

The Case for a Vaccine Purchase Fund¹

Executive Summary

This note proposes that the international community establish a Vaccine Purchase Fund designed to assure pharmaceutical firms of a market if they develop vaccines for tuberculosis, malaria, or AIDS, the world's three most deadly infectious diseases. No expenditures would be made from the fund until an effective vaccine was developed. These diseases account for about 5 million deaths worldwide per year, or about 9% of all deaths. The target for vaccines purchased by the fund will be children born each year in low income countries with high incidence of each disease. Assuming these vaccines are purchased for \$10 - \$40 dollars per protected child, and an estimated total of 160 million vaccine purchases are made, expenditures from the fund would amount to approximately \$1.6 billion to \$6.4 billion per year if vaccines against all three of these diseases are developed. This of course would be a very small amount to save millions of lives.

The late 20th century has been described as the second golden age of vaccines. As a result of recent scientific advances, including, for example, sequencing of the genomes of the agents which cause TB and malaria, efforts to develop vaccines against these diseases in the near future are scientifically warranted. Yet pharmaceutical firms conduct very little vaccine research for these diseases, anticipating that the potential market would not justify the hundreds of millions of dollars in necessary research and development expenditure.

Markets are expected to be limited for two reasons. First, these diseases largely affect poor countries; virtually all malaria infections and more than 95% of new tuberculosis and 95% of HIV infections occur in the developing world. Second, governments and international organizations are typically monopoly purchasers of vaccines, and they use this power to insist on low vaccine prices. Existing vaccines for developing country diseases are typically purchased at pennies per dose. Pharmaceutical companies doubt that they would be able to sell vaccines to governments and international organizations at prices that would cover the research and development expenditures.

An effective strategy for combating these three diseases requires three components: better use of existing prevention, control, and treatment technologies; support for basic research conducted in the public sector and academic institutions, including the work which will form the basis for the applied work of vaccine development; and a commitment to private sector firms that if they succeed at the expensive applied work of developing a vaccine, they will have a market for their product.

A Vaccine Purchase Fund could provide this critical third component. A board representing donors would establish policies for future vaccine purchases. Contributions to the Fund could take the form either of cash or of binding commitments to provide funds if and when an eligible vaccine was developed. Contributions could be made over a number of years, according to an initially agreed timetable, so that the fund would build an endowment over time.

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Malaria, tuberculosis, and HIV are the world's most deadly infectious diseases, killing as many as 5 million people annually. Recent scientific advances make it scientifically justifiable to aim for development of vaccines against these diseases within the next two decades, yet little private sector vaccine research is being conducted, in large part because pharmaceutical firms believe that even if they develop a vaccine, it would be difficult for them to recover their research costs. We propose that donor governments and international organizations establish a Vaccine Purchase Fund to provide a minimum assured market. The Fund would make expenditures only once an effective vaccine had been developed and tested. In the case of malaria, the main target of purchases would be the 25 million children born each year in Africa, and in the case of TB and HIV, the main target would be some or all of the 83.7 million children born each year in all low income countries.² If, for example, TB and HIV vaccines were purchased for all children born in countries with incidence rates of each disease greater than 5 per 10,000, the total size of the main target birth cohort would be about 160 million. If vaccines against each of these three leading killers are developed, purchasing them at \$10-40 per child immunized for this main target birth cohort would cost between \$1.6 and \$6.4 billion annually, making it one of the world's most cost-effective health interventions.

This brief discusses evidence on the human and economic costs of these three diseases, reviews a few of the scientific issues relating to vaccine development, and analyzes the economic barriers that currently limit research. It then explains how a Vaccine Purchase Fund could help encourage private sector research towards vaccine development as part of an overall public health strategy. Finally, it discusses some of the details of how the fund's governing board would

² Low income countries are defined by the World Bank as the 63 countries in which GNP per capita was \$785 or less in 1996.

operate, and what funding would be needed.

The Burden of Malaria, TB, and HIV

The World Health Organization [WHO] estimates that there are 300 to 500 million clinical cases of malaria annually, causing 1.1 million deaths, the vast majority of them children and pregnant women. For a variety of reasons, including drug and insecticide resistance, the disease may pose an even greater burden in the future. Malaria is particularly prevalent in the countries around the equator that tend to be the world's poorest; 90% of malaria cases are in sub-Saharan Africa.

