

NBER WORKING PAPER SERIES

ADVANCED PURCHASE COMMITMENTS
FOR A MALARIA VACCINE:
ESTIMATING COSTS AND EFFECTIVENESS

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Working Paper 11288
<http://www.nber.org/papers/w11288>

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
April 2005

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 Pull Mechanisms Working Group of the Global Health Policy Research Network, a program of the Center for Global Development that is supported by the Bill & Melinda Gates Foundation. We are especially grateful to Henry Grabowski for his generosity in sharing the pharmaceutical sales revenue data with us. All errors and opinions are those of the authors. The views expressed herein are those of the author(s) and do not necessarily reflect the views of the National Bureau of Economic Research.

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NBER Working Paper No. 11288
April 2005
JEL No. I18, O19, O31, O38

ABSTRACT

To overcome the problem of insufficient research and development (R&D) on vaccines for diseases concentrated in low-income countries, sponsors could commit to purchase viable vaccines if and when they are developed. One or more sponsors would commit to a minimum price that would be paid per person immunized for an eligible product, up to a certain number of individuals immunized. For additional purchases, the price would eventually drop to short-run marginal cost. If no suitable product were developed, no payments would be made. We estimate the offer size which would make the revenues from R&D investments on a malaria vaccine similar to revenues realized from investments in typical existing commercial pharmaceutical products, as well as the degree to which various contract models and assumptions would affect the cost-effectiveness of such a commitment for the case of a malaria vaccine. Under conservative assumptions, we document that the intervention would be highly cost-effective from a public health perspective. Sensitivity analyses suggest most characteristics of a hypothetical malaria vaccine would 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.

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1. Introduction

Compared to the social need, there is a dearth of research and development (R&D) on vaccines for malaria and other diseases concentrated in low-income 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.

Two major distortions are relevant for these markets. First, governments and 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 R&D 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 are typically 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.” Because the benefits of scientific and technological advances spill over to many nations, 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 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 specific to markets in low-income countries, and would thereby put diseases like malaria on more equal footing with health conditions of affluent populations in R&D allocation decisions.

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 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.³ A working group comprised of economists, public health specialists,

³ The idea of encouraging R&D by committing to purchase vaccines once they are developed was discussed by the WHO [1996] and was advocated by a coalition of organizations coordinated by the International AIDS Vaccine Initiative at the 1997 Denver G-8 summit. The World Bank AIDS Vaccine Task Force [2000] (see

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 (Levine *et al.* [2005]).⁴

In this article, we estimate what size of a commitment would provide a market comparable to those of 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.

We take the net present value (NPV) of revenues earned by the average of a sample of recently launched commercial products, adjusted for lower marketing costs, as our benchmark revenue. 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 in size to this benchmark revenue, and would also be highly cost-effective from a public health perspective.

2. Background on malaria

The World Health Organization (WHO) estimates that more than 300 million people contract clinical malaria every year, and that 1.1 million annually 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

also Rosenhouse [1999]) explored this idea further. Sachs [1999] and Sachs and Kremer [1999] have advocated the establishment of such programs in the popular press. Maurer *et al.* [2004] also offer a discussion of advance purchase commitments.

limited natural immunity rarely die from malaria, but they often become weak and lethargic with the disease later in life, thus 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 scientific 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 exist such a divergence of opinion on scientific 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 GlaxoSmithKline Biologicals for more than fifteen years, and the vaccine came off the shelf with an influx of financial support, in large part from the Bill & Melinda Gates Foundation. The phase IIb trial was 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), GlaxoSmithKline Biologicals, and the Mozambique Ministry of Health. The study, published in *The Lancet*, found that the

⁴ This report is available online at <http://www.cgdev.org/>.

vaccine's efficacy against severe malaria disease was 58 percent, 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 necessary size of a vaccine purchase commitment⁵

We begin by estimating the total vaccine purchase commitment size that would be necessary to provide a market 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. As described in this section, in deriving our estimates we consider reported sales numbers of existing commercial 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 the revenues realized from investments in existing products.⁶

⁵ For details on the sales revenue data used in this section, see the Appendix. This data is also available online at <http://post.economics.harvard.edu/faculty/kremer/vaccine.html>.

