Advanced Markets for a Malaria Vaccine: Estimating Costs and Effectiveness

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Manuscript Date: 5 January 2005

Abstract

To overcome the problem of insufficient R&D for vaccines for malaria and other infectious diseases, a binding offer could be made to the biotechnology/pharmaceutical industry, ensuring recovery of large initial expenditures if a suitable product were developed and put into use. One or more sponsors would commit to a minimum price that would be paid for an eligible product, up to a certain volume of supply demanded. For additional purchases, the price would drop eventually to short-run marginal cost. If no suitable product were developed, no payments would be made. We discuss the size of the offer required to approximate revenues obtained for typical commercial pharmaceutical products, as well as the degree to which the price and volume would affect the cost-effectiveness of such a commitment for a malaria vaccine. Under conservative assumptions, we document that the intervention would be highly cost-effective (compared to “rule of thumb” thresholds). Sensitivity analyses show that most characteristics of a hypothetical malaria vaccine have little effect on the cost-effectiveness, but that the duration of protection against malaria conferred by a vaccine strongly affects potential cost-effectiveness. Readers can conduct their own sensitivity analyses employing a web-based spreadsheet tool.

1 We thank Pia Bruce, Iain Cockburn, Joseph DiMasi, Amy Finkelstein, Heather Freeman, Henry Grabowski, Hannah Kettler, Andrew Metrick, and Blair Sachs for their helpful comments and input, as well as other participants in the Center for Global Development’s Pull Mechanism Working Group. All errors and opinions are those of the authors.
1. **Introduction**

Compared to the social need, there is a dearth of research and development (R&D) on vaccines for malaria and other diseases that primarily affect poor countries. One commonly cited estimate is that half of all global health R&D in 1992 was undertaken by private industry – but that less than 5 percent of that was spent on diseases specific to poor countries (WHO [1996]).

Biotechnology and pharmaceutical firms that operate under a profit-maximizing business model are reluctant to invest in R&D for these diseases if they fear they would be unable to sell the vaccine at prices that would cover their risk-adjusted costs. The low anticipated price reflects both the poverty of the relevant populations as well as severe distortions in markets for vaccines for these diseases.

Markets are distorted in two major ways. First, governments or other institutions that buy vaccines for these diseases, such as bilateral and multilateral aid agencies, face a time-inconsistency problem. Once pharmaceutical companies have invested in the research necessary to develop vaccines, in the interest of increasing access to life-saving products governments and aid institutions often use their powers as dominant purchasers and arbiters of intellectual property rights to keep prices close to marginal cost. Because the largest part of the industry’s expenditures lies in the initial R&D cost (while the variable costs of production typically are modest), this may imply negative total profits from the investment, thereby deterring industry from investing in the first place.

Second, the knowledge generated by research on these diseases is an “international public good.” The benefits of scientific and technological advances spill over to many nations, so 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.

One way to address these market failures would be for purchasers (for example, foreign aid donors) to commit, in advance of product development and licensure, to fully or partially finance vaccine purchases for poor countries at a pre-specified price. A financially (and otherwise) credible program sponsor (or coalition of sponsors) would sign a contract specifying that a minimum price per person immunized would be paid, up to a certain number of individuals immunized. This type of arrangement, although novel, would reduce economic uncertainty for firms and give investors confidence about the returns they could expect once the scientific challenges were overcome. While the arrangement would not eliminate all risk to developers, it would greatly reduce the uncertainties that are peculiar to the developing country market, and would thereby put decisions about use of R&D for malaria and similar diseases on more of an equal footing with health conditions of affluent populations.

This type of initiative, referred to as a “pull mechanism” or “advance purchase commitment,” has recently been gathering momentum, thus providing additional motivation for examining the details of how such a malaria vaccine purchase commitment could be implemented. For example, in late November 2004 Britain’s Chancellor of the Exchequer, Gordon Brown, committed his government, in cooperation with other donors, to purchasing a malaria vaccine if and when it is developed (Brown [2004]).

Kremer and Glennerster [2004] lay out the rationale for such a commitment and discuss the details of how such a commitment could be structured, such as eligibility requirements.
A working group comprised of economists, public health specialists, representatives of the biopharmaceutical industry, and others, working with contract attorneys knowledgeable about the pharmaceutical industry, was convened by the Center for Global Development in Washington, D.C., and has developed a report that specifies in further detail how such a commitment could be implemented (Center for Global Development [2004]).

