Accelerating an AIDS vaccine for developing countries: Recommendations for the World Bank

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Acronyms and Abbreviations

AFRVP	Africa Region, Office of the Vice-President
AIDS	acquired immune deficiency syndrome
ANRS	Agence nationale de Recherches sur le SIDA
APL	Adaptable Program Loan
AVAC	AIDS Vaccine Advocacy Coalition
CDC	U.S. Centers for Disease Control and Prevention
DEC	Development Economics and Chief Economist
DGF	Development Grant Facility
DPT	diptheria-pertussis-tetanus
FPR	Financial Policy and Risk Management
FPS	Financial Products and Services
FRM	Resource Mobilization Department
GAVI	Global Alliance for Vaccines and Immunization
HD	Human Development
HDN	Human Development Network
HDNHE	Health Nutrition and Population Team
HNP	Health, Nutrition and Population
Hib	haemophilous influenza-type B
HIV	human immunodeficiency virus
IAVI	International AIDS Vaccine Initiative
IBRD	International Bank for Reconstruction and Development
IFC	International Finance Corporation
IDA	International Development Association
LEG	Legal Department
LIL	learning and innovation loan
MIGA	Multilateral Investment Guarantee Agency
NGO	nongovernmental organization
NIH	U.S. National Institutes of Health
OECD	Organization for Economic Cooperation and Development
R&D	research and development
RSB	research support budget
SASHP	South Asia Operations
SRM	Strategy and Resource Management
TB	tuberculosis
TFC	Trust Funds and Cofinancing Department
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Executive Summary

This paper presents the findings and recommendations of the World Bank AIDS Vaccine Task Force, formed in April 1998 to identify how the institution can accelerate the development of an AIDS vaccine for developing countries, as part of its broader program to combat AIDS and in collaboration with its international and development partners.

The AIDS epidemic poses a severe threat to economic development and poverty alleviation, particularly in Sub-Saharan Africa, where the epidemic is most advanced. The World Bank has already taken important steps to reduce the impact of the AIDS epidemic through lending for AIDS prevention and care, analytic publications like *Confronting AIDS*, participation in international partnerships, like UNAIDS and the International AIDS Vaccine Initiative (IAVI), and launching a new anti-AIDS initiative in Sub-Saharan Africa. Nevertheless, progress on potentially one of the most important interventions—a preventive AIDS vaccine—is slow. Further, there is no assurance that once developed a vaccine will be accessible, affordable, or appropriate for use in developing countries.

While there have been substantial public investments in basic research and important initiatives like IAVI to focus subsidies on vaccine candidates for developing countries, this is not likely to be enough to generate the public-private partnership necessary for the rapid development of an AIDS vaccine for developing countries. The technology for an AIDS vaccine is an international public good, of global benefit irrespective of who pays for its development. This creates a "free-rider" problem in which individuals and governments will be willing to pay less than the value of the benefits they receive. Further, the private sector is unlikely to recoup research and development costs for health technologies that primarily benefit countries with low ability to pay. As a result, both public and private investment in AIDS vaccine development is low.

The World Bank, as a major financier of development programs with good access to high-level policymakers in developing countries, may have a comparative advantage in addressing some aspects of these market failures that would complement the ongoing efforts of other agencies. Based on studies of the economics of AIDS vaccine development and demand, review of a broad range of existing and potential new mechanisms to promote an AIDS vaccine, and consultations with industry, international donors, and developing countries, the AIDS Vaccine Task Force recommends that the institution pursue four actions that will aid in the international effort:

1. Enable developing countries to be better partners in AIDS vaccine development, through policy dialogue and lending;
2. Expand childhood immunization rates in developing countries, through policy dialogue, lending, and participation in international initiatives, to strengthen the market and infrastructure for existing vaccines;
3. Generate new knowledge on the potential public and private demand for an AIDS vaccine in developing countries and its strategic use in AIDS prevention programs; and
4. Adopt new mechanisms to ensure adequate finance for an AIDS vaccine in developing countries that will serve as a credible assurance of a future market.

Accelerating an AIDS vaccine for developing countries: Recommendations for the World Bank

I. The development impact of AIDS and the need for an AIDS vaccine

HIV/AIDS is taking a huge toll on developing countries. Worldwide, 33.6 million people are infected with HIV and 16.3 million have already died of AIDS. HIV/AIDS is the leading infectious killer worldwide—surpassing TB and malaria—and the fourth leading cause of death. It has reached every country, industrialized and developing. However, the epidemic is most severe in developing countries: More than nine out of every ten HIV infections are in developing countries, and two-thirds are in Sub-Saharan Africa. India has the largest number of infected persons of any country in the world—4 million—and severely affected countries in East Asia are already feeling the impact. Despite efforts at prevention, HIV continues to spread. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), more than 15,000 people become infected daily.

AIDS is wiping out decades of progress in improving the quality of life of the poorest people. Improving the length and quality of life is the objective of national and international development policies, including investments financed by the World Bank in low-income countries. Between 1950 and 1990, enormous progress was made in this respect: life expectancy in developing countries rose from 40 to 63 years (World Bank 1997). However, AIDS—a single, fatal, infectious disease for which there is no cure—has single-handedly reversed this progress. Countries like Burkina Faso, Côte d'Ivoire, and Zimbabwe have lost 10-20 years in life expectancy from AIDS. There has even been an impact in countries where the epidemic is less advanced—Brazil and Haiti have lost five years of life expectancy and Cambodia, Myanmar and Thailand 2-3 years, so far.

AIDS is worsening the prospects for economic development and poverty alleviation. AIDS is having an enormous impact on the World Bank's clients and on existing programs to alleviate poverty—more so than for any other health problem. Because it is a sexually-transmitted disease, AIDS primarily is killing adults in their most productive years, robbing economies of their most productive members and households of their breadwinners and care givers. AIDS morbidity and mortality are exacerbating poverty and will likely have profound effects on private investments in children's human capital, in countries where human capital is low already. Finally, AIDS is putting enormous strains on the fragile health systems of developing countries: AIDS presents itself as a multitude of infections that develop as the immune system weakens and large numbers of people are infected. These human and economic impacts, plus the opportunity in a number of countries to invest early in prevention and avoid these consequences, justify the key interest of the World Bank in HIV/AIDS prevention.

When backed by serious political commitment, programs to change behaviors that spread HIV/AIDS have been successful in slowing the epidemic. At present, there is no cure for HIV/AIDS and no preventive vaccine. Anti-retroviral therapies that have extended the lives of patients in industrialized countries are out of reach in the poorest developing countries because they are expensive and complex to administer effectively in these settings. Furthermore, these therapies are not a cure and do not eradicate the virus. Viral resistance to these drugs is growing. The best hope for reducing the spread of HIV and its human and economic impacts is

through behavioral change—reducing the number of sexual partners, raising condom use, and promoting safer injecting behavior. Governments like those in Australia and Thailand have shown that these measures *can* have an impact in reducing the spread of HIV on a national scale. Pilot projects and interventions in countries like Brazil and India have also been successful. However, too few governments have shown the level of political commitment necessary for an effective response. The World Bank and its development partners, including the Joint United Nations Program on HIV/AIDS (UNAIDS), are continuing their efforts to raise the level of policy dialogue on AIDS as a development issue, to obtain greater political commitment and more effective programs. Since 1986, the World Bank has lent $966 million for HIV/AIDS prevention and care in 81 projects in 52 countries, primarily for information campaigns, behavioral change (like raising condom use), and treatment of sexually transmitted diseases.[1] Substantial benefits could be gained in terms of slowing the epidemic through concerted public action on prevention, and this strategy must be vigorously pursued.