⁶ See Berndt *et al.* [2003] for other approaches and further discussion.

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 U.S. pharmaceutical market between 1990 and 1994.⁷ An important finding in the Grabowski *et al.* paper is that the revenue distribution over the sample set of products is not only widely distributed, but is also highly skewed.⁸ In particular, in the Grabowski *et al.* [2002] sample the top selling 10 percent of products earn approximately half of the total market revenues (in terms of worldwide sales). Using separate estimates of the cost of pharmaceutical development, Grabowski *et al.* also find that sales revenues of the *median* NCE are insufficient to break even, implying the *mean* sales revenue may provide a more reliable estimate of what level of expected revenues may be effective in spurring industry investment.

We obtained the sales revenue data compiled by Grabowski *et al.* [2002]. The analysis presented in Grabowski *et al.* [2002] utilized this sales data in combination with estimates on the cost of pharmaceutical development in order to estimate total returns; we did not use those cost of development estimates nor any other cost of development estimates in our analysis. Our focus here is strictly on using sales revenue data to estimate the size of commitment needed to generate a market comparable in size to the sales revenues of products in the Grabowski *et al.* sample.

We assume an estimated industry-wide real cost of capital (that is, earnings foregone on other investment opportunities) of 8 percent, close to the annual average return on the

⁷ Grabowski *et al.* note this is a comprehensive sample of the NCEs originating from and developed by the pharmaceutical industry that were introduced into the U.S. in the 1990 to 1994 time period. Due to data limitations we are unable to address whether the sales revenues of this sample of self-originated NCEs is a representative sample of the sales revenues of all commercial pharmaceutical products. Sales revenue data from a larger sample of products is available from (for example) IMS Health or Scott Levin Associates, but is very expensive. Further work could attempt to pursue this and other potential sources of larger samples of sales revenue data.

stock market (Siegal [1998]).⁹ This real rate of 8 percent is equivalent to a nominal cost of capital of 11 percent, assuming 3 percent inflation. Using the sales revenue data together with this assumption of an 8 percent real cost of capital, the NPV of revenues (pre-tax, and gross of plant, equipment, promotion and marketing, production, and distribution cost) derived over the life cycle of the average product in the Grabowski *et al.* sample is \$3.44 billion (in 2004 dollars).¹⁰

The revenues reported by Grabowski *et al.* [2002] are partially spent on marketing. Since under a vaccine purchase commitment a potential vaccine manufacturer would likely need to spend considerably less than average on marketing, we take this into account and consequently adjust down our estimates as derived above. Rosenthal *et al.* [2002] estimate that, relative to sales, expenditures on promotion by U.S. pharmaceutical companies have remained fairly constant at about 15 percent of revenues, and have fallen slightly since 1998.¹¹ It is plausible, however, that promotion/sales ratios are lower in Europe and elsewhere globally. In this sense the 15 percent number can be interpreted as an upper bound of what should be deducted from the overall purchase commitment size.

Furthermore, in the U.S. the 15 percent ratio is partly the result of an accounting nuance, in

⁸ This finding is consistent with the findings of analogous earlier work on products introduced in the 1980s, such as Grabowski and Vernon [1990].

⁹ Siegal [1998] estimates that the annual average return on the stock market over the time period from 1946-1998 was 7.8 percent (p. 318). We approximate this to 8 percent for our analysis.