In this article, we estimate how large a commitment would be required so that the market would be comparable in size to existing pharmaceuticals; we then discuss the cost-effectiveness of such a program under various contract models and assumptions. We here focus on the example of a malaria vaccine; although not discussed here, analogous estimates for HIV and tuberculosis vaccines can be derived via the downloadable spreadsheet tool we discuss in Section 4.

To preview our results, we find that a commitment to pay $15 per person immunized for the first 200 million people would provide a market comparable to that of existing commercial products, and would also be highly cost-effective from a public health standpoint. These revenues would be comparable to the average net present value (NPV) achieved between the 70th and 80th percentile by recently launched commercial products, and above the NPV earned by the average product, adjusting for lower marketing costs. To the extent that developing a malaria vaccine would be more technologically challenging than developing the typical product, the appropriate payment would be greater. Thus, we take the average of the 70th to 80th percentiles as our benchmark revenue.

2. Background on malaria

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2 A draft of this report is available online at [http://www.cgdev.org/globalhealth/proj_pull.cfm](http://www.cgdev.org/globalhealth/proj_pull.cfm).
The World Health Organization (WHO) estimates that more than 300 million people contract clinical malaria every year, and 1.1 million die of the disease (WHO [2001]). Children who survive severe cases of malaria may suffer learning disorders and brain damage, although those who reach age five acquire some immunity. Those with this limited natural immunity rarely die from malaria, but they often become weak and lethargic with the disease later in life, impairing productivity. Almost all malaria cases occur in low-income countries, and about 90 percent of the victims live in sub-Saharan Africa (WHO [2000b]).

The scientific challenges in developing an effective malaria vaccine are formidable. Nonetheless, many scientists are optimistic. A National Academy of Sciences report [1996] concluded that the development of a malaria vaccine is scientifically feasible. More recently, in a review article published in The Lancet, Moorthy et al. [2004] argued that, “Although exact predictions are not possible, if sufficient funding were mobilized, a deployable, effective malaria vaccine is a realistic medium-term to long-term goal.” Other scientists, however, are more pessimistic about the prospects for a malaria vaccine being developed through the research avenues currently being explored. Kremer and Glennerster [2004] argue that such instances in which there exists such a divergence of opinion on prospects for development are especially well-suited for programs such as purchase commitments.

There has also been encouraging news more recently, with the release of results from a recently completed phase IIb malaria vaccine clinical trial. That vaccine has been under development at GSK Biologicals for more than 15 years, and the vaccine came off the shelf with an influx of financial support, in large part from the Bill & Melinda Gates Foundation. The trials were conducted under what is often referred to as a “public-private partnership,” with players including MVI (the Malaria Vaccine Initiative, mostly funded by the Bill & Melinda Gates Foundation), GSK Biologicals, and the Mozambique Ministry of Health. The
study, published in *The Lancet*, found that the vaccine’s efficacy against severe malaria disease was 58%, and argued the results of the trial “demonstrate the feasibility of an efficacious vaccine against malaria” (Alonso *et al.* [2004]). Of course there are many steps before this vaccine or others would be ready for widespread use. However, of primary concern is whether the necessary financial resources will be invested to move this and other candidate malaria vaccines further along in the development pipeline. Malaria vaccine purchase commitments, like Britain’s, can provide financial incentives to pull this candidate vaccine through costly phase III clinical trials and other steps required for licensure, towards potential delivery. Our work explores the details of how such commitments might be designed and implemented.

3. Estimates of the required volume of a vaccine commitment

We begin by providing estimates of the total purchase volume that would be necessary for a vaccine commitment to be comparable to revenues provided by existing commercial products. The resulting dollar amount can then be used to analyze how different prices and quantities specified by the contract would compare to the revenues of commercial products. In deriving our estimates, we consider reported average sales numbers of existing products, and adjust these empirical numbers according to the particularities of a vaccine purchase commitment. Specifically, the main approach of our analysis is to estimate a scale of possible revenue levels that would make the revenues from investing in R&D for a malaria vaccine similar to those from realized investments in existing products.3

An alternative approach would be to use the opinion of outsiders familiar with the industry about the level of revenue needed to spur significant investment. A common

