars. The pharmaceutical industry, which likes to stress the high cost of research, regularly cites these figures. 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 vaccine development process, the standard deviation of cost was greater than the mean cost. Vaccine trials for diseases with low incidence, such as HIV and tuberculosis, require very large samples, and are therefore expensive.\footnote{Regulators may require large samples for vaccines, even 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.}

It is also useful to consider the prices and revenue streams which seem sufficient to induce vaccine research in developed countries. Manufacturing costs for pharmaceuticals are generally very low, so the great bulk of the revenue from new pharmaceuticals can be applied to
cover research and marketing expenditures. Marketing expenditures would probably be quite modest for vaccines, especially if a market is guaranteed in the form of a vaccine purchase fund. In developed countries, new vaccines may sell for as much as $40 to $120 per person immunized. The new Varivax vaccine against chickenpox is expected to average about $177 million in annual revenue for the first 7 years of its sales [Merck Annual Report, 1998].

Vaccines for malaria, HIV, or tuberculosis could generate comparable revenues at much lower prices, since many more children who would potentially take them are born each year in developing countries. Eleven million children are born each year in high-income countries, while 107 million children are born each year in low and lower-middle income countries.¹⁴

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.

One approach to estimating the necessary size of a fund is to ask pharmaceutical executives whether a vaccine purchase fund could serve as an important incentive for research, and how big the fund would need to be do so.¹⁵ 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 vaccine, but also at what level to invest. If a market is seen as less lucrative, they will only pursue one lead at a time. 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

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¹⁴ Following the World Bank, low and lower-middle income countries are defined as those with incomes less than $3,125 per capita, and high-income countries are defined as those with incomes greater than $9,656 per capita.
their profits, without necessarily increasing their incentives to develop a new vaccine. For example, pharmaceutical executives may claim that the most useful motivator for HIV vaccine research would be higher prices on their 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. Finally, the key decision-makers are not just pharmaceutical firms, but also biotech firms and potential investors in biotech firms. Scientists working on vaccines may not have even considered the possibility of starting biotech firms or seeking investors, but if a large market were expected for vaccines, 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. With all these caveats, it may be worth noting that one former executive with a large pharmaceutical firm said that if there were a $500 million market for a malaria vaccine, firms would "scramble" to develop a vaccine.

### 3.3 The Social Value of Vaccines

If the cost of developing a vaccine serves as a lower bound on the revenue that must be generated from a vaccine to make research profitable, the value of vaccines to society should serve as an upper bound on the amount that would be paid for a vaccine. (If it were possible to

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obtain vaccines more cheaply, that would certainly be desirable.) One standard measure of the effectiveness of health programs is the cost of saving a Disability-Adjusted Life Year, or DALY. The World Bank calls health interventions that cost less than $100/DALY highly cost-effective. The following table, taken from a companion paper, “Purchase Pre-Commitments for New Vaccines: Rationale,” shows the net social benefit of an 80% effective vaccine that reached 75% of newborns, assuming a social value of $100/DALY.

<table>
<thead>
<tr>
<th>Number of children born annually in high-prevalence, poor countries</th>
<th>Malaria</th>
<th>HIV</th>
<th>Tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.6 million</td>
<td>81 million</td>
<td>102.9 million</td>
<td></td>
</tr>
<tr>
<td>Annual social benefit of vaccine at $100 per DALY</td>
<td>$2.17 billion</td>
<td>$3.7 billion</td>
<td>$927.5 million</td>
</tr>
<tr>
<td>Annual benefit per child vaccinated</td>
<td>$41.29</td>
<td>$45.30</td>
<td>$9.01</td>
</tr>
</tbody>
</table>

Notes: Marginal manufacturing and delivery costs assumed to be $1.50. DALY burdens from WHO [1999a]. Each country’s DALY burden per capita assumed to be that for its region. 75% of the population assumed to be vaccinated.

The total social benefit would be larger for a program that also vaccinated some older people, but the benefit per person immunized might be slightly lower, because vaccinating a newborn against tuberculosis, for example, provides lifelong protection, whereas vaccinating an older person provides fewer years of protection.

3.4 A Schedule of Vaccine Prices

One approach to determining the appropriate price to pay for vaccines would be to guarantee a certain price initially and have the price rise according to a pre-announced schedule until a vaccine was actually developed, or the key patents for a vaccine were taken out. This
procedure mimics auctions, which are typically efficient procurement mechanisms in situations in which production costs are unknown and there is no market price for the good. If nobody is willing to produce vaccines at a low price, the fund will try a higher price until a vaccine is developed or the price reaches a limit set by the fund. Both the base price and the maximum bonus price should rise over time.