¹⁰ The appropriate level at which to set the cost of capital is somewhat controversial. Grabowski *et al.* assume a real cost of capital of 11 percent, and previous analyses by two of the present authors (Kremer and Glennerster [2004]) used this assumption in calculating the NPV of revenues from existing commercial products. In this work, our preferred estimates use an assumed 8 percent real cost of capital for two reasons. First, 8 percent is close to the annual average return on the stock market (Siegal [1998]). Second, this allows for consistency in our analysis between estimating the NPV of revenues of existing products and estimating the NPV of revenues under a vaccine purchase commitment. With an 11 percent real cost of capital, the NPV of revenues for the average product would be \$2.81 billion rather than \$3.44 billion.

¹¹ 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 percent 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

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 percent of drug manufacturer's total promotional costs in the U.S. (see Rosenthal *et al.* [2002]). Given these considerations, reducing the commitment size by 10 percent as an adjustment for promotional/marketing expenditures seems appropriate. After this adjustment, the program would need to pay out \$3.1 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. On the other hand, the promising results of the recent GSK trials (as discussed in Section 2) suggest that developing a malaria vaccine may not be as technically difficult as many had previously thought.

In Table 1, we report the necessary NPVs of sales that would make a malaria vaccine comparable to each of five different representative products from the Grabowski *et al.* sample, corresponding to the averages of the five upper deciles of the sales distribution.¹² (Specifically, in the first decile, the reported number represents the average among the top selling 10 percent of NCEs. For the second decile, it is the average of the next 10 percent, *etc.*).

expenditures include non-marketing related general administration, and therefore likely overstate total marketing and related promotion expenditures.

¹² Figures for the 1st decile, 2nd decile, and average product are taken directly from Grabowski *et al.*'s data. Deriving the 3rd, 4th, and 5th decile figures required slight approximation due to data limitations. Details on these calculations are available from the authors.

Table 1. Net present value (NPV) of sales (in 2004 dollars), adjusted down 10 percent for lower marketing costs					
Typical product in 1st decile	Typical product in 2nd decile	Typical product in 3rd decile	Average product in entire sample	Typical product in 4th decile	Typical product in 5th decile
15.80 billion	5.73 billion	3.61 billion	3.09 billion	2.48 billion	1.34 billion

Source: Grabowski *et al.* [2002] data, authors' calculations.

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.¹³

An alternative method of estimating the necessary purchase commitment size would be to ask individuals outside of but familiar with the industry their opinion on what level of expected revenue is needed to spur substantial R&D investments; these opinions can arguably serve as one rough check on our estimates as derived above. A common perception among analysts and potential developers (as well as many in industry) is that large biopharmaceutical companies need to anticipate annual sales of \$500 million or more in years with peak sales, assuming that the revenue distribution over the lifecycle is equal to the average distribution in the industry, in order to be willing to invest in R&D for a new

¹³ 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 on hepatitis B vaccines in response to the Advisory Committee on Immunization Practice (ACIP) recommendation in 1991 to give hepatitis B immunization to American infants. Immunization rates strongly increased thereafter, to almost 90 percent, 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 size to a single product with a NPV of sales (assuming an 8

product (see Robbins-Roth [2000]). Assuming the typical product life cycle as in Grabowski *et al.* [2002] and a real cost of capital of 8 percent, after adjusting down by 10 percent for lower marketing costs this corresponds to an NPV of about \$3.38 billion, a number fairly close to that which our procedure yields.¹⁴

To summarize our work in this section, an estimate of the net present value of revenues that a malaria vaccine commitment would need to offer in order to match existing commercial products would be \$3.1 billion, in year 2004 dollars. Because the starting year of purchases under the program is highly uncertain, the commitment should be indexed to account for inflation. We here 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

percent real cost of capital) of approximately \$6.49 billion. Details of this calculation are available from the authors.

¹⁴ With an 11 percent real cost of capital (as in Grabowski *et al.* [2002]), this figure changes from \$3.38 billion to \$2.76 billion.