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3 See Berndt *et al.* [2003] for other approaches and further discussion.
perception among analysts and potential developers is that the large biopharmaceutical companies need to anticipate annual sales of $500 million or more, in years with peak sales, to be willing to invest in R&D for a new product (see Robbins-Roth [2000]). This $500 million number appears to reflect a consensus among many in the industry, but it usually refers to a typical distribution of sales over the life cycle of a pharmaceutical product. Assuming the typical product life cycle as in Grabowski et al. [2002], this corresponds to an NPV of about $3.3 billion, if one assumes a real cost of capital of 8 percent (or a nominal cost of 11%, assuming 3% inflation). As will be clear below, this number will be fairly close to that which our procedure yields.

The most recent comprehensive evidence of sales revenues for biopharmaceutical products is a paper by Grabowski et al. [2002], in which the authors report on 118 new chemical entities (NCEs) that were introduced into the US pharmaceutical market between 1990 and 1994. Earlier work on products introduced in the 1980s was published by Grabowski and Vernon [1990], as well as by others. An important finding in these papers is that the revenue distribution over the sample set of products is not only widely distributed, but it is also highly skewed. In particular, in the Grabowski et al. [2002] sample, the top selling 10% of products earn about half the total market revenues (in terms of worldwide sales). The authors also find that sales revenues of the median NCE are insufficient to break even, using separate cost estimates. The mean sales volume may therefore provide a more reliable estimate of what may be effective in giving appropriate incentives to industry.

Using an estimated industry-wide nominal cost of capital of 11%, the NPV of revenues (pre-tax, and gross of production and distribution cost) derived over the life cycle of the average product in their sample is $2.84 billion (in 2004 dollars).
The revenues reported by Grabowski et al. [2002] are partially spent on marketing. Arguably, under a vaccine purchase commitment, a potential vaccine manufacturer would need to spend considerably less on promotion, so this requires an additional adjustment. Rosenthal et al. [2002] estimate that relative to sales, expenditures on promotion by U.S. pharmaceutical companies has remained fairly constant at about 15% of revenues, and has fallen slightly since 1998. It is plausible, however, that promotion/sales ratios are lower in Europe and elsewhere globally. In this sense the 15% number is an upper bound of what should be deducted from the overall purchase size commitment. Furthermore, in the U.S. the 15% ratio is partly the result of an accounting nuance, in which values of free samples given to physicians by drug representatives are assessed at average retail price, not manufacturer's production costs. For most drugs, manufacturers' marginal drug production costs are quite low. Moreover, samples comprise about 50% of drug manufacturer's total promotional costs in the U.S. (see Rosenthal et al. [2002]). Given these considerations, a promotion/sales adjustment of reducing the program size by 10% seems appropriate. After this adjustment, the program would need to pay out $2.56 billion to match the average revenue brought in by existing NCEs.

The sample of existing products includes the “low-hanging fruit” of products that were easy to develop. To the extent that developing a malaria vaccine is more technologically challenging than developing the typical product, the appropriate payment would be greater.

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4 It is worth noting some argue that in fact marketing and related promotion expenditures are a much higher percent of revenues; Angell [2004, p. 12], for example, argues they may be as high as 36% of revenues. While precise measurement of this ratio is inherently difficult (and controversial, given difficulties in allocating some educational and R&D activities as partly promotional), we note that the larger percentages, such as those cited by Angell, typically refer to total selling and general administrative (S&GA) expenses. These S&GA expenditures include non-marketing related general administration, and therefore likely overstate total marketing and related promotion expenditures.
In Table 1, we report the necessary NPVs of sales that would make a malaria vaccine comparable to each of five different representative products, corresponding to the averages of the five upper deciles of the sales distribution. (Specifically, in the first decile, the reported number represents the average among the top selling 10% of NCEs. For the second decile, it is the average of the next 10%, etc.).