The price paid for the vaccine would not increase substantially faster than the interest rate. This would avoid creating an incentive for firms to sit on a vaccine they have developed while waiting for the price to rise. To see this, note that a firm which delays announcing a vaccine and selling it to the fund postpones its returns into the future, and therefore has to discount these returns at the interest rate. Moreover, delay risks the possibility that a competitor will introduce a vaccine at some time during the life of the fund, which would likely reduce both the quantity of vaccine the original developer could sell and the price at which each dose would be sold. Finally, if the vaccine developer has already taken out a patent, delay uses up some of the patent life. Increasing the price over time may induce firms to delay starting research on a vaccine, or slow down the pace of this research, but strategic delay will not be large if there are many competing firms.

It would probably be best to determine the price not by when the first vaccines were purchased by the fund, but rather by when the final major patent used in preparing the vaccine was applied for. Pharmaceutical firms are not likely to risk delaying patent applications for fear that a competitor will preempt them. Note that delay is especially unlikely in the patenting stage, since there are potentially many competing biotech firms that could patent vaccines, whereas only a few large pharmaceutical firms actually conduct clinical trials and manufacture vaccines.\(^\text{16}\) As discussed in Appendix 2, delay is more likely if there are only a few competing

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\(^{16}\) One potential problem with this approach is that vaccine developers might incorporate unnecessary late-patented
Section 3: Vaccine Pricing

firms. Moreover, while vaccine trials could not be conducted secretly, research towards patents could be, and this would make it much more difficult for potential vaccine developers to collude to increase the price by delay.

Appendix 2 uses techniques from the economic theory of auctions to examine this procedure. The main results are as follows. If there are many competing firms, a schedule of rising prices will generate a vaccine at close to the lowest possible cost. The fewer the number of 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 a 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.

4. Co-Payments

Co-payments from countries receiving vaccines should be set somewhere between the marginal production cost of vaccine and the willingness to pay of recipient countries. On the one hand, once a vaccine 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, an important goal of a vaccine purchase fund is to encourage vaccine development, and developed countries are unlikely to contribute enough to a fund to increase the private incentive for developing vaccines anywhere near to their social value. From this standpoint, it is desirable to require developing countries to provide co-payments at close to their willingness to pay for the 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.
vaccine, since this maximizes the incentive to develop a vaccine. The tradeoff between these considerations suggests that co-payments from countries receiving vaccines should be set as close as possible to their estimated willingness to pay for vaccines, without unduly risking the chance that countries will not be able to purchase vaccines. Since richer countries are likely willing to pay more for vaccines than poorer countries, this suggests that co-payments should rise with income.\textsuperscript{17}

The vaccine purchase fund should probably refuse to be a party to vaccine purchases at prices greater than those offered by the fund, even if the vaccine developer insisted on a higher price and the country or its donors were willing to make up the difference between the selling price and the contribution from the vaccine purchase fund. Allowing unrestricted co-financing broadens the scope for vaccine developers to demand a price greater than that offered by the vaccine purchase fund, and these higher prices could potentially exclude some countries from access to vaccines. For example, if the vaccine 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 vaccine.

This provides another rationale for setting the required co-payments close to countries’ willingness to pay for vaccines. Doing so reduces vaccine developers’ temptation to try to extract supplemental payments from purchasing countries, and makes it possible to prohibit supplemental co-financing without substantially reducing the total resources available for vaccine purchases, and thus the incentives for vaccine development.

\textsuperscript{17} Willingness to pay is also likely to rise with the burden of disease, but requiring a larger co-payment from countries with a higher disease burden seems inequitable and is likely to be politically infeasible.
5. Other Design Issues for a Vaccine Purchase Fund

This section discusses a number of other issues that would have to be decided for a vaccine purchase fund.

1) The scope of a purchase pre-commitment program would have to be set. The fund could be established for a particular disease, such as malaria, or it could cover vaccines for multiple diseases. Potentially, it could be used to compensate inventors of other techniques for fighting disease. For example, compensation could be provided to the inventor of an ecologically safe insecticide that killed the mosquitoes which transmit malaria.

On the one hand, 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.

On the other hand, restricting eligibility to vaccines for these three major killers would make eligibility criteria clearer and reduce the resources wasted in attempts to obtain resources from the fund. For example, assuming that inventors were paid per life or DALY saved, firms that could meet the eligibility standards would likely hire experts to conduct studies demonstrating that their innovations saved many DALYs. Developers of new HIV counseling techniques could seek to gain the bonuses for work done in promoting safe sex. A lot of resources could be wasted if many companies sought to get different types of innovations accepted by the fund. If only vaccines for malaria, tuberculosis, and HIV were eligible, the resources wasted on administration and on attempts to influence the committee might 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 funds, and there are reasonably clear-cut standards for evaluating the effectiveness of vaccines. However, if any improvement in health technology qualified, all sorts of people could come forward with spurious claims.