An AIDS vaccine is urgently needed to improve the effectiveness of prevention programs in countries at all stages of the epidemic. A vaccine that is effective and affordable would greatly improve the prospects for reducing the scope of the epidemic worldwide. Immunization of those most likely to spread infection to others could break the transmission chain in the population through reducing the number of secondary infections. In addition, a vaccine would be an important prevention tool for people with low-risk behavior—like many monogamous women—who are primarily exposed to the risk of HIV infection through the behavior of their partners or spouses. At present, there is little that they can do to reduce that risk, particularly if their ability to negotiate condom use is low and if they want to have children. Given the long incubation period of HIV and the large numbers of people already infected, a vaccine will not be a panacea. However, it will be an important part of the response and can have a dramatic impact on the spread of infection.

While scientists now believe that an AIDS vaccine is scientifically feasible, market failures and other obstacles are likely to impede its development and development of other international public goods for poor countries. Successful vaccine development requires both public and private finance—in the latter case, to transform the science into a product that can be manufactured and sold on a large scale. However, there are at least two reasons why private investment in an HIV vaccine is less than the socially optimum amount:

- The technology for an HIV vaccine is an *international public good*. Regardless of which firm or country develops it, the benefits of an HIV vaccine technology will be global.

- HIV/AIDS is primarily affecting developing countries with low ability to pay.

Thus, the incentives to invest in the R&D for an AIDS vaccine are low because the developer will not be able to recoup revenue from many who would benefit. These issues equally affect development of other important vaccines to control infectious disease, such as malaria and

[1] In addition, the World Bank has contributed $18 million over the past 13 years to the Global Programme on AIDS and its successor, the Joint United Nations Programme on HIV/AIDS (UNAIDS) through the Development Grant Facility (DGF).

tuberculosis, in low-income countries. Further, even after the technology is developed, it can take 10-15 years for prices drop low enough for vaccines to be accessible to developing countries. At the current rate of investment it is could be several decades before an effective AIDS vaccine becomes available in OECD countries. If the international community relies on the existing incentive structure, it will take even longer to develop a vaccine that is effective and affordable in developing countries and to ensure its availability. It is precisely because of these market failures of international public good that accelerating this vital technology will require the concerted action of the international community.

II. The AIDS Vaccine Task Force: Objectives and Findings

Objectives

In April 1998, at the initiative of Human Development (HD) and Development Economics and Chief Economist (DEC) vice presidencies, an institution-wide Task Force was set up to explore ways in which the World Bank could accelerate the development of an AIDS vaccine for developing countries, as one element of its broader program to combat AIDS and in collaboration with its international and development partners.[2] Up to that point, the Bank's main involvement with AIDS vaccines was through its contribution to the International AIDS Vaccine Initiative (IAVI) through the Development Grant Facility (DGF)[3] and its participation on the IAVI Board of Directors. The mandate of the AIDS Vaccine Task Force was to examine new and innovative ways to encourage development of an AIDS vaccine—an international public good—that would complement the ongoing activities of other organizations.

The Task Force embarked on a four-pronged strategy to address this issue:

- Analysis of ***industry's perspective*** on research and development of an AIDS vaccine
- Review of existing information on the ***potential demand*** for an AIDS vaccine in developing countries
- Evaluation of ***existing instruments and proposed new mechanisms*** that could be used to address the market failures leading to under-investment in an AIDS vaccine
- Broad ***consultation*** with industrialized countries, the European Commission, UNAIDS, IAVI, policymakers in developing countries, industry, and Bank staff on their perspectives on AIDS vaccine development and the best course of action for the World Bank

The effort was funded by a grant of $265,000 from the 1998 Innovation Marketplace and staff time contributed by HD, DEC, TFC and FRM.

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[2] The Task Force includes representation from the Human Development Network (HDN), Development Economics (DEC), Africa Region (AFRVP, ACTAfrica), Resource Mobilization (FRM), Trust Funds and Cofinancing (TFC), Financial Products and Services (FPS), Financial Policy and Risk Management (FPR), Legal (LEG), Strategy and Resource Management (SRM), South Asia Operations (SASHP), the International Finance Corporation (IFC), IAVI, and UNAIDS. The Task Force is overseen by Callisto Madavo, Eduardo Doryan and (until December 1999) Joseph Stiglitz.

[3] 1998: $1 million ($400,000 from the Global Forum for Health; $600,000 from the DGF); 1999: $940,000 from the DGF; 2000: $700,000 from the DGF.

Findings

The recommendations of the Task Force are based on its findings on current spending on vaccine development, why industry is not investing, the potential demand for an AIDS vaccine, the scope of the options considered for the Bank, and the results of consultations with development partners.

1. The status of AIDS vaccine for developing countries

Scientists are now convinced that an AIDS vaccine is scientifically feasible, but progress has been slow. While more than 25 candidate AIDS vaccines have been developed and tested for safety and immune response in small groups of volunteers, only one candidate vaccine is currently in large-scale efficacy trials in a human population.[4] The results of those trials will not be available before the fall of 2001. The correlates of immunity for HIV are unknown—those who are infected with HIV eventually become ill, despite antibodies their bodies generate to fight the infection. Thus, there is considerable debate about the likely effectiveness of the one candidate in the field, which relies only on the humoral branch of the immune system, the part that generates antibodies. To make more rapid progress, more approaches need to be tested in parallel in large efficacy trials, including those that target cellular immunity—the other arm of the immune system.

Global expenditure on research and development (R&D) for an AIDS vaccine is quite low, considering the huge public health significance of the AIDS epidemic. Total global research and development (R&D) for preventive HIV vaccines in both the public and private sectors in 1999 was on the order of only US$300 million.[5] Most of this is public expenditure and is focused on basic research, as opposed to applied research and vaccine development. Privately funded R&D on HIV vaccines was in the range of $50-$124 million per year and fewer than 200 scientists in the private sector worldwide were dedicated to AIDS vaccine-related work, some of it subsidized by the public sector (Batson and Whitehead 1999, Rosenhouse 1999b). The incentive for investing in AIDS treatment is far greater. Demand for treatment is always more robust than for prevention, and roughly 3 million of those infected with HIV worldwide live in industrialized countries where purchasing power is high. An estimated $2.9-$3.3 billion was spent for purchase of anti-retroviral drugs for AIDS patients in North America and Europe in 1997 (Hogg and others 1998).[6] Middle-income countries are also becoming important purchasers of these expensive drugs, which must be taken continuously for the rest of the patient's life at a cost of $7,000-$12,000/year. In 1998, the Brazilian government spent $303 million on anti-retroviral drugs for treating AIDS patients, and in 1999 was projected to spend $544

[4] VaxGen is supporting a trial of a bivalent B/E gp120 envelope vaccine in Thailand and is also conducting a US trial of a clade B vaccine. That vaccine is administered in six doses over 18 months.

[5] Based on consultation with IAVI, the US National Institutes of Health (NIH), and the AIDS Vaccine Advocacy Coalition (AVAC), global public and private (profit and non-profit) spending in 1999 was in the range of $283 million-$351 million (Rosenhouse 1999b).

[6] The authors assumed that a quarter of all HIV-positive persons in those countries are using anti-retroviral therapy at any point in time; they used the average 12-month drug costs in British Columbia as the average annual expenditure per patient treated in North America and Western Europe.

million.[7] As a result of these market incentives, an estimated $2 billion annually is being spent worldwide on research for AIDS treatment, much of it in the private sector.[8]

Existing research is focusing on an AIDS vaccine that may be of limited use in developing countries. There are 10 or more subtypes of HIV in the world. Research to date has focused on a vaccine for HIV subtype (or class) B, which is the predominant strain in North America, Europe, Australia, and Japan. However, the predominant subtypes in Sub-Saharan Africa and Asia—where the epidemic has hit hardest—are subtypes A, C, D, and E. There is no guarantee that a vaccine based on subtype B will be effective against these other subtypes. Even if a vaccine is not specific to a subtype of the virus, the effectiveness could vary across populations, since cellular immunity is influenced by the genetic makeup of the individual. According to IAVI, only about $5-10 million per year is being spent on AIDS vaccines that are specifically designed for use in developing countries. In its 1998 "Scientific Blueprint", IAVI estimated that it would cost $350-$500 million to develop an AIDS vaccine for world use by 2007 (IAVI 1998).