We now consider the net present value of revenue and health cost-effectiveness estimates that would be generated by a vaccine purchase commitment under various scenarios. These estimates have been generated by a spreadsheet tool (available online at <http://post.economics.harvard.edu/faculty/kremer/vaccine.html>) that allows the user to 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 one particular set of contract provisions and vaccine characteristics under variable assumptions about which countries would participate in the program, vaccine 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, thus 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 compiled 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.¹⁵

Since the values of revenues and cost per DALY saved are expressed in real terms at the time the vaccine is developed, even though altering the years until a vaccine is developed will change the nominal price paid, it will not alter the results of the calculations presented here.

As a benchmark for cost-effectiveness comparisons, 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]). More recently a country's gross national product (GNP) per capita has also been used as a benchmark (GAVI [2004]; WHO [2000a]), and in the United States, the cost-effectiveness threshold is estimated to be as high as \$50,000 to \$100,000 per DALY saved (Neumann *et al.* [2000]). As an alternative benchmark, even at the lowest of recently negotiated estimates of antiretroviral prices, the cost of purchasing and delivering antiretrovirals using a directly observed treatment short-course (DOTS) is estimated to cost \$613 per year of treatment.¹⁶

To summarize our results as described in this section, we find that under a reasonably conservative set of assumptions, a price commitment for a malaria vaccine 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 purchase and delivery costs of the vaccine. Sales under the program would provide about \$3.2 billion in total NPV of revenues to the vaccine developer, comparable to the \$3.1 billion in total NPV of revenues of the average product as discussed in Section 3. This result is derived from baseline assumptions which are detailed below. 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

¹⁵ Disability adjusted life years, or DALYs, are a commonly used metric which attempt to account for both life lost due to premature death and the loss of healthy life resulting from disease morbidity or disability.

¹⁶ 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 antiretroviral treatment (Adams *et al.* [2001]) estimated that purchasing and delivering antiretrovirals using a DOTS approach would cost \$1,100 per year. That analysis assumes an average cost of \$650 per patient per year for costs of

We consider a commitment that would offer an initial price of \$15 per person (in 2004 dollars) 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. We consider a real rate of eight percent, close to the annual average return on the stock market (Siegal [1998]).

Vaccine characteristics

In our base case, we consider a three-dose, 60 percent effective vaccine that would protect for five years and could be added to 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 six traditional 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]). Both yellow fever and hepatitis B were expensive vaccines, so we assume 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

antiretrovirals. Adjusting that analysis for the lowest of the recently negotiated estimates of antiretroviral costs,

vaccines that are not compatible with the EPI schedule, but in the base case for malaria discussed here 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 adoption rates differs widely across countries. In the spreadsheet tool, we allow selection by several different criteria, including a gross national income (GNI) per capita cutoff (\$1000, the cutoff currently used by the Vaccine Fund¹⁷, is the default), a ‘manual’ selection of countries, and a minimum disease prevalence cutoff. In the baseline case presented here we use the \$1000 GNI per capita cutoff to define eligibility, and from there assume that eligible countries will participate if vaccination is cost-effective (*i.e.* less than \$100 per DALY saved) at delivery cost in that country. That is, 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

\$140 per year (McNeil [2004]), suggests a cost per year of treatment of approximately \$613.

¹⁷ 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

form of malaria, is only a problem for a tiny fraction (less than 1 percent) 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.

Adoption of the vaccine will likely gradually increase over several years and eventually reach a steady-state level. In our base case scenario we consider a linearly increasing take-up path that takes seven years to reach the steady state. In this base case, 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. This assumes 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. We argue it is appropriate to assume the addition of five percentage points to the current DPT3 rates for several reasons, including the likely increase in immunization rates that will result from the recent influx of financial support for immunizations (for example, from the Bill & Melinda Gates Foundation), that economic development that will likely increase immunization rates (for example, due to increased urbanization), and that immunization rates may be higher if parents value immunization more if a malaria vaccine is available. The

their basic immunization services; and (3) safe injection equipment in the form of auto-disable syringes and safe disposal boxes. More information is available online at <http://www.vaccinealliance.org>.

spreadsheet also allows the user to base uptake rates on diphtheria-pertussis-tetanus first-dose (DPT1) or measles coverage rates, or to 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 are in their first pregnancy and thus need to be vaccinated is approximated by taking one fourth of annual births.¹⁸ The default immunization rate for this population is set to the tetanus toxoid (TT2) rate reported by WHO [2002] plus five percentage points (for the reasons described above). The tetanus toxoid vaccine is already given to pregnant women and thus can serve as a proxy for the availability of vaccinations to that group.