Similar, but less severe, issues arise in extending a purchase pre-commitment program beyond malaria, HIV, and tuberculosis to other infectious diseases affecting developing countries. Moreover, even in the absence of spurious claims, the share of the Fund’s resources that go to the administrative costs of establishing prices and bonus payments, rather than actually compensating vaccine developers, is likely to be larger for vaccines covering diseases responsible for fewer DALYs. The cost of conducting epidemiological surveys to assess the DALYs saved due to a vaccine is likely to include a large fixed component independent of the severity of the health problem. It also may be useful to first experiment with purchase pre-commitments for vaccines against one disease and then extend the program to cover other diseases if it seems successful.

2) Pre-commitments could be made more or less binding. The options range from a simple announcement of an intention to purchase vaccines, to an announcement with more details on eligibility and pricing, to an escrow fund, to allowing courts to rule on the eligibility and appropriate pricing of vaccines. The more binding the commitment, the stronger the incentives for potential vaccine developers. On the other hand, putting money in escrow now might be politically difficult if it requires appropriation from current budgets. Under U.S. budget rules, it should be possible to make an advance appropriation. There is also a tradeoff between commitment and flexibility. While a strong commitment would be best, weaker commitments might be better than nothing.

3) For vaccine purchase pre-commitments to spur research, it is essential that intellectual
property rights be respected. If the fund purchases vaccines from imitators, rather than respecting the intellectual property rights of the original developers, incentives for vaccine development will be vitiated. If the vaccine purchase fund 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.

4) Procedures would have to be established for dealing with multiple vaccines, should they be independently developed. Presumably each country could decide which vaccine it wished to purchase if multiple vaccines were available.

5) Some procedure should be developed for determining how large an account each country should have within the fund. Poor countries with high disease prevalence should receive the highest priority.

6) It may be necessary to set standards for the number of antigenic targets used in a vaccine. Individual countries will not have appropriate incentives to guard against the evolution of resistant strains, since resistance would affect the whole world. Ideally, bonus payments would be based on DALYs saved over a long enough period to create incentives for the development of vaccines which target a range of antigens. If this is not practical, it might make sense to incorporate explicit rules on the number of antigens targeted by vaccines.

7) Sunset provisions would be necessary. 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 committee determined that the burden of malaria had been cut more than 50% through other techniques,
such as insecticides, and if, in the judgment of a scientific committee working with the fund, this
reduction in burden was sustainable. Sunset provisions could be continuous, so that the amount
in the fund 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.

8) It is not clear what role the World Bank could play in such a program. The World
Bank has considered pre-approving loans for HIV vaccine purchases as a way of encouraging
HIV vaccine research. For a developing country to have incentives to take out such a loan, it
would have to be at highly concessional terms, and therefore would have to be an International
Development Association (IDA) loan. Moreover, the loan would have to represent additional
IDA funding, rather than simply an IDA loan that would otherwise have been given to the
country for some other purpose. Otherwise the developing country would be better off letting
other countries borrow to purchase the vaccine at prices sufficient to induce research. Once a
vaccine had been invented, the non-participating developing country could then offer to purchase
the vaccine at the marginal production cost.

One approach would be require all countries taking out IDA loans, or perhaps health-
sector IDA loans, to use part of the loan to partially finance their sub-account within a vaccine
purchase fund. Given that research on vaccines is an international public good, this
conditionality seems appropriate as a way to overcome free-rider problems between countries.

Conclusion

This paper has proposed a design for a vaccine purchase fund that attempts to
compromise between flexibility and commitment. A key challenge would be to design vaccine
eligibility and pricing rules that are sufficiently flexible, but still provide a credible promise that
good vaccines will be rewarded. To be eligible, vaccines should meet both the minimal
scientific test of regulatory approval and the market test that developing countries be willing to
provide a co-payment for the vaccine and spend from accounts established within the fund. To
provide incentives for development of a high-quality vaccine, bonus payments for vaccines
should be tied to measures of effectiveness – ideally the number of lives or DALYs saved by the
vaccine. An auction-like mechanism could be used to set the maximum price per dose that
would be paid by the fund.

Appendix 1 sets out an illustrative proposal for a vaccine purchase fund, with some very
rough cost estimates.