Each year, about 7.5 to 8 million people contract tuberculosis, over 95% of whom live in developing countries. Two billion people are estimated to carry the TB bacterium worldwide. With up to 17% of infections resistant to all five major anti-tubercular drugs, the spread of resistance poses a threat to developed countries as well as developing countries.

38.5 million people are infected with HIV worldwide, 95% of whom live in developing countries. About 5.8 million new infections were estimated in 1998, two-thirds in sub-Saharan Africa. New life-extending HIV treatments are far too expensive for most individuals and governments in low-income countries.

The Importance of Vaccines

In the long-run, vaccines are likely to be the most effective and sustainable way to fight these three leading killers. A recent National Academy of Sciences report [1996] concludes that development of a malaria vaccine is scientifically feasible. Candidate vaccines have been shown to protect against malaria in several rodent and primate models. Moreover, immunity against malaria infection has been observed in humans after injection of irradiated sporozites, suggesting

that in principle the human immune system can be primed against natural malaria infection.³ The existing Bacille Calmette-Guérin (BCG) vaccine prevents severe tuberculosis in young children, indicating that the human immune system can be primed against tuberculosis infection.⁴ Recently, candidate vaccines have been shown to induce protection against TB infection in animal models. A number of candidate HIV vaccines have been shown to confer protection against infection in monkeys, and to induce immune responses in humans. In each case, however, formidable scientific and technological obstacles remain. For different reasons, all three of these diseases evolve very rapidly, making it difficult to design vaccines which are effective against all strains. Moreover, the specific immune response mechanisms against each of these diseases is not well understood.

Recent advances have given scientists new tools to help overcome these barriers. Advances in immunology have begun to unravel the immune response mechanisms to these diseases. Advances in cloning technology offer new hope in the development of better animal models, as well as the development of novel vaccines which can target many different antigens, and are more likely to be effective in the face of genetic diversity. The genome of the most important bacterium responsible for TB has been fully sequenced, the function and structure of all 9 genes of HIV-1 are well characterized, and the genome of the most important malaria parasite species will soon be completely sequenced.

Inadequacy of Current Research

Current vaccine research for these three diseases is miniscule in view of the human and

³ This could not serve as an effective vaccine, since the sporozites cannot be grown in laboratory culture, the procedure for obtaining them is too expensive and time-consuming to be performed on a large scale, and protection only lasts for about nine months.

⁴ The effectiveness of the BCG vaccines is extremely variable, and protection is short lived. A much

economic burdens involved. According to a Wellcome Trust study, public and non-profit malaria research amounted to about \$84 million in fiscal year 1993, with vaccine research being only a small fraction of the total. This amounts to \$42-\$65 per malaria fatality, compared with research expenditures of up to \$789 per fatality for asthma. Private sector spending is even lower.

The U.S. National Institutes of Health, one of the world's leading funders of basic research, has been spending around \$65 million per year on tuberculosis research (compared with \$2.7 billion on cancer research).

Spending in applied HIV research is overwhelmingly oriented to treatment, which is likely to be infeasible in poor countries, rather than to vaccines. Virtually all candidate HIV vaccines tested worldwide are based on clade B, the strain of the virus transmitted in the United States, Europe, Australia, and Southeast Asia. None of the candidate HIV vaccines are based on clades A, C, or D, the strains most common in Africa, where two-thirds of new infections occur. . It is uncertain whether a vaccine developed for one clade would protect against other clades.

Two reasons underlie the paucity of research on malaria and tuberculosis, and the concentration of HIV research on treatments rather than vaccines, which would be more appropriate for poor countries. First, these diseases primarily strike residents of poor countries, who cannot afford to pay much for vaccines. Second, the market for vaccines is further limited by severe distortions. People who take vaccines may protect not only themselves, but also others, and hence do not receive the full benefit of immunization. Moreover, once pharmaceutical firms have invested hundreds of millions of dollars in vaccine development, governments will be tempted to mandate that vaccines be sold at a price that covers only production costs and not research costs. Governments have this power because they -- or international agencies acting on

improved new vaccine is vital.

their behalf -- are typically monopsonistic or near-monopsonistic vaccine purchasers;⁵ because they can regulate vaccines; and because they can threaten to impose compulsory licensing of vaccines without paying reasonable royalties to the inventor.