Even if the AIDS vaccines currently under development are shown to be technically efficacious for the strains of HIV in developing countries, they may not be affordable or effective in low-income settings. An HIV/AIDS vaccine for use in developing countries should be inexpensive and easily administered (preferably oral), require a minimum number of doses, confer long-term immunity, tolerate heat, and have a long shelf life. In addition, since it would be costly to screen every potential recipient for HIV, the preventive vaccine should not be harmful to people who are already infected.

The "gap" in time between AIDS vaccine development and its availability in low-income countries will likely be large. Historically, vaccines become available and affordable for developing countries after the market in OECD countries has matured. Only after substantial saturation of the OECD market do competition and over-capacity generate the willingness among firms to sell their product at marginal prices that are affordable in developing countries. For example, the hepatitis B vaccine appeared in 1982 but only effectively became available in developing countries after 10-15 years, when its price dropped from $150 to about $2-4 for the 3-dose vaccine series. Thus, even when a new product becomes available in OECD countries, it has historically taken many years for the product to become available and affordable in developing countries.

2. Why isn't industry investing?

In the fall of 1998, the Task Force commissioned a study, co-funded by IAVI, of industry's perspective on HIV/AIDS vaccine research and development (Batson and Whitehead 1999). Seventeen pharmaceutical, vaccine and biotechnology firms were interviewed. The sample included firms that had significant AIDS vaccine programs, large firms that had not chosen to invest in AIDS vaccines, and a few that had previously invested but discontinued their programs. In addition, experts from seven institutions were interviewed. The study concluded that

[7] Pedro Chequer, Brazil AIDS Control Program (personal communication, 7/99).

[8] The NIH budgeted $482 million for research on therapeutics and $526 million for research on etiology and pathogenesis of HIV/AIDS in FY 1999, out of a total AIDS research budget of $1.73 billion.

scientific obstacles remain a short-term impediment to AIDS vaccine development and that most companies do not believe there will be a realistic commercial return on the required investment for an HIV vaccine in developing countries.

The potential market for an AIDS vaccine is perceived to be small and confined to OECD countries. Private investment in research on an HIV/AIDS vaccine is justified mainly on assessment of the potential market in high-income, OECD countries. Some firms believe that there will be substantial demand for a safe and efficacious HIV vaccine in OECD countries similar to that for the hepatitis B vaccine. Other firms believe that because the size of the risk group is small in industrialized countries and therapies have been successful in extending the life of patients, the OECD market will be small at the outset and slow to develop. The market for an AIDS vaccine in developing countries is generally not a factor in private sector R&D decisions. The more involved was a firm in supplying vaccines to developing country markets already, the lower was its estimate of the potential sales of an HIV/AIDS vaccine in those markets. Even firms that anticipated some developing country demand expected that their R&D costs would be recouped in the OECD market. Lower-than-expected uptake of new vaccines developed since the 1970s, like hepatitis B, yellow fever, and haemophilous influenza-type B (Hib), suggested that development of future "high-priority" vaccines like an AIDS vaccine may not be rewarded by adequate sales.

The late-stage development costs of an HIV vaccine are high and the probability of success uncertain. There are many steps in bringing new vaccines to the market, a process that can take decades (see Box 1). Ultimately, a large-scale trial is needed to show the efficacy of any given vaccine candidate, but because of the huge expense of such trials ($10-30 million), industry is unwilling to launch them unless there is a high degree of certainty that the product will prove efficacious. Efficacy trials also involve some limited investment in manufacturing process and plant, investment that is lost if an efficacy trial does not result in a commercial product. There has been no good animal model for an AIDS vaccine. The correlates of immune protection from HIV remain unknown. Safety issues have prevented the testing of live attenuated or whole killed vaccine candidates in humans. Thus, empirical testing of alternative approaches is likely to be necessary to discover an effective vaccine, but the probability of success for any one approach is perceived to be low. The returns for an AIDS vaccine are far in the future and therefore highly discounted in investment decisions. Even after these scientific hurdles and uncertainties have been overcome, the perception of the lack of a viable market in developing countries will limit the interest of firms in adapting the product for that market where the public health need is greatest.

Box 1: Vaccine clinical trials

Once a vaccine has been shown effective in animal models, it must be tested in people. These studies, called clinical trials, determine the safety, immunogenicity, and efficacy of candidate vaccines. They provide the data necessary for regulatory agencies to decide whether or not a product should be licensed for use in their market. Before a vaccine will be recommended globally, efficacy studies are also required in different epidemiological sites (Asia, Africa, Europe, North America, Latin America). Often, governments will also require efficacy studies be repeated in their own country before agreeing to license a product. There are three types of human clinical trials that must be conducted without exception before a vaccine will be considered for licensure.

Phase I: Safety Phase I trials determine the safety and preliminary dosing studies of a vaccine candidate in a small sample of 10-30 people. They are generally conducted in healthy adults at low risk of HIV infection, take six months to one year, and cost about $1-3 million.

Phase II: Immunogenicity. Phase II trials measure the safety and immune response in a larger sample of several hundred volunteers. They measure whether the vaccine candidate is stimulating the immune function or some other marker that may be indicative of protection. These studies are usually conducted in persons at high risk of HIV infection, typically take 6-24 months, and cost roughly $2-4 million.

Box 1: Vaccine clinical trials (contd.)

Phase III: Efficacy. In the third and final phase before licensure, the efficacy of the vaccine candidate in protecting against disease is tested in a large population (5,000 to over 50,000 people). Efficacy is measured as the difference between rate of disease in people who receive the vaccine and in others who receive a placebo. The lower is the incidence of the disease in the population or the smaller is the anticipated impact of the candidate vaccine, the larger must be the sample of people who participate to demonstrate an effect. These studies take 2-4 years and can cost $10-30 million, depending on the size of the study.

A high level of efficacy does not guarantee an equivalent level of effectiveness when a vaccine is offered in the field. Efficacy trials typically select healthy volunteers and administer the vaccine or placebo under very carefully controlled conditions. Neither of these are assured in field conditions in developing countries. In a number of instances, so-called "Phase IV" "effectiveness" trials have been conducted to demonstrate the true costs and effectiveness of vaccines in typical field conditions.

3. The potential demand for an AIDS vaccine in developing countries

In the face of the huge public health threat and development impact of HIV/AIDS, one might wonder why the potential demand for an AIDS vaccine is in question. There are 2.5 billion adults of reproductive age in developing countries who are not infected with HIV, including 260 million in the hardest-hit region, Sub-Saharan Africa. This is the number of people who might benefit today from an AIDS vaccine. In addition, almost all children under the age of 15 are uninfected and would benefit when they reach adulthood. However, this "need" is not the same as the "demand" for the vaccine, which is the number of doses that would be purchased by government and private individuals at different prices.

The size of the potential market—the sum of public and private willingness to pay for an AIDS vaccine—is key to private firms' R&D investment decisions and is at the heart of the market failure surrounding AIDS vaccine development. Because of the positive externalities of vaccination, vaccine purchase and immunization are usually heavily subsidized by the public sector, and in the case of an AIDS vaccine the greatest need is in the countries with lowest ability to pay. Since an AIDS vaccine is not the only way of preventing the epidemic, the issue of the cost-effectiveness of AIDS vaccine relative to other preventive measures is likely to be an important factor in evaluating the public willingness to pay in poor countries. **Knowledge of the potential demand is equally valuable to the international community, to assess the level of financial support required for eventual purchase of vaccine for the poorest countries and the types of policies that will induce higher private investment.**

Industry's assessment of the potential demand for an AIDS vaccine is based on public sector demand for other childhood vaccines in developing countries. Global spending on childhood vaccines is estimated at $4 billion annually, of which spending in low- and middle-income countries accounts for only about $200 million, most of it financed by the public sector. Private purchase of childhood immunizations in developing countries is very small. The price of all four basic childhood vaccines[9] combined is less than US$1 per child. Nevertheless,

[9] BCG, oral polio vaccine (4 doses), diptheria-pertussis-tetanus (DPT, 3 doses), and measles.

even at these low prices, coverage is far from universal—about 70-80 percent of children under one year of age. The total cost of delivering childhood vaccines to infants in the poorest developing countries has been estimated at about $20 per child (WHO 1999). In contrast, the initial price of an HIV/AIDS vaccine is likely to be measured in dollars or tens of dollars, not cents. The costs of administering an HIV immunization program could also be higher, since immunization delivery systems for other groups in the population, like young adult, sex workers, truck drivers, and other high-risk groups, would have to be set up. Given the small market for childhood immunization at low prices and the likelihood that an AIDS vaccine will cost substantially more, the presumption by industry is that the market for an AIDS vaccine in developing countries would not be large enough to warrant the investment.