<table>
<thead>
<tr>
<th>Typical product in 1st decile</th>
<th>Typical product in 2nd decile</th>
<th>Typical product in 3rd decile</th>
<th>Average product in entire sample</th>
<th>Typical product in 4th decile</th>
<th>Typical product in 5th decile</th>
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<tr>
<td>13.17 billion</td>
<td>5.00 billion</td>
<td>3.04 billion</td>
<td>2.56 billion</td>
<td>2.10 billion</td>
<td>1.13 billion</td>
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The average product lies in the fourth decile of sales, and it can be seen in the table that the top two deciles of the distribution generate the largest part of sales revenue. Therefore, if the development of a malaria vaccine were to be made comparable to the more profitable existing products, the returns to the supplier would need to be increased substantially.5

Summing up, a conservative estimate of the net present value of revenues that a malaria vaccine commitment would need to offer to match existing commercial products

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5 It is noteworthy that very few of the products in the Grabowski et al. [2002] sample are likely to be vaccines. Among the existing vaccines, the Hepatitis B vaccine may be the best case to compare a hypothetical malaria vaccine to, as it is a relatively new antigen that has seen a widespread increase in demand during the last decade. As evidence of a demand-induced R&D activity, Finkelstein [2004] reports an increase in R&D investment in response to the Advisory Committee on Immunization Practice (ACIP)’s recommendation in 1991 to give Hepatitis B immunization to American infants. Immunization rates strongly increased thereafter, to almost 90%, and a significant number of additional clinical trials were conducted. The worldwide market for Hepatitis B vaccines currently lies at around $1 billion annually, which makes the set of all Hepatitis B vaccines comparable in market
and spur significant R&D would be $2.56 billion, in year 2004 dollars. To the extent that a malaria vaccine may be more difficult to develop than the typical new chemical entity, the reward would need to be higher. Thus, we take $3.0 billion as our target revenue as it is a substantial improvement over the mean revenue but does not attempt to match the top blockbuster drugs. Because the starting year of purchases under the program is highly uncertain, the commitment should be indexed to account for inflation. We express everything in 2004 dollars.

Much has been written recently concerning the apparent low productivity of biopharmaceutical R&D investments in generating new therapies and successfully bringing them to market. A pessimistic interpretation of this phenomenon is that new drug and biologic development is becoming ever more difficult, and that developing a vaccine for malaria will be very, very costly. On the other hand, industry observers also point out that the biopharmaceutical industry is unlikely to be as successful in the future as it has been in the past in bringing “blockbuster” drugs to market, and that instead it must focus on more targeted and smaller population therapies. If the latter is true, the implementation of a purchase commitment program for a malaria vaccine could be particularly timely for an industry that is changing its focus.

4. Cost effectiveness of a vaccine purchase commitment

We now turn to a discussion of net present value of revenue and the health cost-effectiveness would be under various scenarios. These estimates have been generated by a spreadsheet tool (available for download at http://post.economics.harvard.edu/faculty/kremer/vaccine.html) that allows the user to size to a single product with a NPV of sales of at least $4.60 billion. Details of this calculation are
manipulate all relevant variables in a flexible and user-friendly way, thereby permitting the generation and analysis of a large number of different scenarios.

We will consider the impact of a particular set of contract provisions and vaccine characteristics, under variable assumptions about the countries that participate in the program, adoption rates and sources of additional revenue to the vaccine supplier (e.g. travelers’ or military purchases). However, these parameters and assumptions can be modified in the spreadsheet, allowing the user to investigate the impact of alternative contract parameters and different assumptions regarding take-up, malaria burden, etc. For example, the spreadsheet allows the user to assess the revenue and cost-effectiveness consequences of different combinations of price, quantity and vaccine characteristics. Based on the user inputs as well as recent data on disease burden and population, the spreadsheet outputs the cost per disability adjusted life year (DALY) saved by the program and the NPV of revenues that would accrue to the vaccine supplier.

As a benchmark for comparison of cost effectiveness, we note that health interventions in the poorest developing countries that cost about $100 per DALY saved are generally regarded as highly cost effective (World Bank [1993]). However, more recently a country’s per capita gross national product (GNP) has been used as a benchmark (GAVI [2004]; WHO [2000a]), and in the United States, the cost-effectiveness threshold is as high as $50,000 to $100,000 per DALY saved (Neumann et al. [2000]).