Pharmaceutical companies therefore expect that they will sell medicines in the poorer countries at deeply discounted prices relative to those charged in the high-income markets. The five vaccines currently distributed as part of the Expanded Program on Immunization are purchased for a total of about \$1 per dose. For comparison, the U.S. CDC pays \$9.25 per dose for the diphtheria pertussis tetanus vaccine, while the Pan American Health Organization, which distributes the vaccine to Latin America, pays only \$0.05 - \$0.06 per dose. Total UNICEF spending on all vaccines is below \$70 million per year.

The Place of the Vaccine Purchase Fund Within an Overall Public Health Strategy

A successful strategy for controlling these three diseases will involve three components. First, existing technologies, including case management and public education, should be deployed more effectively to help control these diseases until a more fundamental solution, such as a vaccine, is available. Second, scientists in public and university laboratories must continue to conduct basic research, including the work which will lay the groundwork for development of a vaccine. Finally, the private sector needs incentives to use the basic research performed in the public sector to create an actual vaccine. A Vaccine Purchase Fund could provide this third (currently missing) component.

There are two reasons why a commitment to purchase vaccines is preferable to direct

⁵There may be many reasons for the government's large role as vaccine purchaser, including problems of public information regarding vaccine usage and efficacy, economies of scale in vaccine distribution, externalities in vaccine usage, and political factors.

public research funding for the later, more applied stages of the vaccine development process. First, by purchasing vaccines, governments pay for research output, rather than research inputs. This provides stronger incentives for researchers to focus on developing a vaccine, rather than pursuing issues of purely theoretical and scientific interest towards which their intellectual curiosity and career incentives might orient them. Second, if governments make funding decisions, each researcher will try to argue that he or she has found a very promising line of research, and it may be difficult for science administrators to identify which approaches, if any, are worth pursuing. With an assured vaccine purchase, any pharmaceutical firm contemplating pursuing a line of research will have incentives to check whether it is worth risking its own money. Taxpayers pay nothing until an actual vaccine is produced.

Fund Operations

The Vaccine Purchase Fund, through its governing board, would establish and publicize policies for future vaccine purchases, including guidelines on pricing, volume, and criteria for eligibility of vaccines. One approach would be to constitute an international Council of Scientific Advisors to help establish minimum criteria for vaccines (extent of protective immunity, duration of immunity, risk of adverse side effects, ease of handling and administration, etc.). The Board could then announce minimum purchase prices and volumes for vaccines meeting these criteria, as well as price-setting procedures for vaccines which exceed the minimum standards. Alternatively, given that it is difficult to fully specify all the relevant characteristics of a vaccine in advance, the fund could pay vaccine developers based on the estimated number of deaths or Disability-Adjusted Life Years (DALYs) averted by the vaccine. Information revealed through the clinical trials required for vaccine approval would help the scientific advisors estimate this number. A

third approach would be for the Fund to help individual nations purchase eligible vaccines of their choice, by providing funds for vaccine purchases, subject to a modest co-payment that would vary with the income level of the country.

Donor governments will receive voting power on the Board in proportion to their contributions, and will appoint the board members, who would serve long terms to insulate them from political pressures.

Since no expenditures from the Fund will take place until an effective vaccine is available, contributions could take the form either of cash, or of binding commitments to provide funds if and when an eligible vaccine was developed. Contributions could be made over a number of years, according to an initially agreed timetable, so that the Fund will build its endowment over time.

Size of the Fund

For pharmaceutical firms to invest in developing a vaccine, they must expect to recover their research expenditures, plus production costs. It costs approximately \$300 million to develop a typical new pharmaceutical. Developing any of these vaccines could potentially cost several times as much given the scientific challenges involved. Pharmaceutical production costs are typically fairly low per dose, so most vaccine revenue can go towards covering these research costs. In developed countries, new vaccines may sell for as much as \$40 to \$120 per course of treatment. Merck, one of the world's largest vaccine manufacturers, generated about \$847 million in revenue from sales of its seven vaccines in 1998, several of which had been licensed within the past 3 years. The new Varivax vaccine against chickenpox is expected to average about \$177 million in annual revenue for the first 7 years of its sales.