However, both public and private willingness to pay for an AIDS vaccine may be substantially greater than implied by current spending on childhood vaccines. First, private demand for an AIDS vaccine may be greater because AIDS is nearly 100% fatal and primarily affects prime-age adults with the means to pay for their own vaccination. In heavily-infected countries (some of which have infection rates exceeding 10% of the population), the perceived risk of infection is quite high and the private willingness to pay may be large, despite low incomes. Second, public sector willingness to pay for an AIDS vaccine may also be greater because AIDS has far greater public health significance and economic impact than any of the childhood diseases. Countries like Brazil are already spending huge sums on AIDS treatment. Third, the market for childhood vaccines in developing countries represents a "maintenance" phase for newborn children. Older children were immunized in previous years. When an HIV/AIDS vaccine becomes available, there will be initial large "catch up" demand among adults and children, since none of the population will have been previously immunized.

The evidence to date on the potential demand for an AIDS vaccine is speculative. There have been no published empirical studies of the public or private willingness to pay for an AIDS vaccine in developing countries. Demand will depend, among other things, on:

- the price of the vaccine and the costs of delivering it;
- its characteristics—efficacy, safety, the number of doses, and ease of administration;
- the ability to pay in developing countries and willingness to pay by international donors for the poorest countries or the poorest people;
- the perceived vulnerability of different populations to becoming infected, their potential for spreading the virus, and their political clout; and
- the costs and effects of alternative prevention measures (like condom use) and treatments.

One calculation suggests—assuming that the vaccine is relatively efficacious, that countries were willing and able to buy a vaccine that cost less than the present discounted value of medical treatment for AIDS, and that the marginal cost of producing the vaccine were $10—766 million doses would be purchased worldwide, of which 235 million would be in developing countries (Bishai et al 1999). This would translate into an initial global market of nearly $8 billion. However, even when the benefits of HIV immunization are large, the ability to pay for a costly vaccine is likely to restrict the market and lead to rationing by public authorities. Targeting an expensive vaccine to those most likely to spread HIV can improve its cost-effectiveness. In Thailand, a middle-income developing country with one of the most severe epidemics in Asia,

coverage of the groups most likely to spread HIV (sex workers, injecting drug users, male STD patients, transport workers) would initially require 532,000 doses and 15,000 doses annually thereafter (Tangcharoensathien et al 2000). Were the vaccine to cost $20, this would require $10.6 million initially, or 27% of the 2000 AIDS program budget. To date, however, no study has attempted to measure empirically the "willingness to pay" for an AIDS vaccine in the public or private sectors.

The low efficacy of the earliest AIDS vaccines may initially constrain public and private demand. The first vaccines shown to have any efficacy are likely to be relatively expensive and substantially less than 100% efficacious. Epidemiological models have shown that wide coverage of a vaccine—even with low efficacy—can have significant impacts on the spread of infection in the population (Anderson and Garnett 1996; Anderson et al 1995; Haber et al 1995). However, these results assume that a vaccine would build on the success of existing prevention measures, like increased condom use. Immunization with an HIV/AIDS vaccine might also lead recipients to increase risky behavior, which could worsen the epidemic if the vaccine is only somewhat efficacious. In Thailand, for example, an enormously successful AIDS prevention campaign has raised condom use in brothels to well over 90% and lowered the HIV infection rate among young army conscripts by half. Immunizing sex workers and their partners with a partially effective AIDS vaccine could slow the epidemic even further, provided that condom use remains high (Tangcharoensathien et al 2000). If condom use were to drop, HIV transmission might actually increase. It is very difficult to predict public demand and resource needs for an AIDS vaccine without understanding these tradeoffs in different settings. **A better understanding of the cost-effectiveness of an AIDS vaccine relative to other behavioral prevention measures when it is less than fully efficacious and the extent to which a vaccine will substitute, complement or require increased funding of existing prevention efforts is essential for assessing the public sector demand and future financing needs.**

4. Mechanisms for the World Bank to accelerate an AIDS vaccine

World Bank activities to accelerate development of an AIDS vaccine should complement the efforts of other agencies: international agencies like the WHO/UNAIDS joint program on AIDS vaccines; national research institutes like the U.S. National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), France's Agence Nationale de Recherches sur le SIDA (ANRS), and other public research institutes in developed and some developing countries; multilateral donors like the European Union, which has its own task force and activities for AIDS vaccine promotion; national and international NGOs, like the International AIDS Vaccine Initiative (IAVI) and the AIDS Vaccine Advocacy Coalition (AVAC). These organizations are involved in activities such as advocacy, technical expertise, capacity building, direct funding for basic research or (in the case of IAVI) for applied research for a vaccine for developing countries. Each is making an important contribution, although overall spending on developing an AIDS vaccine—particularly one for developing countries—remains inadequate. Each also has a comparative advantage related to its mandate. The European Union governments of industrialized countries are in unique positions to offer tax breaks to industry for certain types of R&D or to negotiate patent law, both of which affect incentives to invest in R&D.

There are nevertheless areas in which the World Bank has a comparative advantage in helping to accelerate an AIDS vaccine. As one of the world's premier financial institutions with a mission of poverty alleviation, the World Bank has extensive contacts with policymakers in developing countries and high credibility in economic analysis of developing countries. Its large lending portfolio and resource base could potentially have an important influence on firms' assessment of the future market for an AIDS vaccine in developing countries. However, it is also first and foremost a lending institution with limited technical or scientific expertise on AIDS vaccines. It is organized operationally around country-specific programs and budgets, but participates in international initiatives in health, agriculture, and the environment, for example, through a very small facility for grants.

The Task Force evaluated many potential mechanisms for stimulating development and rapid availability of an AIDS vaccine that is effective and affordable in developing countries. The mechanisms, which build on the Bank's mandate as a lending institution, fall within three main approaches:

Policy dialogue. The Bank's credibility and access to treasury and finance officials, as well as development/health leaders, puts it in a strong position to engage all actors in the policy dialogue surrounding the development impact of AIDS and the key responsibility of government to prevent the epidemic. Such a dialogue will condition the effectiveness of any other instruments or mechanisms that the Bank might propose to accelerate an AIDS vaccine, and can also help to broaden and reinforce the commitment within governments and thereby buttress the work of agencies with a more specialized health focus. Building on this dialogue on HIV/AIDS, the Bank can raise the level of political commitment to support HIV/AIDS vaccine research and development and help to forge partnerships between developing countries, industry, and international donors.

"Push" mechanisms. These are interventions that the World Bank could undertake to reduce directly the costs and risks of AIDS vaccine R&D. The main mechanisms for Bank involvement in "push" interventions are through its contribution to IAVI (see Box 2) and lending to developing country governments for key inputs for vaccine development or clinical trials.