It is worth speculating briefly on the politics surrounding a vaccine purchase fund.

Those with a stake in current aid programs and in grant-funded research programs may
object to a guaranteed market program, fearing that resources would be drawn from their work.
Organizations involved in efforts to encourage condom use among sex workers, for example,
may feel that funds for an AIDS vaccine would be drawn from prevention efforts. Academic and
government scientists working on HIV research may be concerned that funds for vaccine
purchases will be drawn from national science budgets. These groups are well placed to affect
the political decision-making process.

These groups might be less likely to object to a vaccine purchase fund that was financed
through pledges, rather than one that involved setting up an escrow account using funds from
current budgets. Pre-funding might come out of aid or research budgets, whereas pledges might
not count as spending now under budget rules. When a vaccine became available, it might be
seen as justifying increasing the total aid budget. Even if the development of a future vaccine led
to other reductions in future aid budgets, 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.

Governments are often reluctant to try major new initiatives. A private foundation could
conceivably play a major role, both on its own, and by catalyzing other resources. In particular,
the Gates Foundation has $17 billion in assets, and one of its main priorities is children’s health
in developing countries, and vaccines in particular. A U.S. law requires private foundations to
spend at least 5% 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% of
its assets annually on grants for vaccine research. Meanwhile, the foundation could put the
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 1: An Illustrative Proposal for a Vaccine Purchase Fund

This appendix sets forth, for the sake of discussion, an illustrative proposal for a Millennial Vaccine Purchase Fund (MVPF) which would pre-commit to purchase vaccines for malaria, tuberculosis, and HIV and distribute them to poor countries in exchange for modest co-payments. The calculations are extremely crude – among other things, they use WHO estimates of the burden of disease at a regional level, rather than information disaggregated to the country level, and they rely on crude assumptions about the percentage of the population that would be vaccinated. The calculations set forth how a Millennial Vaccine Purchase Fund could work if it were financed with $100 in pledges for each person whose life could be potentially saved by a vaccine over a twenty-five-year period. This would amount to about $10 billion in donor pledges over a five-year period. If the United States paid 20%, its share would be $2 billion, or $400 million annually for 5 years.

Coverage, cost, and financing

The MVPF will include separate sub-funds for malaria, tuberculosis, and AIDS. If the amount in each sub-fund were equal to $100 for each person whose life could potentially be saved by a vaccine over a twenty-five year period, $5.7 billion would be needed for HIV, $2.8 billion for malaria, and $3.7 billion for tuberculosis. A total of $12.2 billion would be needed for the MVPF as a whole. As discussed below, approximately $2 billion, or 16% of this sum, will be raised in co-payments from participating developing countries, so donors would have to pledge approximately $4.8 billion, $2.4 billion, and $3.1 billion for HIV, malaria, and tuberculosis respectively. Vaccine prices will be set by dividing the total amount in each sub-
fund by the likely number of people needing vaccination in the countries covered by the MVPF.\textsuperscript{19} Countries will be covered if their GNP per capita is less than $3,125\textsuperscript{20} and they have sufficient disease prevalence to make vaccination cost-effective.\textsuperscript{21} Under these assumptions, the maximum price per person immunized for HIV, malaria, and tuberculosis would be approximately $4.70, $10.00, and $2.20 respectively.\textsuperscript{22}

Contributions will be in the form of legally binding pledges that are callable only if and when a vaccine is developed.

**Vaccine eligibility and pricing**

To be eligible for purchase, candidate vaccines will have to satisfy both minimal technical requirements and a market test.

Minimum technical requirements will be set by a Scientific Committee established by the MVPF. These will include approval by regulators in donor countries, with FDA clearance required if US pledges are to be called.

Covered countries wishing to purchase vaccines will have to provide a co-payment. The co-payment percentage will be proportional to the country’s GNP per capita, reaching a

\textsuperscript{18}Based on current mortality rates, and attributing deaths of people with AIDS who have opportunistic tuberculosis infections to AIDS.

\textsuperscript{19}Based on typical vaccination coverage rates in developing countries, 75% of newborns are likely to be vaccinated. The coverage rate for older children and adults is likely to be significantly lower. These calculations assume that 1/3 of the existing population will be vaccinated against HIV and tuberculosis, and 75% of first-time mothers will be vaccinated against malaria. (Most people who survive to age 5 in regions with endemic malaria develop limited immunity.)

\textsuperscript{20}The World Bank cutoff for lower-middle income countries.