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 total market of \$750 million in NPV of revenues (2004 dollars) in high- and middle-income countries. This estimate is based on annual purchases

of malaria prophylaxis drugs, as presumably people would be willing to pay comparable amounts for a malaria vaccine as for malaria prophylaxis drugs. 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 in the Grabowski *et al.* [2002] sample, the total net present value of those sales would be about \$750.7 million.¹⁹ Adding in \$100 million of additional revenues from private sales in low- and middle-income countries yields a default of \$850 million in net present value of revenues outside the commitment program.

Baseline results

Given the assumptions outlined above, along with a recent collection of data from the World Health Organization [1997] and the U.S. 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 because the low price

¹⁸ The average fertility rate (births per woman) in low-income countries in 2002 was four (World Bank [2005]), hence our assumption of one-fourth of total births being first pregnancies.

¹⁹ With an 11 percent real cost of capital (as in Grabowski *et al.* [2002]), this figure changes from \$750.7 million to \$613.9 million. Note that for both of these figures, we have *not* subtracted out 10 percent for lower marketing expenditures, as we did for our previous work, as that correction would here seem inappropriate.

would presumably be close to the marginal cost of production and because for later sales it is increasingly less likely that the supplier would remain the same.

We then calculate the expected number of DALYs that would be saved by the program each year by multiplying the number of immunizations by vaccine efficacy and by 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). As previously discussed, we follow the public health literature and discount both future DALYs saved and future expenditures to the program sponsor at a real discount rate of 3 percent. 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 percent. 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. For example, these calculations do not include any epidemiological benefits—that is, 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 into clinics to vaccinate them against malaria.

For a given set of specified assumptions, the main outputs of the spreadsheet tool are the total NPV of revenues that would accrue to the vaccine supplier and the cost per DALY of the vaccine, 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 \$3.2 billion (in 2004 dollars), comparable to the \$3.1 billion benchmark for the average existing NCE as discussed in Section 3.