As an alternative benchmark, although estimates of the cost of antiretroviral treatment per year of life saved are sensitive to assumptions about the cost of delivery and the epidemiological effects of treatment (which could be either positive or negative, depending on behavioral response), the 2001 call by 133 Harvard faculty members for available from the authors.
antiretroviral treatment (Adams et al. [2001]) estimated that purchasing and delivering antiretrovirals using a directly observed treatment short-course (DOTS) approach would cost $1,100 per year. Kremer and Glennerster [2004] estimate that adjusting that analysis for the lowest of the recently negotiated estimates of antiretroviral costs suggests a cost per year of treatment of approximately $613.

To summarize the results, we find that under a reasonably conservative set of assumptions a price commitment for malaria that commits to pay $15 per person immunized (or $5 per dose for a three-dose vaccine) for the first 200 million people immunized would cost less than $15 per DALY saved, including both the costs of purchase and delivery of the vaccine. The sales under the program would provide about $3.1 billion in total NPV of revenues to a vaccine developer, comparable to the $3.0 billion average of products between the 70th and 80th percentiles of existing commercial products. This result, detailed below, is derived from baseline assumptions described in the following paragraphs. Sensitivity analyses presented in Section 5 demonstrate that cost-effectiveness is robust to variation in vaccine efficacy, slow or low adoption, and contract provisions, but more sensitive to changes in the duration of protection of the vaccine and delivery costs.

*Contract provisions*

We consider a commitment that would offer an initial price of $15 per person in 2004 terms for the first 200 million people immunized, after which the price would drop to $1 per person immunized.

Following the public health literature, we apply a default annual discount rate of three percent to future DALYs saved and future expenses to the program sponsor. Firms, however, may discount future revenues at a higher rate reflecting the cost of capital (earnings
foregone on other investment opportunities). We consider a real rate of eight percent, close to the annual average return on the stock market (Ibbotson Associates [2004]).

Vaccine characteristics

In our base case, we consider a three-dose, 60% effective vaccine that would protect for five years and could be added the standard package of vaccines that are delivered under the WHO’s Expanded Programme on Immunization (EPI). That package, which includes three contacts with each child, costs $15, or $5 for every contact (World Bank [1993]). The majority of this cost is due to delivery costs, as the price of the traditional six EPI vaccines is very low. The World Bank estimated that adding the one-dose yellow fever vaccine and the fairly expensive three-dose hepatitis B vaccine 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]). These were expensive vaccines, so we estimate that the incremental cost of adding a three-dose vaccine to the EPI package would be no more than $0.75. However, as discussed in the sensitivity analysis below, even at several multiples of this cost, delivery would still be quite inexpensive. (Note that in the spreadsheet tool, extra delivery costs can be specified for vaccines that are not compatible with the EPI schedule, but in the base case for malaria we consider vaccines that do conform to the EPI delivery.)

Vaccine efficacy reflects the percentage of infections that are prevented by immunization, and defaults to 60 percent. The duration of protection reflects the number of years after immunization that the vaccine protects against infection, and defaults to five years.

Countries covered
An important set of assumptions concerns the countries that will participate in the program, i.e. the populations for which the vaccine doses will be purchased. This selection has a considerable impact on the effectiveness of the program, because the burden of malaria and vaccine adoptions rates differs widely across countries. In the spreadsheet tool, we allow selection by several competing criteria: a gross national income (“GNI”) per capita cutoff ($1000, the cutoff currently used by the Vaccine Fund\(^6\), is the default and is used in the analysis presented here), a ‘manual’ selection of countries, or by minimum disease prevalence.

We assume that countries in which vaccination would not be cost-effective at delivery cost would not participate in the program. In addition, China is not included in the program because its GNI will soon surpass the $1000 cutoff, and because falciparum malaria, the most deadly form of malaria, is only a problem for a tiny fraction (<1%) of China’s population.

**Adoption**

Obtaining cost-effectiveness estimates for a vaccine requires us to make some assumptions about the adoption patterns for the vaccine. Because there is little historical data to guide assumptions, in general we make conservative assumptions about take-up rates. In addition, the robustness checks we will present in Section 5 suggest our estimates are relatively insensitive to assumptions about adoption.

