

PREPARING NOW TO ASSURE ACCESS

*Pre-Press Edition*



**AIDS VACCINES FOR THE WORLD:**

**PREPARING NOW  
TO ASSURE  
ACCESS**

**JULY 9, 2000**

**AN IAVI BLUEPRINT**

Many organizations and individuals contributed ideas and information to help in the preparation of this document. The principal author was Roy Widdus, Ph.D. Michael T. Isbell, J.D., contributed invaluable editorial assistance in the style and presentation of the information.

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The International AIDS Vaccine Initiative (IAVI) is probably best known for its efforts to accelerate the development of preventive AIDS vaccines by creating awareness of the need for a vaccine, accelerating applied vaccine development, and advocating for incentives to encourage industrial involvement. IAVI's Scientific Blueprint for AIDS Vaccine Development, released in 1998 at the World AIDS Conference in Geneva, outlined the steps needed to assure the earliest possible emergence of an effective vaccine against AIDS. Relying on the Scientific Blueprint as its guide, IAVI has created and funded four international AIDS vaccine development partnerships, and additional product development efforts will receive IAVI's support by year's end.

However, IAVI's stated purpose—"To ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world"—requires more than the successful development of an effective vaccine. It also demands meaningful access and the actual, effective use of such a product in all places where it is needed. Thus, in addition to the scientific obstacles to a preventive vaccine, IAVI's mission requires that we assure that the world addresses the economic, political, and logistical impediments to wide-scale use of new vaccines in all areas.

This new Blueprint—*AIDS Vaccines for the World: Preparing Now to Assure Access*—reveals that true access to a safe and effective AIDS vaccine cannot be assumed, especially in poor countries or in high-risk groups. On the contrary, we know for certain that 'business as usual' will result in years, perhaps decades, of delay in the achievement of optimal levels of vaccination in the regions of the world hit hardest by AIDS. Such a delay would cost millions of lives and trigger social catastrophe in many parts of the world.

This Blueprint outlines a five-step global action plan to ensure timely use of a preventive vaccine in all at-risk populations, regardless of where they are found. Simultaneous introduction of vaccines in both 'North' and 'South,' although feasible, has not been attempted or accomplished to date. To succeed where the world has previously failed, we must aggressively—and immediately—pursue the strategies needed to ensure that systems for AIDS vaccine supply and use are in place as soon as a vaccine is available. The world must, in essence, learn new ways of doing business within and between public and private sectors, while respecting intellectual property and ensuring that adequate incentives are in place for the private sector, where most vaccine development expertise resides.

Two years ago, the Geneva conference adopted the theme "One World, One Hope." Although a preventive vaccine remains the world's best hope for bringing AIDS to an end, there is a real risk that it is a hope that only the rich will be able to afford.

This latest Blueprint poses fundamental moral, political, and logistical challenges. History will judge how we respond.

Seth Berkley, M.D.  
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July 9, 2000

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	<p><b>1. Effective pricing and global financing mechanisms must be developed to assure that vaccines are promptly available for use where they are needed.</b></p> <p>Key political leaders and institutions should join with the private sector in endorsing the use of a tiered pricing structure for AIDS vaccines that enhances access by enabling poorer countries to pay what they can afford and at the same time permits companies to obtain a satisfactory return on investment.</p> <p>Global mechanisms to purchase and deliver vaccines for use in developing countries should be created, and the G-8 nations should immediately make credible financial commitments for the support of such mechanisms.</p> <p><b>2. Mechanisms must be developed to make reliable estimates of demand for specific vaccines and to ensure creation of production capacity to permit accelerated worldwide access.</b></p> <p>To ensure appropriate preparation and coordination for the swift introduction of a preventive vaccine, an international body should be convened to monitor and evaluate vaccine candidates undergoing testing.</p> <p>Based on evaluation of available data regarding particular vaccines, appropriate utility studies should be commenced in regions where efficacy trials are not occurring.</p> <p>Analytic studies are needed to inform decisions regarding introduction of AIDS vaccines in developing countries.</p>

A comprehensive effort should be initiated immediately to assess and predict private market and public sector demand for AIDS vaccines.

Based on sound estimates of demand, appropriate multinational and national financial institutions should collaborate with private industry and/or explore other mechanisms to ensure that sufficient production capacity exists to ensure worldwide introduction of new vaccines.