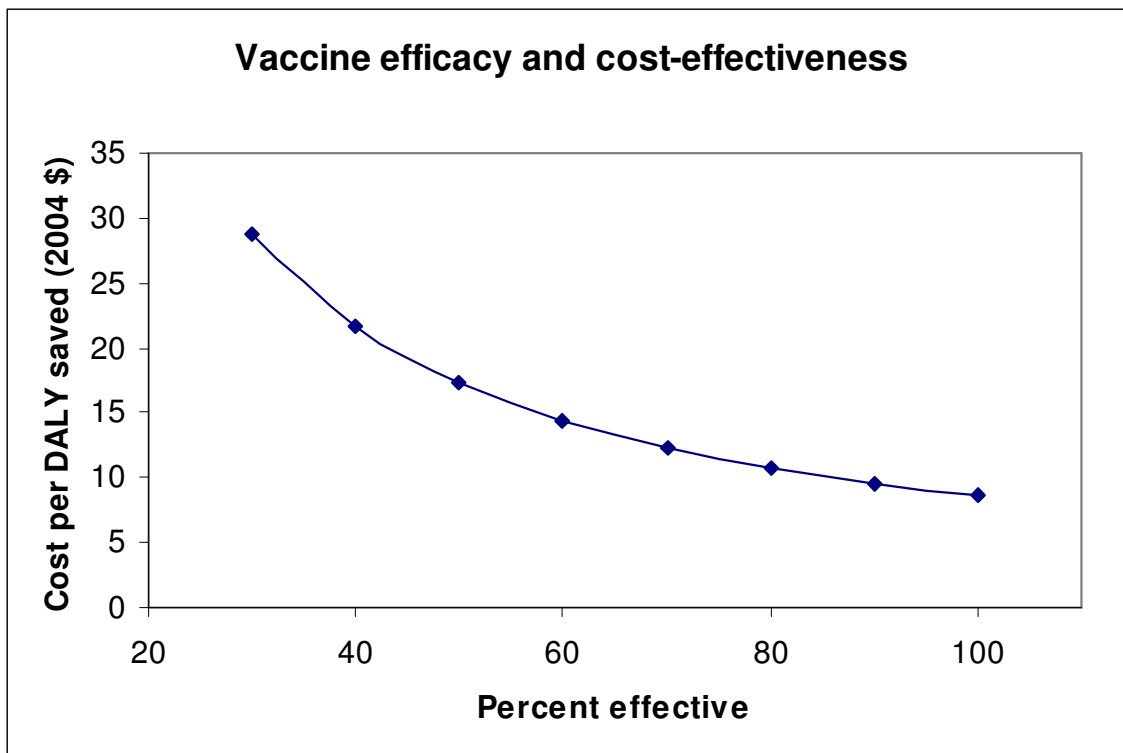
The spreadsheet tool also reports the annual number of vaccinations in the steady state, the annual number of DALYs saved in the steady state, and the overall cost per DALY saved. Under the baseline assumptions, over 54 million people would be immunized annually, saving almost 14 million DALYs per year in the steady state. Overall, the program would cost less than \$15 per DALY saved, which is highly cost effective relative to, for example, 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 the base case assumptions 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 constant all other inputs, including the set of countries participating in the program. Even a 30 percent effective vaccine would be highly cost-effective.

Figure 1.



Even if adoption of the vaccine is very slow, the program would still remain very cost-effective from a public health perspective and would still provide a considerable amount of revenue to the vaccine developer – although somewhat less revenue than in the case of a quickly adopted vaccine, since under this type of contract the value of payments for the high-price vaccine doses declines as a result of discounting if these vaccinations are

pushed further into the future. Even if it takes fifteen years for adoption to reach steady-state levels and adoption only reached levels ten percentage points below the DPT3 rates, the program would still cost less than \$20 per DALY saved and would generate \$2.7 billion in NPV of revenue for biopharmaceutical companies (in 2004 dollars).

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 70th and 80th percentile and generating a market roughly comparable to \$3.61 billion in net present value of sales, a commitment could offer \$17 per person immunized for the first 200 million people immunized, at a cost of about \$16 per DALY saved. To match the revenues of drugs falling between the 80th and 90th percentile and generating a market roughly comparable to \$5.73 billion in net present value of sales, a commitment could offer \$25 per person immunized for the first 250 million people immunized, at a cost of about \$23 per DALY saved. As discussed below, if raising the price offered per person immunized accelerated the vaccine development time, a higher commitment might prove more attractive than a lower one.

Cost-effectiveness is 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, because adding one additional vaccine to this package is relatively inexpensive. We have assumed in the baseline case a \$0.75 cost of adding a three-dose vaccine, although even at several multiples of this the delivery would be quite inexpensive. For example, assuming an incremental delivery cost of triple that amount (\$2.25 per person immunized) increases the cost per DALY saved to about \$20 if the set of countries included is held fixed, 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 the vaccine. In contrast, delivery outside the EPI schedule would be relatively costly. For example, at our assumed cost of \$5 per dose, adding two doses outside of the EPI schedule would bring the cost per DALY to about \$60 per DALY saved if the set of participating countries is held constant, or about \$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. For example, if a vaccine provided only two years of protection, the cost per DALY saved would rise to \$26. This number would decrease if people could be re-vaccinated but 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 vaccine at the pre-specified price would 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 – namely, 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. Although it is difficult to know how much a

vaccine commitment would speed up vaccine development, one indication that the effect may 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's price is paid on a per-person immunized basis. 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.²⁰ Given that malaria kills a million people each year, the health benefits of speeding development and adoption of a malaria vaccine would be tremendous.