These vaccines could generate comparable revenues at much lower prices, since many

more children who would potentially take them are born each year in developing countries. A malaria vaccine sold at \$10 per immunized child for the 25 million children born annually in Africa would generate \$250 million in revenue, while one sold at \$40 per immunized child would generate \$1 billion in annual revenue. A TB vaccine sold for these prices to the 82 million children born annually in low income countries with high TB incidence rates could generate \$820 million to \$3.3 billion per year. This is likely to be more than enough to spur vaccine development.

If vaccines against each of these three diseases were developed, the annual cost of this program would be \$1.6 billion to \$6.4 billion. Some of the purchase costs may be co-financed through other international institutions, or co-payments from developing countries linked to their income. The delivery cost might be about \$3 per vaccine per child, adding an additional \$480 million to the program cost.

Even if all three of these vaccines were developed and purchased at the upper end of the range, the total costs would be very small relative to the enormous burden of these three diseases. Annual spending would amount to around 7% – 28% of the current \$27 billion in overseas development assistance flows to all low-income countries. Moreover, these estimates are based on full vaccine coverage of all newborns, a relatively generous price, and no co-payments or contributions from other donor countries. Clearly, other arrangements could be envisaged to reduce the overall costs of the Fund.

One measurement of the burden of a disease is the years lost due to premature death and disability caused by the disease, or the Disability Adjusted Life Years (DALYs). A standard way to assess the cost-effectiveness of health programs is the cost per Disability Adjusted Life Year (DALY) averted. The World Bank defines a highly cost-effective health intervention as one that

cost less than \$100 per DALY averted. Moderately cost-effective interventions cost less than \$1000 per DALY averted. An effective malaria vaccine, which reduced the DALY burden from malaria by 80%, could save around 23 million DALYs annually if it were distributed across Africa, at a cost of \$250 million to \$1 billion. Therefore, mass administration of an effective vaccine would cost between \$11 and \$43 per DALY averted.

In low income countries, each death caused by HIV results in an average of 29.4 DALYs (depending on age at infection and duration between infection and death). A vaccine which prevented 80% of the 3.7 million new infections each year in the main target countries could save about 86.1 million DALYs, at a present cost of \$510 million - \$2 billion, therefore costing \$5.90 - \$24 per DALY averted.

Similarly, each case of tuberculosis results in an average of 6.1 DALYs. A vaccine which prevented 80% of the approximately 5.3 million new clinical cases of TB each year in low income countries could avert 25.9 million DALYs, at a cost of \$32-\$130 per DALY.⁶

Even at the very top of this range, these vaccines would be among the most cost-effective health interventions available.

Even expecting, very optimistically, vaccines against each of these three leading causes of death worldwide to be available in 8 years, in order to purchase 160 million vaccinations per year for 10 years, the present value of the fully capitalized fund would be about \$8.7 billion to \$35 billion (assuming a discount rate of 5% per annum). Unfortunately, some or all of these vaccines are unlikely to be available for purchase in only eight years, so spending from the fund is likely to be much less than this, at the cost of tens of millions of lives in the main target population.

⁶ These estimates reflect the cost-effectiveness of these vaccines for the first several years after their deployment. Although it would no doubt be of the same magnitude, precise assessments of cost-effectiveness many

One option would be to start out with a Fund of \$8 billion, enough to purchase immediately 160 million vaccinations at \$10 per immunized child for five years. There could be a prearranged schedule according to which prices would gradually increase over time. If a Fund of this size turned out to be insufficient to motivate research, the amount in the Fund would gradually increase, rising to a maximum of \$35 billion. The Fund would include sunset provisions so that the program could be cancelled if some scientific development should render one or more of these vaccines unnecessary, for example by sustainably reducing the burden of disease by half. Under these circumstances, the funds could be returned to the donors or used for other international public health priorities.

The Vaccine Purchase Fund is overwhelmingly justified in terms of cost-effectiveness, and offers the best chance to mobilize the private sector in the crucial effort against the world's three leading infectious killers. It also offers the public the assurance that public funds will be used only when an appropriate vaccine has been developed. It is an opportunity which should not be missed.

years after deployment will require more complex epidemiological methods using population projection models.