Box 2: IAVI

The International AIDS Vaccine Initiative (IAVI), is an international non-profit, non-governmental organization set up by the Rockefeller Foundation in 1996. IAVI's mission is to ensure the development of safe, effective, accessible preventive HIV vaccines for use throughout the world, including developing countries, by stimulating investment and demand for HIV vaccines. IAVI works with both the public and private sectors, pursuing this objective through advocacy, targeted support to R&D for novel vaccine approaches, and measures that reduce obstacles to private investment. In the last year, IAVI worked with academia and industry to launch two vaccine development partnerships in sub-Saharan Africa. It has also helped set up national vaccine efforts in China, India, and South Africa, is about to launch two more Vaccine Development Partnerships for Africa in the coming months and is developing HIV vaccine technology transfer projects with China and India. The World Bank was a founding partner of IAVI. Since IAVI's inception, World Bank finance has grown from $200,000 in 1997 to roughly $1 million annually in 1998 and 1999, funded primarily through a grant from the Development Grant Facility (DGF). The Bank is represented on IAVI's Board of Directors.

"Pull" mechanisms. These mechanisms raise the expectation of a future return for a safe, affordable, and low-cost vaccine that is effective in developing countries. In many cases, the mechanisms would also reduce the lag between development of the technology and availability on the ground in developing countries. Given the instruments, experience, and comparative advantage of the World Bank, the Task Force considered several "pull" mechanisms, among them:

- *Expanded lending for existing vaccines* and immunization infrastructure
- A *vaccine purchase fund*, capitalized now or in the future, financed by donors or developing countries (see Box 3)
- *Contingent loans and guarantees*, in which countries contract now to purchase a future vaccine (see Box 4)
- *Generating knowledge* of the potential public and private demand for an AIDS vaccine and its strategic use

The Task Force examined the advantages, disadvantages and implementational issues of all of these interventions, which are discussed in a background paper (Rosenhouse 1999a). While the "pull" instruments focused on what might be done under the existing mandate, additional measures to assure future use through modest reform of IDA were also debated. Regulatory policies on patents and liability in industrialized countries may also have an important effect, but they are not easily influenced by the World Bank and thus were not included in the menu of options discussed by the Task Force. A successful strategy is likely to incorporate intense policy dialogue accompanied by both "push" and "pull" interventions, and the simultaneous involvement of numerous international actors.

Box 3. Vaccine purchase fund.

A fund could be established for the purchase of HIV vaccines for the poorest countries or to provide matching funds provided by middle-income developing countries. The fund would be capitalized by contributions primarily from industrialized countries, although middle-income countries would also be invited to contribute. It could be financed now and accrue interest, or in the future through government pledges or promissory notes. The fund monies would become available to purchase AIDS vaccines only if and when a vaccine was developed that meets very specific criteria, in terms of price, effectiveness, and applicability for developing countries. This fund could be managed by the World Bank through an independent facility, according to agreed-upon access rules and a "trigger" mechanism that defines when the criteria for a vaccine have been met.

The World Bank has ample experience in setting up and administering trust funds created for specific purposes. The Global Environmental Facility (GEF) and the Heavily Indebted Poor Countries Initiative (HIPC) are two examples. It is also quite experienced in dealing with donor pledges, as they constitute the bulk of IDA's resources. However, the trust funds administered by the World Bank generally disburse soon after they are replenished, and the government promissory notes that finance IDA are valid over a 3-year time frame. In contrast, an HIV/AIDS vaccine for developing countries could take 10-15 years to develop.

From the perspective of industry, purchase fund—if large enough and financed now—would seem to be a highly credible precommitment to purchase vaccines and could disburse funds rapidly. The main issue is whether the international community would be willing to tie up such a large sum of money for 10-15 years while a vaccine is developed and whether such a fund is politically viable. It is unclear how credible industry would view purchase fund capitalized in the future, and how quickly the notes could be called in to finance purchase of vaccines.

Box 4. Contingent loans and credits

The World Bank could issue IBRD loans and/or IDA credits to developing countries to finance the strengthening the borrower's vaccine delivery capacity and the purchase of HIV/AIDS vaccines when a suitable vaccine is developed. The loans or credits would be agreed to in the present; part or all of the disbursements would be contingent on the development of a viable vaccine, one that meets the same criteria as might be established for a purchase fund.

The World Bank has some experience in contingent lending. It has made loans to back up government facilities that provide guarantees against commercial and political risk to the private sector (South Africa, Moldova, Ukraine). These loans only disburse if claims are made, and the Bank makes these types of loans only when conditions do not permit the involvement of the Multilateral Investment Guarantee Agency (MIGA), which cannot cover short-term non-equity transactions, or IFC, which cannot lend to governments. Contingent loans have also been used to reduce the impact of liquidity shocks on the borrower's banking system in the event of severe capital flight (Argentina). However, the period over which risk is covered in both cases has never exceeded five years, and these have never been used in the health sector. Given the unknown demand for funds for alternative uses in the distant future by both the World Bank and client countries, the main issues for contingent loans for an HIV/AIDS vaccine are, first, whether the IBRD and IDA would be willing to commit resources with such a long time horizon, reducing the availability of resources for other problems in the future and, second, whether developing countries would be willing to borrow on a contingent basis so far out into the future. A related issue is whether such "promises to borrow" are viewed as credible by firms that invest in AIDS vaccine R&D.

The World Bank has recently developed a new lending instrument—the Adaptable Program Loan (APL)—that is designed to fund a program of activities to achieve an agreed upon development objective over a long-term horizon. The project is designed as a sequence of loans for phased support of the program, with agreed objectives, triggers, and indicators of outcomes/impacts for each phase of the program. Conceivably, an APL might be adapted to the issue of AIDS vaccines (see Rosenhouse 1999a).

5. Consultations with development partners

Prior to making its final recommendations, the AIDS Vaccine Task Force sought the advice and views of many key audiences within and outside of the World Bank: the HNP Sector Board; the Bank's Executive Directors (informally and as part of related seminars on AIDS and on vaccines); representatives of the G7 treasuries and foreign affairs ministries; the European Commission; the U.S. National Institutes of Health; World Bank staff in resident missions; developing country policymakers; NGOs; developing country scientists; and industry representatives.[10] Five formal consultative meetings were jointly organized with local World Bank offices, the national AIDS control programs, UNAIDS, and IAVI, which asked participants to

[10] In addition, the findings have been disseminated at numerous international meetings on vaccines—the Global Alliance for Vaccines and Immunization (GAVI) Task Force on Financing, the American Symposium on Microbiology, a conference on "Vaccines for Developing Economies" sponsored by the Sabin Institute, the UNAIDS Vaccine Advisory Committee, the Microbicides 2000 group on economics of new product development, the WHO Commission on Macroeconomics and Health.

recommend how the Bank could accelerate development of an AIDS vaccine for developing countries.

- **Paris, France (April 1999)**: Consultative meeting chaired by World Bank Senior Vice President Joseph Stiglitz with G-7 representatives, other European donors, representatives from five developing countries (Brazil, Russia, South Africa, Thailand, Uganda).
- **Bangkok, Thailand (May 1999)**: Consultative meeting chaired by Jayasankar Shivakumar, World Bank Country Director for Thailand, with Thai policymakers, members of the Technical Subcommittee on AIDS vaccine, scientists, pharmaceutical representatives, NGOs, VaxGen (which is financing the first phase III AIDS vaccine trial in Thailand), and members of the UNAIDS Theme Group.
- **Midrand, South Africa (July 1999)**: Consultative meeting sponsored by the South African Medical Research Council, chaired by Malegapuru William Makgoba, with policymakers from South Africa, Botswana, Swaziland and Mozambique, large parastatal employers, representatives of the pharmaceutical manufacturers association, and NGOs.
- **New Delhi, India (August 1999):** Consultative meetings chaired by Peter Heywood, Principal Health Specialist based in New Delhi, and Prasada Rao, head of the National AIDS Control Organization (NACO), with representation of Indian policymakers, the Indian scientific community, NGOs, bilateral donors, UNAIDS, and the domestic vaccine industry.
- **Brasilia, Brazil (September 1999):** Consultative meeting co-chaired by Patricio Millan of the World Bank Brazil Office and Pedro Chequer, head of the Brazil AIDS control program, with policymakers, members of the national AIDS Vaccine Committee, local vaccine manufacturers, and NGOs.