**3. Appropriate delivery systems, policies, and procedures must be developed for adolescents, sexually active adults, and other at-risk populations.**

Developed and developing countries, health experts, multilateral institutions, non-governmental organizations, and other appropriate parties should collaborate to design and establish vaccine delivery systems in developing countries.

Strategic plans should be developed—at international, regional, and country levels—to communicate and advocate regarding AIDS vaccines. Such efforts should be directed to policy makers, the general public, and populations most affected by HIV/AIDS.

Model approaches to individual education, counseling and informed consent should be developed, piloted, and evaluated.

**4. National regulations and international guidelines governing vaccine approval and use must be harmonized.**

**5. To demonstrate global commitment to effective worldwide deployment of important vaccines, immediate efforts should be undertaken—using approaches articulated in this document, and building on existing mechanisms, such as the Global Alliance for Vaccines and Immunization (GAVI) and the Global Fund for Children’s Vaccines (GFCV)—to achieve maximum use in developing countries of one or more currently under-utilized non-AIDS vaccines.**

Efforts should be undertaken to educate decision-makers and finance personnel about the cost-effectiveness of vaccines.

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The historical paradigm for fostering use of new vaccines in developing countries has been a colossal public health failure.

Because vaccine development is a risky, privately financed enterprise, vaccines are almost always initially marketed exclusively in industrialized countries that have the ability to pay full price. As years pass and the manufacturer's production capacity and efficiency increase, the price of the vaccine slowly declines. Eventually, the price becomes sufficiently low to permit external aid donors and selected developing country governments to purchase the vaccine. Over time—a substantial period of time—the vaccine is introduced piecemeal into poorer countries, with many years passing before optimal vaccination levels are achieved.

Overall, 15 years or more are usually needed following initial licensure before even a moderate level of vaccination is reached in poorer countries.

This approach—deplorable for any serious disease—is utterly unacceptable in the case of HIV, which is almost universally fatal and infects an additional 6 million people each year. At the current infection rate, even a five-year delay in introducing a preventive vaccine—a major

improvement over current practice—would nonetheless mean up to 30 million needless infections (and countless additional infections stemming from those that should have been prevented). Ensuring swift, equitable access to AIDS vaccines is a global moral and public health imperative, but one that will require radical changes in the global approach to vaccine production, licensure, pricing, purchasing, and distribution.

There are numerous reasons why simultaneous introduction of vaccines in the 'South' and 'North' has never been achieved or even attempted:

- The economics of vaccine development and production discourage companies from initially installing sufficient production capacity to ensure timely, worldwide use.
- Sufficient financing does not exist to make new vaccines widely available in poorer countries.
- Both industrialized and developing countries place a low priority on disease prevention, discouraging leaders from exhibiting the political will needed to accelerate access to vaccines.
- Legal mechanisms for the approval and distribution of vaccines are fragmented and uncoordinated.

- Some domestic political lobbies in developed countries are not sympathetic to developing country needs and do not look favorably on differential, or tiered, pricing under which poor countries pay sharply lower prices than rich countries.

These impediments, as real today as in the past, are compounded in the case of HIV/AIDS by additional obstacles:

- Policies to ensure rapid access will need to be formulated before the characteristics of individual vaccines are fully known, and the rapid evolution of vaccine 'generations' will complicate policy development even further.
- Distribution channels do not currently exist for adolescents, sexually active adults, and other high-risk groups, the likely initial populations for AIDS vaccination.
- Planning of production capacity and supply may be complicated by the potential need to create vaccines specific to the HIV strain(s) prevalent in a given area.
- AIDS vaccination will need to be accompanied by appropriate counseling to maintain or reduce behavioral risk.
- Social stigmatization and fear associated with HIV/AIDS must be overcome, and AIDS vaccination efforts must adhere to the

**Simultaneous introduction of a vaccine in the North and South will require unprecedented global cooperation.**

highest ethical and human rights standards.

As critical HIV-related care and prevention needs proliferate in Africa, Asia, and other parts of the world, it is tempting to delay tackling the daunting barriers to vaccination until a later day, when the prospect of a safe and effective vaccine is more apparent. To do so, however, would ensure that we will repeat with HIV/AIDS the intolerable experience with other vaccines.