If a vaccine purchase 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 cost-effectiveness threshold for the poorest countries.

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. As

²⁰ We estimate delays in access based on the historical record, but one could argue that the circumstances would be different now or in the future. 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. In this case, if the money will 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.

previously discussed, paying \$25 per person for the first 250 million people immunized rather than \$15 per person for the first 200 million people would roughly 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 and adoption by only three years relative to the smaller commitment, and would cost about \$26 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. Our estimates suggest that a commitment of \$3.1 billion in 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 focused here on the example of a malaria vaccine; however, our general analysis applies more broadly. In particular, estimates for HIV and tuberculosis vaccines analogous to those presented here for malaria can be derived via the downloadable spreadsheet tool.

Appendix.

This appendix presents the sales revenue data underlying our analysis in Section 3. Special thanks to Professor Henry Grabowski of Duke University for generously sharing this data with us.

year	mean product			product in top decile		
	<i>sales</i>	<i>NPV of sales (8% real cost of capital)</i>	<i>NPV of sales (11% real cost of capital)</i>	<i>sales</i>	<i>NPV of sales (8% real cost of capital)</i>	<i>NPV of sales (11% real cost of capital)</i>
t=-1	0.0	0.0	0.0	0.0	0.0	0.0
t=0	0.0	0.0	0.0	0.0	0.0	0.0
t=1 (launch)	83.0	83.0	83.0	293.5	293.5	293.5
t=2	155.6	144.1	140.2	545.6	505.2	491.5
t=3	211.6	181.4	171.7	791.0	678.2	642.0
t=4	267.6	212.4	195.7	1094.8	869.1	800.5
t=5	325.7	239.4	214.5	1447.7	1064.1	953.6
t=6	371.6	252.9	220.5	1729.4	1177.0	1026.3
t=7	414.7	261.3	221.7	2000.4	1260.6	1069.5
t=8	434.5	253.5	209.3	2200.5	1284.0	1059.9
t=9	457.4	247.1	198.5	2381.2	1286.5	1033.3
t=10	457.8	229.0	179.0	2503.5	1252.4	978.7
t=11	444.4	205.8	156.5	2539.2	1176.1	894.3
t=12	441.4	189.3	140.0	2587.2	1109.6	820.9
t=13	416.2	165.3	119.0	2582.1	1025.4	738.1
t=14	391.8	144.1	100.9	2565.9	943.5	660.8
t=15	307.8	104.8	71.4	1989.8	677.4	461.6
t=16	232.1	73.2	48.5	1486.0	468.4	310.6
t=17	185.7	54.2	35.0	1188.8	347.0	223.8
t=18	148.5	40.1	25.2	951.0	257.0	161.3
t=19	118.8	29.7	18.2	760.8	190.4	116.3
t=20	95.1	22.0	13.1	608.6	141.0	83.8
sum	5961.3	3132.8	2561.8	32247.0	16006.4	12820.2
sum in 2004\$	6539.4	3436.6	2810.3	35374.3	17558.7	14063.5
less 10% (for lower marketing expenditures)	5885.5	3092.9	2529.3	31836.9	15802.8	12657.2

Notes: All figures are in millions of year 2000 dollars, except as noted otherwise. The sales distribution for the mean product, as presented above, was scaled for several cases discussed in this paper such that the peak (year 10) sales were equal to the following: \$500 million for the “industry outsider” estimate, \$100 million for the outside-of-program purchases market estimate, and \$865.2 million for the hepatitis B vaccine market estimate. Details of these calculations are available online at

<http://post.economics.harvard.edu/faculty/kremer/vaccine.html>.

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