The findings on the current state of vaccine development, industry's perspective, potential demand, and the advantages and disadvantages of different options were disseminated in an issues paper, "Accelerating an AIDS vaccine for developing countries: Issues and options for the World Bank" (Ainsworth et al 1999), which served as background for the consultations. The last version of the issues paper and the reports of these individual consultations can be viewed on-line at the AIDS Economics Website (www.worldbank.org/aids-econ/).

The consultations brought out important new perspectives beyond those obtained from industry—particularly perspectives from developing countries on their own role in AIDS vaccine development. Among the key themes:

The Bank's dialogue with industrialized and developing country policymakers on AIDS and AIDS vaccines is seen as critical in bringing the issue to the center of economic and development decision making and a prerequisite for reaching agreement on future mechanisms to promote an AIDS vaccine for developing countries. The level of knowledge of policymakers in the North and South on issues surrounding development of an AIDS vaccine is low. Policy dialogue with the international donors must address the market failures leading to underinvestment in R&D for an AIDS vaccine for developing countries; in developing countries the policy dialogue must emphasize the need for political commitment to create international partnerships for AIDS vaccine development.

The successful and rapid development of an AIDS vaccine that is effective and affordable cannot be achieved without the cooperation and active involvement of developing countries. This is the only way to guarantee that vaccines are developed for local HIV strains, genetic stock and health systems, to ensure acceptance of the vaccine by high risk groups and by civil society. There is also clearly a political dimension, a perception that developing countries will need to be actors and partners in developing a vaccine and not merely passive recipients if future use is to be assured. The World Bank and the IFC can facilitate the formation of public-private partnerships between developing countries and industry for AIDS vaccine development.

While the developing countries consulted all had serious AIDS problems, a highly qualified scientific community and local vaccine manufacturing capacity, there was wide recognition that progress on development of an indigenous AIDS vaccine was most likely through international partnerships with industry and public sector research institutions. National AIDS vaccine plans have generally been passive, focusing on the regulatory and ethical aspects of testing. There is no strategic plan for organizing the scientific community in logical steps that will lead to a vaccine in the shortest time. In Brazil, as in the North, the scientific community has not reached a consensus on the best candidate to test. All of the countries have indigenous manufacturing capability in vaccines, but it is highly publicly subsidized and not involved in vaccine development. Governments have not actively courted private sector partners, and in many countries there is widespread public distrust of the motives of international pharmaceutical companies, which will have to be addressed to make public-private partnerships viable. In Thailand, work to generate a political consensus to participate in AIDS vaccine testing began years ago; collaboration is underway with VaxGen in the first Phase III efficacy trial of an AIDS vaccine, in a cohort of injecting drug users in Bangkok. The involvement of WHO/UNAIDS in facilitating this partnership was pivotal. Thailand's experience demonstrates the important steps in consultation and consensus building that are prerequisites for collaboration. During all of the consultations, it was felt that developing countries participating in these trials should have some special consideration in terms of public sector ownership of some of the intellectual property rights or access to the product at a low price as part of the agreement for their participation.

There was substantial support for World Bank lending to developing countries for "push" activities that would enable countries to be better partners in AIDS vaccine development. This reflected in part the active participation of the local research community in the consultations, but in one consultation (South Africa), "pull" mechanisms were seen to be primarily benefiting drug companies. While lending for "push" mechanisms could be important, ways need to be found to take into account the positive externalities to the rest of the world of AIDS vaccine development, such as through a subsidy of some types. There was also a consensus that "push" lending should focus on finance of key milestones in a well-defined scientific plan to develop a vaccine (not for basic research) and that it should not divert public funds away from key investments in other HIV prevention, which will still be necessary even after a vaccine is developed. The World Bank Thailand Office suggested that one promising way that these activities could be packaged is in a "learning and innovation loan" (LIL) linked to public-private partnerships in vaccine development. The "buy in" from a developing country into an AIDS vaccine trial through such a loan could be used to leverage better terms from its

pharmaceutical partner on quick and low-cost access to the resulting vaccine and/or advance agreement on sharing of intellectual property rights.

Expectations for an AIDS vaccine were unrealistically high—many participants (policymakers and scientists) assumed that an AIDS vaccine will stop the epidemic and make behavioral interventions unnecessary. The strategic use of an AIDS vaccine by the public sector , the characteristics of a vaccine that would be useful, how a vaccine would complement other prevention efforts, to whom it should be targeted, and the interaction between vaccine effectiveness and behavior change had not been previously explored. There was strong support for research on the potential public and private demand for a vaccine, including modeling the population impact of different types of vaccines on HIV prevalence, compared with other preventive interventions. This was particularly true in Thailand, where the public sector will have to make important decisions on resource allocation for AIDS vaccines when the first trial concludes in the fall of 2001.

International donors agreed that the Bank's comparative advantage would be in assuring a future market for an AIDS vaccine, but a consensus has not yet been reached concerning the optimal mechanism. There was general support for greater financial support for strengthening immunization delivery capacity and the use of existing vaccines, but a sense that this alone would not be enough to greatly accelerate AIDS vaccine development. On the other hand, the opportunity cost of tying up resources now in a fund to purchase an appropriate AIDS vaccine in the future was felt to be too high, and there was therefore a call for more creative approaches. The World Bank effort should be part of a larger, coordinated global effort, in which multiple incentives are generated through different approaches of each partner. Further, there is an interest that the "solution" for the AIDS vaccine effort be consistent with that for other global public goods in health.

The Task Force convened a meeting on January 19, 2000, to brief representatives of 10 pharmaceutical and biotechnology firms on the mechanisms under consideration for accelerating an AIDS vaccine and on the results of the consultations with international partners. Those present strongly endorsed the proposals for the Bank to advance policy dialogue on AIDS vaccines and childhood vaccines, to build capacity in developing countries for collaboration in clinical trials, to strengthen and expand childhood immunization programs, and to generate new information on the extent of demand for vaccines of varying efficacy. However, the participants stressed that these mechanisms would not be sufficient to dramatically accelerate AIDS vaccine development; some sort of mechanism to ensure a credible future market for the vaccine would be essential.

III. Recommendations

The AIDS Vaccine Task Force recommends that the World Bank pursue a four-pronged strategy to accelerate development of an AIDS vaccine that is effective and affordable in developing countries. The strategy builds on the comparative advantage of the World Bank in economic and financial aspects of poverty alleviation and economic development. It incorporates elements of policy dialogue, "push", and "pull" mechanisms. It generates commitment, ownership and capacity in developing countries in the short run, encourage public-private partnerships for vaccine development, and increase the confidence of industry that there will be a viable market in

developing countries. The first three recommendations mobilize existing instruments—policy dialogue, lending, and analytic resources—to accelerate an AIDS vaccine; the fourth proposes a new and innovative mechanism to guarantee adequate finance of AIDS vaccines for the poorest countries, thereby strengthening the future market for an AIDS vaccine. All of these recommendations are important, but the fourth one most directly addresses the source of market failure leading to under-investment in an AIDS vaccine and is one that the World Bank is uniquely positioned to affect.

1. Enable developing countries to be better partners in AIDS vaccine development

An inexpensive and effective AIDS vaccine for use in poor countries cannot be developed without the political commitment and active involvement of developing countries. **The Bank can play an important role in generating the political support and an enabling environment for public-private partnerships in AIDS vaccine development through policy dialogue and lending for: (a) capacity building and engaging civil society; and (b) applied research, including vaccine clinical trials**.[11] Countries may be able to use the occasion of borrowing for clinical trials to negotiate good terms with private partners on the future availability and price of a successful vaccine candidate.