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\(^6\) For those readers who may be unfamiliar, the Vaccine Fund is the financing arm to the Global Alliance for Vaccines and Immunization (GAVI). The Vaccine Fund offers support to qualifying governments of the world’s poorest countries for: (1) new and under-used vaccines; (2) funding to help government strengthen their basic immunization services; and (3) safe injection equipment in the form of auto-disable syringes and safe disposal boxes. More information is available at [http://www.vaccinealliance.org](http://www.vaccinealliance.org).
Adoption of the vaccine will likely gradually increase over several years to a steady-state level. In our base case we consider a linearly increasing take-up path that takes seven years to reach the steady state. Altering the years until a vaccine is developed will change the nominal price paid, but will not alter the results of the calculation, since those reflect the value of revenues and the cost per DALY in real terms at the time the vaccine is developed.

In the base case scenario, the uptake rates for new cohorts (infants) are set to the country-by-country immunization rates for the diphtheria-pertussis-tetanus three-dose vaccine (DPT3) reported by WHO [2002], plus five percentage points. We assume that the immunization rates would be at least as high as the current DPT3 rates if the vaccine could be added to the EPI schedule, and higher if parents particularly value immunization against malaria. The addition of five percentage points could also be interpreted as accounting for the economic benefits that would follow from the reduction of the disease burden. The spreadsheet also allows the user to base uptake rates on diphtheria-pertussis-tetanus first-dose (DPT1) or measles coverage rates, or specify a single rate for all countries.

In the transition years of the program, there may be backlog immunizations of children who have not yet acquired natural immunity to the disease. Given that expanding the program beyond those relatively easy to reach will be difficult, we assume that only a minority of this population will be reached. Specifically, we assume that 10 percent of the children aged 0-4 will be immunized.

Women temporarily lose their natural immunity to malaria during their first pregnancy, and thus we include some immunizations of pregnant women. The number of pregnant women who need to be vaccinated is approximated by taking one fourth of annual births. The default immunization rate for this population is set to the tetanus toxoid (TT2) rate reported by WHO [2002] plus five percentage points, since the tetanus toxoid vaccine is
already given to pregnant women and may be taken as a proxy for the availability of vaccinations to that group. We add five percentage points to the TT2 rate for the same reasons described above – since malaria is a more threatening disease, people may seek vaccination at higher rates than those for tetanus toxoid.

Additional revenues

The vaccine developer would also receive revenue outside of program purchases, such as private purchases in covered countries and purchases in non-covered countries (such as the travelers’ and military markets in high-income countries, as well as middle-income countries where malaria is prevalent).

In the base case we project a market of $650 million in NPV of revenues (2004 dollars) in high- and middle-income countries based on annual purchases of malaria prophylaxis drugs. Presumably people would be willing to pay comparable amounts to get vaccinated. An estimate from the popular press (Reuters [2003]) and correspondence with Pfizer suggest that the annual market for malaria prophylaxis drugs from sales to travelers and tourists from industrialized countries and the military could be as much as $200 million, but others cite much lower figures. If a vaccine captured $100 million in peak sales and the profile of sales over time followed that of a typical pharmaceutical (Grabowski et al. [2002]), the net present value of those sales would be about $650 million. Adding in $100 million of additional revenues from private sales in low- and middle-income countries yields a default of $750 million in net present value of revenues outside the commitment program.
Given these inputs, along with a recent collection of data from the World Health Organization [1997] and the United States Bureau of the Census [2000] on disease burden and fertility, as well as estimates of the distribution of the burden of disease by age and gender, the spreadsheet tool projects the total discounted number of DALYs that would be saved by the program. It also calculates the total cost, including delivery costs, and the revenues to the vaccine supplier from purchases at the initial (high) price. The purchases at the subsequent lower price are ignored for the NPV calculations for the developer, because the low price would presumably be close to the cost of production, and because for later sales it is increasingly less likely that the supplier would remain the same.

We then calculate the number of DALYs saved by the program each year by multiplying the number of immunizations by vaccine efficacy and the DALY burden of disease faced by members of the population immunized over their lifetime or the lifetime of the vaccine. The cost of the program in each year is calculated as the number of vaccinations multiplied by the total cost of each vaccination (purchase price and delivery cost). These are discounted into the future at the real discount rate of 3%. The total discounted revenue to the supplier in each year is calculated as the number of purchases at the initial price multiplied by the initial price, discounted at the real cost of capital of 8%. In order to evaluate the appropriateness of the size of the price commitment, one can then compare the NPV of revenues from a new vaccine to the adjusted distribution of revenues from a sample of existing commercial products, as detailed in Section 3.