Simultaneous introduction of a vaccine in the ‘South’ as well as the ‘North,’ while feasible, will require unprecedented global action and collaboration. To succeed, we must begin immediately.

The world must forge a new paradigm for AIDS vaccines that builds on a knowledge of vaccine supply economics and a new commitment to tackle the rich-poor public health inequities highlighted by the global AIDS pandemic. IAVI proposes the following immediate five-step global action plan to assure simultaneous access throughout the world to any safe and effective vaccine:

**1. Effective pricing and global financing mechanisms must be developed to assure that vaccines are promptly available for use where they are needed.**

World leaders must reach consensus on the desirability of tiered

pricing for AIDS vaccines, and developed and developing nations and multilateral financial institutions must immediately make firm commitments to underwrite the purchase and delivery of safe and effective vaccines in developing countries. Strategies must sensitively balance the global imperative of worldwide access with private industry’s expectation of and right to obtain a sufficient return on investment.

**2. Mechanisms must be developed to make reliable estimates of demand for specific vaccines and to ensure creation of production capacity to permit accelerated worldwide access.**

An international body of experts should be assembled to monitor and evaluate vaccine candidates as they proceed through clinical testing. In appropriate circumstances, international mechanisms must exist to support sufficient production capacity in time to ensure that promising vaccines are ready for worldwide distribution upon approval. This will necessitate the development of a new kind of relationship between public and private sectors, as commercial manufacturers are unlikely on their own to undertake the risky pre-approval investment that the world will need. Efforts to ensure appropriate

capacity must be based on accurate estimates of global demand for each AIDS vaccine, which requires the development of new techniques to assess demand in developing countries.

**3. Appropriate delivery systems, policies, and procedures must be developed for adolescents, sexually active adults, and other at-risk populations.**

Because existing vaccine delivery mechanisms do not generally reach the populations who should be prioritized in AIDS vaccination efforts, the world must mobilize to create such delivery systems. As in all other aspects of planning for AIDS vaccination, affected communities must be integral partners in the development and implementation of new delivery vehicles. Communications strategies must be devised to educate communities and key decision-makers about AIDS vaccines and to build popular support for vaccination. AIDS vaccination delivery will require rigorous adherence to the highest ethical standards; this will, among other means, necessitate that vaccinees give genuine informed consent and that they be counseled on the need to maintain risk-reduction behaviors.

| **World leaders must reach  
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of tiered pricing for AIDS  
vaccines.** |

4. National regulations and international guidelines governing vaccine approval and use must be harmonized.

Safety will be a critical factor in countries' decisions whether to approve AIDS vaccines for use, yet no consensus exists regarding how to measure the safety of such products. Furthermore, no official attention has yet been paid to issues of liability, which could significantly affect both the pace of vaccine development and the speed with which new vaccines are introduced to multiple markets. Not only must a global consensus process be initiated, but the hodgepodge of applicable national requirements and international guidelines must also be harmonized. Otherwise, approval of vaccines will be delayed, as companies are forced to perform additional studies or 'repackage' data countless ways to meet diverse safety criteria.

5. To demonstrate global commitment to effective worldwide deployment of important vaccines, immediate efforts should be undertaken—using the approach articulated in this document, and building on existing mechanisms, such as the Global Alliance for Vaccines and Immunization (GAVI) and the Global Fund for Children's Vaccines (GFCV)—to achieve maximum use in developing countries of one or more currently underutilized pediatric vaccines.

Accelerating the introduction of currently underutilized vaccines will save lives, help build infrastructure for future vaccine delivery efforts, and increase private industry's confidence that the public sector is serious about assuring the wide-scale use of life-saving vaccines.



## AIDS VACCINES FOR THE WORLD: PREPARING NOW TO ASSURE ACCESS

### **INTRODUCTION**

As this Blueprint goes to press, nearly 40 million people throughout the world are living with HIV. Each year, almost six million people—including 600,000 infants—contract HIV infection. The epidemic in Africa now rivals the medieval European plague in its devastation, and many other parts of the world—including Asia, the Caribbean, and Eastern Europe—are witnessing dramatic increases in new infections.