\textsuperscript{21}A disease burden of more than 0.008 Disability-Adjusted Life Years (DALYs) per capita, as estimated by the WHO. (This is the disease burden at which the vaccination cost per discounted lifetime DALY saved is $100, assuming an 80% effective vaccine and a $1.50 cost of producing and delivering vaccine to an additional person.) This calculation assumes that the reduction in disease burden is linear in the number of people vaccinated. This assumption needs to be refined, since epidemiological models suggest that the true relationship is non-linear and in particular, that there is some threshold level of immunization above which the disease will be eradicated.
maximum of 67% for countries with the maximum eligible GNP per capita of $3,125\textsuperscript{23}. The total co-payments will equal $2 billion, or approximately 16% of the MVPF value. Requiring co-payments will help build ownership among participating countries and ensure they are satisfied that the vaccine is effective given their needs and field conditions.

Any vaccine which meets the minimal technical requirements and which a covered country wishes to purchase will be eligible for purchase at a base price equal to one-half of the maximum price. Depending on efficacy, vaccines may receive a bonus payment equal to this base, bringing the total price up to the maximum price of $4.70, $10.00, and $2.20 for HIV, malaria, and tuberculosis respectively. Bonus payments will be linked to the Scientific Committee’s estimates of the number of Disability-Adjusted-Life Years (DALYs) saved by the vaccine. Thus, a vaccine which was 100% effective and caused no side effects would receive the maximum price.

If a vaccine has not been developed and ruled eligible by 2005, the minimum price and the schedule of bonus payments will increase by 7.5% annually until a vaccine is developed or the price doubles (in approximately 2015). A second round of pledges will be solicited for this purpose.

**Membership and governance**

Board members will be appointed by donors, with voting rights proportional to contributions.

\textsuperscript{22}Developers will base their decision on whether to invest in developing a vaccine primarily on the total size of the sub-fund, rather than on the price per person immunized, as the marginal cost of producing additional doses is likely to be small.

\textsuperscript{23} To be precise, the co-payment percentage will equal the country’s GNP per capita divided by $4,688. Thus a country with a per capita GNP of $468 would pay a 10% co-payment.
The board will appoint a Scientific Committee which will draw up minimal eligibility requirements for vaccines, set forth procedures for calculating bonus payments, and rule on eligibility and bonus payments for specific candidate vaccines. Members of the Scientific Committee will serve ten-year terms, and will be selected from the fields of science, industry, and public health.

**Intellectual property rights**

Funds from each donor nation will be spent in accordance with the intellectual property rights laws of that country. Thus, for example, U.S. funds will not be used to purchase vaccines that violate U.S. patents.

**Sunset provision**

If no vaccine for a particular disease has been discovered by 2050, or if the scientific committee determines that the burden of the disease has been cut by more than 50% due to other factors and that this reduction in the burden of disease is sustainable, the donors will have the option of canceling their callable capital.
Appendix 2: A Procedure for Vaccine Pricing

This appendix analyzes the effects of the proposed pricing procedure 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 $i$, $c_i$, is denoted independently drawn from a distribution $F$ with finite upper support $\bar{p}$ and that there are $N$ symmetrical pharmaceutical firms. The price $p$ starts at some value $p < \bar{p}$ and then grows at a constant rate until a vaccine is invented, or until $p$ reaches $\bar{p}$.

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 $p$ as fixed, will speed the time until a vaccine is developed. This is despite the fact that the first-order condition implies

\[ 24 \text{ Note that this condition may not be sufficient.} \]
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 \( \bar{p} \). 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 \( p \), 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 \( p \), 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 \( \bar{p} \), 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 $\bar{p}$, then increases in the growth rate of $p$ can lengthen the expected time until a vaccine is
developed.

Holding constant $\bar{p}$ and the growth rate of the price, the higher $p$, the shorter the time
until a vaccine is developed. This suggests that the more a vaccine is valued, the greater $p$
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 $p$ close to
$\bar{p}$. 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 western
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
fund 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.$^{25}$

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

$^{25}$ 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 dose, while the cost of developing an HIV vaccine is such that research would be profitable at between $15 and $16 a dose. Starting the auction at more than $6 a dose would provide unnecessary rents to developers of a malaria vaccine. Starting the auction at less than $15 per dose 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 fund. 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.26

One disadvantage of gradually increasing the compensation to mimic an auction is that it may be difficult to prevent collusion in this setting. In some types of auctions, collusion can be reduced by requiring bids to be sealed. Vaccine researchers could probably easily communicate their progress and their overall level of research effort, and this could facilitate collusion. (However, the possibility that some small biotech firm was secretly making rapid progress would tend to break down collusion.)

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26 For example, rotavirus vaccine was recently withdrawn from the U.S. market, at least temporarily, following reports of side effects.
References:


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