These calculations may underestimate the cost-effectiveness of the vaccine. They do not include any epidemiological benefits—vaccinating a significant fraction of the population may slow the spread of a disease, and thus benefits may spill over to the unvaccinated. They also do not include health benefits to people in middle- and high-
income countries, or benefits to adults in low-income countries who purchase a vaccine privately. They assume that the vaccine would be given randomly throughout a country and thus do not factor in any benefits of targeting vaccine delivery within countries to areas that have the most severe disease problems. Finally, they do not include the benefits of increasing vaccination rates for other diseases that might result from parents bringing their children in to clinics to vaccinate them against malaria.

The main outputs of the spreadsheet tool are the total NPV of revenues to the vaccine supplier and the cost per DALY of the vaccine under the conditions specified, both in 2004 dollars. Under the base case assumptions described above, a commitment to pay $15 per person immunized for the first 200 million individuals immunized would produce a total NPV of revenue of $3.1 billion (in 2004 dollars), slightly above the $3.04 billion benchmark for the 70\textsuperscript{th} to 80\textsuperscript{th} percentile of existing NCEs.

The spreadsheet tool also reports the annual number of vaccinations in the steady state, the annual number of DALYs saved in the steady state, and the overall cost per DALY saved. Under the baseline assumptions, over 57 million people would be immunized annually, saving almost 14 million DALYs per year in the steady state. Overall, the program would cost less than $15 per DALY saved, which is highly cost effective relative to the $100 per DALY cost-effectiveness standard.

5. **Sensitivity analyses**

In this section, we discuss the cost-effectiveness of a vaccine purchase commitment program when assumptions in the base case are varied. The sensitivity analyses reported below also highlight the key aspects of a vaccine that make it cost effective and that
therefore should be considered in the choice of eligibility criteria for a product to be purchased under the program. The cost-effectiveness of the vaccine is relatively insensitive to changes in assumptions about efficacy, take-up rates, and the per immunized-person price offered. For example, a malaria vaccine that was only 50 percent effective would still cost less than $20 per DALY. Figure 1 shows the relationship between efficacy and cost per DALY, holding all other inputs constant, including the set of countries participating in the program. Even a 30 percent effective vaccine would be highly cost-effective.

**Figure 1.**

![Vaccine efficacy and cost-effectiveness graph](image)

If adoption of the vaccine is very slow the program would remain very cost-effective, while still providing a considerable amount of revenue to the vaccine developer, because under this type of contract the value of payments only declines as a result of discounting, as
high-price vaccinations are pushed further into the future. Even if it takes 15 years for adoption to reach steady-state levels and adoption only reaches levels ten percentage points lower than the DPT3 rates, the program would still cost less than $20 per DALY saved and generate $2 billion in NPV of revenue for biopharmaceutical companies (in 2004 dollars). Including the private market for the vaccine in low- and middle-income countries, as well as travelers' and military markets in richer countries, the total revenue would surpass the $2.5 billion average NPV of revenue for existing biopharmaceutical products (adjusted for lower marketing costs).

A vaccine commitment would also be cost-effective at the time of vaccine development under a wide range of contract provisions. For example, to match the revenues of drugs falling between the 80th and 90th percentile and generating $5.0 billion in net present value of sales, a commitment could offer $25 per person immunized for the first 225 million people immunized. This would cost about $21 per DALY saved. As discussed below, if this accelerated the vaccine development time, this higher commitment might prove more attractive than a lower one.

Cost-effectiveness is more sensitive to assumptions about the number of doses and the duration of protection. Even vaccines with relatively low efficacy will be cost effective if they can be delivered with the current (three-dose) EPI vaccine package. This is because adding one more vaccine to this package is relatively inexpensive (we have assumed a $0.75 cost of adding a three-dose vaccine, although even at several multiples of this the delivery would be quite inexpensive). Assuming an incremental delivery cost of triple that amount ($2.25 per person immunized) increases the cost per DALY saved to about $20 holding the set of countries included constant, and augments the cost per DALY by only pennies if we assume that only countries in which the vaccine would be cost-effective at delivery cost
adopt it. In contrast, delivery outside the EPI schedule would be relatively costly (we have assumed a cost of $5 per dose). For example, adding two doses outside of the EPI schedule would bring the cost per DALY to about $55 per DALY saved, holding the set of participating countries constant, or $25 per DALY if countries with low disease burdens opt out because delivery of the vaccine would not be cost-effective.