Support for ***capacity building and engaging civil society*** might include financing of:

- Assessing the nature and scope of the AIDS problem, the barriers to AIDS vaccine development, the potential demand and costs of a vaccine, and the role of a vaccine among other prevention policies
- Disseminating information to policymakers and the public on the need, objectives and ethical aspects of AIDS vaccine testing
- Strengthening the national pharmaceutical regulatory authorities, such as food and drug administrations, and ethical infrastructure for AIDS vaccine trials
- Building capacity to manage vaccine trials, including cohort development, monitoring, and quality control
- Developing national strategies and scientific plans for applied AIDS vaccine research in collaboration with international technical agencies, like IAVI, WHO/UNAIDS, and the NIH.

Lending for ***applied research for vaccine development*** should be considered for selected countries, conditional on successful institutional development and political consensus, the requisite indigenous research capacity, a feasible and scientifically valid vaccine development plan, identification of suitable international technical and commercial partners, adequate ethical

[11] Given that virtually all other agencies involved in the AIDS vaccine effort and the private sector are engaged in "push" activities to finance research, this might not seem to be the comparative advantage of the Bank. One might also argue that lending for AIDS vaccine development might be inappropriate, given that the technology is a global public good. However, push activities in developing countries are still under-funded. Furthermore, there is demand for financing "enabling" activities and applied research in science-capable developing countries with serious AIDS epidemics. India, for example, has the most AIDS cases of any country in the world and would benefit substantially from a low-cost AIDS vaccine, even if there were spillover benefits for the rest of the world.

safeguards and strong, well-targeted HIV prevention programs. This might include lending for infrastructure for vaccine clinical trials, implementation of the trials, and other applied research linked to critical pathways in AIDS vaccine development that is not repetitive of activities elsewhere, is scientifically appropriate, and will move the field forward. Countries that borrow for applied AIDS vaccine research would have to be willing to undertake the work as part of a global effort. International technical agencies would be responsible for reviewing proposals during project appraisal to ensure that they are scientifically appropriate, not repetitive of activities elsewhere and will move the field forward. Since applied research has important global public goods components, World Bank lending should be used as a "seed" to mobilize additional grant resources from donors and industry, whenever possible.[12]

2. Expand coverage of childhood immunization programs

Expanding coverage of childhood immunization programs and increased use of newly developed vaccines will stimulate AIDS vaccine R&D.[13] Industry gauges the potential market for an AIDS vaccine largely on the current market for childhood vaccines. Furthermore, strengthening the immunization infrastructure, including training, may also help to reduce the gap in time between the discovery of an AIDS vaccine and its availability, since some of this infrastructure may be involved in AIDS vaccine distribution. To realize the full benefits of vaccine technology, the world should be spending about $3.8 billion for immunization in developing countries (including labor, infrastructure and vaccines), but only about half that amount ($2 billion) is currently being spent.

This is a "pull" strategy with immediate benefits: An estimated 2 million children die each year in developing countries from vaccine-preventable disease. After meeting an international goal of 80% coverage of childhood immunizations in the early 1990s, donor funding for childhood vaccines declined and the immunization infrastructure of developing countries is now crumbling. Vaccination rates have not been sustained, despite the relatively low cost and high cost-effectiveness of the basic childhood immunizations. Average coverage rates for DTP in Africa, for example, have fallen below 50 percent. Countries have been slow to adopt new vaccines that are slightly more expensive but highly cost-effective, like hepatitis B, yellow fever, and Hib.

The World Bank has an important role to play in reversing these trends, ensuring the adoption of new vaccines when they are cost-effective, and saving millions of lives through:

- *Policy dialogue* on public health priorities, the cost-effectiveness of childhood vaccines, and the increasing need for developing countries to commit their own resources to ensuring coverage.
- *Expanded lending* for immunization infrastructure, training, policy development, cost-effectiveness studies for new vaccines in selected countries, and vaccine purchase

[12] Countries that are good candidates for vaccine clinical trials are likely to have a severe AIDS problem and at least one population group with high incidence of HIV. Thus, the benefits to countries that request this type of lending are likely to be great even though there will be some spillover benefits to the rest of the world.

[13] This will also raise investment in vaccines for malaria and TB.

- *Participation in international initiatives* such as the Global Alliance for Vaccines and Immunization (GAVI), which has set global goals for childhood vaccination and renewed effort by the international community and developing country governments to introduce new vaccines in settings where they are highly cost-effective.

The World Bank's commitment to finance immunization programs is on the rise. Lending for vaccines and immunization programs historically has been low—less than $20 million annually. However, Mr. Wolfensohn met with heads of public agencies and the vaccine industry in March 1998 to discuss "Vaccine Development and Delivery: Leadership for the 21st Century". With technical input from partners such as WHO, UNICEF, and the U.S. Centers for Disease Control and Prevention (CDC), World Bank lending initially focused on strengthening immunization efforts and adoption of new vaccines in 6-8 countries. For example, a large project is under preparation in India to assure polio eradication, strengthen delivery systems for childhood vaccines, and develop a strategic plan for expanding coverage of existing and new vaccines. Immunization-related outcome measures have been integrated into a health project in Bolivia. Building on this experience, a review of potential support for immunization is being prepared for each region to identify priority countries for further attention. The Bank has committed to working more closely with industry, foundations, WHO, and UNICEF in this effort. The Gates Children's Vaccine Program has financed a $3.7 million Trust Fund for the World Bank for five years to facilitate the Bank's contribution to immunization.

3. Generate new knowledge on the economics of AIDS vaccines in developing countries

The World Bank can draw on its expertise in research on household economic behavior in developing countries, cost-effectiveness of interventions, and public economics by generating new knowledge on:

- the *impact* of an AIDS vaccine relative to other preventive measures in countries at different stages of the epidemic, assuming vaccines with different levels of efficacy and duration of effectiveness, and under different public sector targeting strategies;
- the *cost-effectiveness* of an AIDS vaccine relative to other interventions under these different assumptions of vaccine efficacy and targeting; and
- the *public and private willingness to pay* for an AIDS vaccine in developing countries with different levels of income and types of HIV epidemics.

These studies would be conducted with the collaboration of the international research community and developing country researchers. The results would be disseminated widely to national policymakers, industry, and the international community.

Generation of this new knowledge—available to all—is a global public good. It is essential for understanding the role of an AIDS vaccine as one of many public health interventions to control the epidemic, for estimating the resource requirements for eventual purchase of a vaccine for the poorest countries, and for the design of innovative "pull" mechanisms to raise private R&D for AIDS vaccines for developing countries. To the extent that any of this information currently exists, it is largely proprietary, part of the marketing estimates collected by industry that are not available to the public.

4. Adopt new mechanisms to ensure finance for purchase of an AIDS vaccine

The Task force recommends that World Bank management open a dialogue with member countries and the international community on new mechanisms that the Bank can adopt to ensure "up front" adequate finance for an AIDS vaccine for the poorest countries. Consultations with industry underscored that the key to increasing private investment in an AIDS vaccine for poor countries is to ensure an adequate market at a fair price. Increased funding for "push" activities and lending for existing vaccines are necessary but not sufficient to reach the desired outcome of rapid development and availability of an effective and affordable AIDS vaccine to benefit the poorest countries. By credibly demonstrating the means by which an AIDS vaccine can be purchased for the poorest countries in the future, the World Bank and international community would essentially raise the certainty of a future market—a powerful "pull" mechanism. At the same time, such a mechanism would help to reduce the lag in time between development of a vaccine and its availability in developing countries.

The Task Force examined several mechanisms that build on existing instruments—contingent loans and purchase funds for eventual finance of an AIDS vaccine. These ideas should be actively pursued. However, there are important drawbacks to each. Contingent loans rely on countries to guarantee or finance their own AIDS vaccine markets on a country-by-country basis, ignoring the global public good nature of the technology and the "free rider" problem that will reduce incentives to borrow. Vaccine purchase funds tie up resources that could be used to save lives now; a promise to contribute to such a fund in the future may not be sufficiently credible to generate "pull" that would raise investment. To be effective not only in assuring future finance but generating "pull", a new mechanism would have to be large, visible, and highly credible.