Similarly, cost-effectiveness is sensitive to changing assumptions about duration of protection. Because malaria primarily kills children under the age of five who have not yet gained natural immunity, the cost per DALY increases rapidly for vaccines that provide less than five years of protection. If a vaccine provided only two years of protection, the cost per DALY saved would rise to $26. This number could be less if people could be re-vaccinated but that would depend on how often boosters were needed. A lesson to be learned from these sensitivity analyses is that any vaccine commitment for malaria should take these considerations into account when specifying the product profile.

**Cost-effectiveness in the case of accelerated development and distribution**

The above calculations demonstrate that once a vaccine is developed, purchasing it at the agreed price will be a very cost-effective expenditure. There is little reason to fear, therefore, that a vaccine commitment would tie donors to future purchases that would not be worthwhile, if a vaccine were developed. We now examine a somewhat more complex issue – the value of the commitment in accelerating the development and distribution of a vaccine. To assess this, we need to make assumptions about what would have happened in the absence of a commitment.

In the absence of a price commitment both development and adoption of the vaccine could be pushed further into the future. It is difficult to know how much a vaccine
commitment would speed up vaccine development, but one indication that the effect is likely to be substantial comes from the Orphan Drug Act. While only ten new orphan drugs were discovered in the decade prior to the Orphan Drug Act, 200 were discovered in the next decade (Grabowski [2003]). A vaccine commitment is also likely to substantially accelerate access in the poorest countries, since the sponsor would pay for it instead of the recipient populations. When the hepatitis B vaccine was introduced at $30 per dose, it was rarely used in low-income countries (Muraskin [1995], Galambos [1995]). The historical record suggests adoption of new vaccines in developing countries could be delayed by ten to 15 years in the absence of a purchase commitment. As we show below, the health benefits of speeding development of a malaria vaccine would be tremendous, for the disease kills a million people each year.

If a vaccine commitment advanced vaccine development by ten years and accelerated access in poor countries by ten years, it would still cost only about $23 per additional DALY saved. Even in the extreme case in which a price commitment accelerated vaccine development by only one year and adoption in poor countries by only two years, the program would cost about $80-$90 per additional DALY saved—still slightly less than the $100 per DALY threshold for the most cost-effective interventions.

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7 We estimate delays in access based on the historical record, but one could argue that the circumstances would be different here. However, if one believes that even in the absence of a commitment, donors would immediately buy a vaccine and distribute it at an on-patent price comparable to the initial price offered under the vaccine commitment, then the cost of purchasing and distributing the vaccine would be the same with or without a vaccine commitment, and any benefits of accelerated development associated with announcing a commitment in advance would be without cost in the ultimate price tag for a vaccine. If the money is going to be spent on the vaccine anyway, it is clearly more cost-effective to reap the benefits of faster development by announcing this policy in advance and entering into a vaccine commitment. Conversely, if one believes that companies would have to give away a vaccine in poor countries at cost, it is difficult to argue that a vaccine commitment would not be critical in advancing vaccine development.
By a similar line of reasoning, if increases in the size of the commitment accelerated development of a vaccine, it may be worthwhile to undertake a larger commitment. Paying $25 per person for the first 225 million people immunized rather than $15 per person for the first 200 million people would meet the average net present value of products between the 80th and 90th percentiles of existing commercial products. The larger commitment would cost less than $100 per additional DALY saved if it advanced development by only three years relative to the smaller commitment, and would cost about $21 per DALY saved overall.

6. Conclusions

A variety of simulations suggest that under a large range of values, a vaccine commitment may be sufficient to stimulate substantial research towards a malaria vaccine, yet still be extremely cost-effective. A commitment of $2-3 billion 2004 dollars in net present value of sales would be appropriate. Of course in expectation, the larger the commitment, the more biopharmaceutical firms will enter the search for a vaccine, and the faster a vaccine is likely to be developed.

We here focused on the example of a malaria vaccine; however, our general analysis applies more broadly. In particularly, estimates for HIV and tuberculosis vaccines analogous to those presented here for malaria can be derived via the downloadable spreadsheet tool.
Works Cited