One innovative approach that could satisfy criteria of size, visibility, and credibility would be to use resources from IDA, and possibly also from other multilateral concessional funds, to establish a "replenishing" source of finance of, say, $1 billion to accelerate development of and access to an AIDS vaccine for the poorest countries, "topped off" as necessary through successive IDA replenishments, thereby providing continuing financial commitment. Priority use would be the purchase of AIDS vaccines through IDA credits, as the price and efficacy of AIDS vaccines reach the point at which they are cost-effective relative to other conventional prevention programs. Until then, the resources could be used to lend for other "push" and "pull" mechanisms that will accelerate AIDS vaccine development, including finance of existing vaccines, AIDS prevention, and developing country participation in vaccine trials. *Since the same market failures and low ability to pay exist for other key technologies, and given the possibility of replenishing the resources periodically, it might be applied more broadly to finance credits that would purchase or promote development of other new technologies for the control of communicable disease in poor countries, like vaccines for malaria or TB, or vaginal microbicides to prevent the spread of HIV.*

To address the global public good nature of the development of AIDS vaccine and other high-priority technology, a portion of these resources might be reserved for financing global partnerships or initiatives. These are extremely important to address the needs of poor countries but difficult to finance under the existing structure of country-level lending and operational

programs. Simultaneous initiatives or matching grant funds by other donors and private foundations could multiply the impact of World Bank action. A "pure" form of such a facility might be a sort of replenishing fund (given the very long maturities of concessional lending, a fund could not be set up on a "revolving" basis, i.e., using loan repayments by borrowers). It needs to be recognized, however, that there are compelling arguments against firmly earmarking IDA resources for particular purposes: rather than do so, IDA donors have therefore preferred to give strong inidications of intent with respect to IDA's priorities, and then to commit (and in due course replenish) resources on that basis.

Important details would have to be worked out through broad discussion among IDA donors and recipients, including: possible use of resources for global push initiatives that cannot be backed on a country-by-country basis whether lending could be available to non-IDA countries to borrow for activities with a high global public good content (e.g., AIDS vaccine trials) that will clearly, if indirectly, benefit IDA countries; how to attract additional resources from industry and donors that do not diminish funding of other initiatives; and the potential role of the IFC in this mechanism. If IDA donors supported the broad approach, these resources could be available to countries outside the normal IDA performance-based framework, although lending for this purpose should remain strongly linked to the efficacy of the supported programs.

Successful pursuit of any of these innovative new instruments for guaranteeing a market for an AIDS vaccine will require a broad consensus among the Bank's shareholders and clients of the urgency of the problem and the inadequacy of existing mechanisms for ensuring rapid development of the technology for an AIDS vaccine. The AIDS Vaccine Task Force, with resources provided from the 1998 Innovation Marketplace, has already made important inroads in raising awareness of this issue among important constituencies in the North and the South. A useful starting point for launching this discussion will be to brief the Board on findings and recommendations. Further guidance will come from a discussion of Bank action on communicable diseases at the June 2000 meeting of IDA Deputies in Lisbon.

IV. Resource requirements

Assuring the implementation and active pursuit of this agenda will require a combination of world Bank budgetary resources and additional financing from the Development Grant Facility to participate in international initiatives and leverage funding from outside sources.

Staff time. At least **$1 million annually from operational budgets** would be needed for full-time staff for the next 3-5 years for:

- central support to country departments to develop innovative "push" lending for AIDS vaccine R&D as part of AIDS strategies in selected countries
- core analytic and strategic work
- coordination with development partners, international technical agencies, and industry
- management of the consensus-building process on innovative instruments for ensuring adequate financial resources in the future for purchase of an AIDS vaccine, ensuring a credible market that will generate "pull"

These resources would be in addition to the full-time staff member in HDNHE already engaged in raising use of existing vaccines and a half-time technical expert seconded from the CDC for the same purpose.

Grants to support international partnerships. For the present, the only source of finance for global partnership activities like IAVI is through the Development Grant Facility. An additional **$2 million annually would be needed from the DGF** for support of these partnerships.

External resources. Resources to facilitate expansion of World Bank *lending for childhood immunization* have already largely been mobilized. The Gates Children Vaccine Program has contributed $3.7 million to a World Bank trust fund over the next five years and the CDC has contributed a half-time technical adviser on secondment.[14] Additional external funding of roughly $600,000 is needed to support *generating new knowledge* on the demand for an AIDS vaccine, modeling of the epidemiological impact relative to other preventive measures, and strategic planning in selected countries on the use of an AIDS vaccine.[15] This would be managed using staff time from DECRG financed out of new institutional resources (discussed above), supplemented as necessary with funds from the research support budget (RSB).

Other external grant support for accelerated development of an AIDS vaccine in the context of specific operations could be leveraged—particularly for "push" interventions—through the strategic use of lending resources in the proposed IDA revolving fund.

V. Conclusion

The AIDS epidemic is exacerbating poverty among the World Bank's client countries and reversing decades of progress in improving the quality of life. There is no cure for AIDS and it is nearly 100% fatal. AIDS prevention policies are therefore central to poverty alleviation strategies that are at the core of the World Bank's mission. Programs to prevent HIV by changing high-risk behavior have met with some success and must be reinforced. An AIDS vaccine that is effective and affordable—while not a panacea—could contribute enormously to HIV/AIDS prevention and poverty alleviation in developing countries.

Progress on an AIDS vaccine has been slow, partly for reasons of science but also because of market failures that reduce the incentives for private industry to invest in a low-cost vaccine for the strains of HIV and health infrastructure in poor countries. These market failures are related to the public good nature of the technology for an AIDS vaccine and the low ability to pay of those most likely to benefit. In the absence of action to address these market failures, it could be decades before an effective vaccine is discovered and years more before a candidate that is both effective and affordable in developing countries would be available. There is substantial scope for the international community to affect the incentives facing developers of an AIDS vaccine—either by subsidizing or reducing the cost of research and development ("push"

[14] Discussion is underway with the CDC for an additional full-time secondee to support these activities.

[15] A proposal, entitled "The economics of an HIV/AIDS vaccine in developing countries: Potential impact, cost-effectiveness, and willingness to pay" has already been submitted to the European Commission for funding. An outcome is pending.

strategies) or by ensuring a future market for the vaccine, especially for countries where ability to pay is likely to be low ("pull" strategies).

Most of the international actors involve in AIDS vaccines to date—WHO/UNAIDS, IAVI, the U.S. National Institutes of Health, and other national research agencies—have a comparative advantage in promoting "push" strategies. However, despite these efforts, "push" interventions oriented toward the poorest countries in greatest need are still under-funded. In light of its large lending program, its involvement in financial markets, and its excellent access to key financial policymakers in developing countries, there is substantial scope for the World Bank to complement the efforts of partner agencies through increased activities to support "push" and for enhancing the perceived market through "pull".

The AIDS Vaccine Task Force, following an 18-month process of information gathering and consultation, has proposed a four-pronged strategy that includes both "push" and "pull" interventions that build on the comparative advantages of the World Bank. The proposed strategy uses existing instruments—lending, policy dialogue, and analytic capacity—to enable developing countries to be better partners in AIDS vaccine development, to increase the coverage of childhood immunization programs with existing cost-effective vaccines, and to generate new knowledge on the potential benefits, strategic use, and public and private demand for an AIDS vaccine in developing countries. In addition, to ensure the effectiveness of these efforts, the Task Force proposes that management launch a broad discussion with the IDA community concerning new IDA-based mechanisms that would assure adequate finance for a vaccine when it becomes available, serve as a large, visible, and highly credibly commitment to the market for an AIDS vaccine for developing countries, and in the short run finance key activities to accelerate the process. Implementation of this program would require an additional $1 million annually for staff time over the next 3-5 years and an additional $2 million of DGF funding for global partnerships to support development of an AIDS vaccine.

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