Since its first appearance, AIDS has exhibited a remarkable capacity to clarify the realities of life in our time. Recently, it has highlighted the unconscionable disparities between rich and poor in access to the fruits of modern medicine. While therapeutic approaches developed over the last several years have sharply reduced the pain, illness, and mortality associated with HIV/AIDS in industrialized countries, suffering and death continue on as before in most developing nations, where 95% of the world's HIV-infected live. Barring an unprecedented global mobilization to expand health care access, it is a virtual certainty that the vast majority of persons currently living with HIV will not be alive 10 years from now.

Scientists and health experts

broadly agree that the world's best hope for conquering the greatest health threat of our era lies with a preventive vaccine. Yet, even in the hoped-for vaccine era, it is probable that the same inequities that presently provoke such dismay will continue to perpetuate the pandemic. In the absence of a monumental shift in the world's approach to new vaccines, richer countries will quickly enjoy the benefits of an AIDS vaccine, while developing countries and key high-risk groups will wait many years, probably decades, before gaining access. Throughout huge swaths of the globe, an additional generation will have been lost, notwithstanding the existence of a product capable of bringing the pandemic to an end.

IAVI believes that a different outcome is both possible—and imperative—in the case of AIDS vaccines. With foresight, courage, and determination, the world can avoid with a preventive vaccine the inequities we now witness in AIDS treatments. Ensuring timely, universal access to AIDS vaccines will require that the world dispense with usual ways of doing business and instead adopt an entirely new paradigm for new vaccines. It will require a careful balancing of the world's need for maximum access with private

industry's legitimate expectation of just compensation for the risks and costs associated with producing life-saving products.

Time is ripe for such a focused and sweeping re-thinking of global health practice. In recognition of the need for dramatic action to overcome the failures of 'business as usual,' a new coalition—the Global Alliance for Vaccines and Immunization (GAVI)—has emerged to accelerate the introduction of pediatric vaccines in developing countries. Efforts to assure worldwide access to AIDS vaccines when they are developed should build on this momentum, but it is clear that HIV/AIDS presents a unique and unprecedented challenge that requires its own global initiative.

This Blueprint outlines the steps needed to assure that the promise of a preventive AIDS vaccine is realized throughout the world. The first section describes both the historical barriers to early access to new vaccines and the unique obstacles presented by HIV/AIDS. The Global Action Plan (p. 20 ) delineates a five-step global action strategy to achieve simultaneous, universal access to new AIDS vaccines.

## VACCINATION AGAINST AIDS: BACKGROUND AND CHALLENGES

### **THE HISTORICAL PARADIGM FOR NEW VACCINES: A COLOSSAL PUBLIC HEALTH FAILURE**

During the last 30 years, scientists developed numerous important vaccines. Although these vaccines were generated primarily to combat diseases prevalent in industrialized countries, they were widely recognized as having worldwide applicability. Within a few years of their development, these vaccines were in widespread use in developed countries, typically through systematic delivery to successive birth cohorts.

In developing countries, by contrast, the experience has been starkly different. Hepatitis B (HB) vaccine—a safe, effective, inexpensive product first licensed in 1981 to combat a disease that kills more than one million people annually—now enjoys 35% to 40% global coverage of infants, but essentially no coverage in the poorest parts of the world. Likewise, around 10 years after licensure of the *Haemophilus influenzae* type b (Hib) vaccine (Figure 1), global coverage is still estimated to be under 15% (Figure 2), with virtually no use of the vaccine in the poorest countries. For developing countries overall, 15 years are likely to be required with historical approaches to achieve even a moderate level of coverage for the Hib and HB vaccines.

Far from being unusual, the delays associated with the Hib and HB vaccines reflect standard operating procedures. Rather than undertake global efforts to accelerate the control of serious diseases through aggressive vaccination programs, the world routinely waits for new vaccines to ‘trickle down’ slowly to developing countries. Left to function on its own, the free market fails to supply private companies with the economic incentives needed to serve developing countries.

To a large degree, the slowness with which new vaccines are introduced in developing countries stems from the peculiar economics of vaccine development and adoption. Individual steps in the vaccine development and distribution process are taken sequentially, causing the transition from licensure to wide-scale global use to be drawn out over a generation or more.

A time line and analysis of these steps for accelerating AIDS vaccine development and utilization are presented in appendix 1.

Simply put, vaccines take the following circuitous route to persons in poor countries:

- Vaccine makers typically invest 10 years or more in the development of a new vaccine (including basic research and clinical testing

for safety and efficacy).

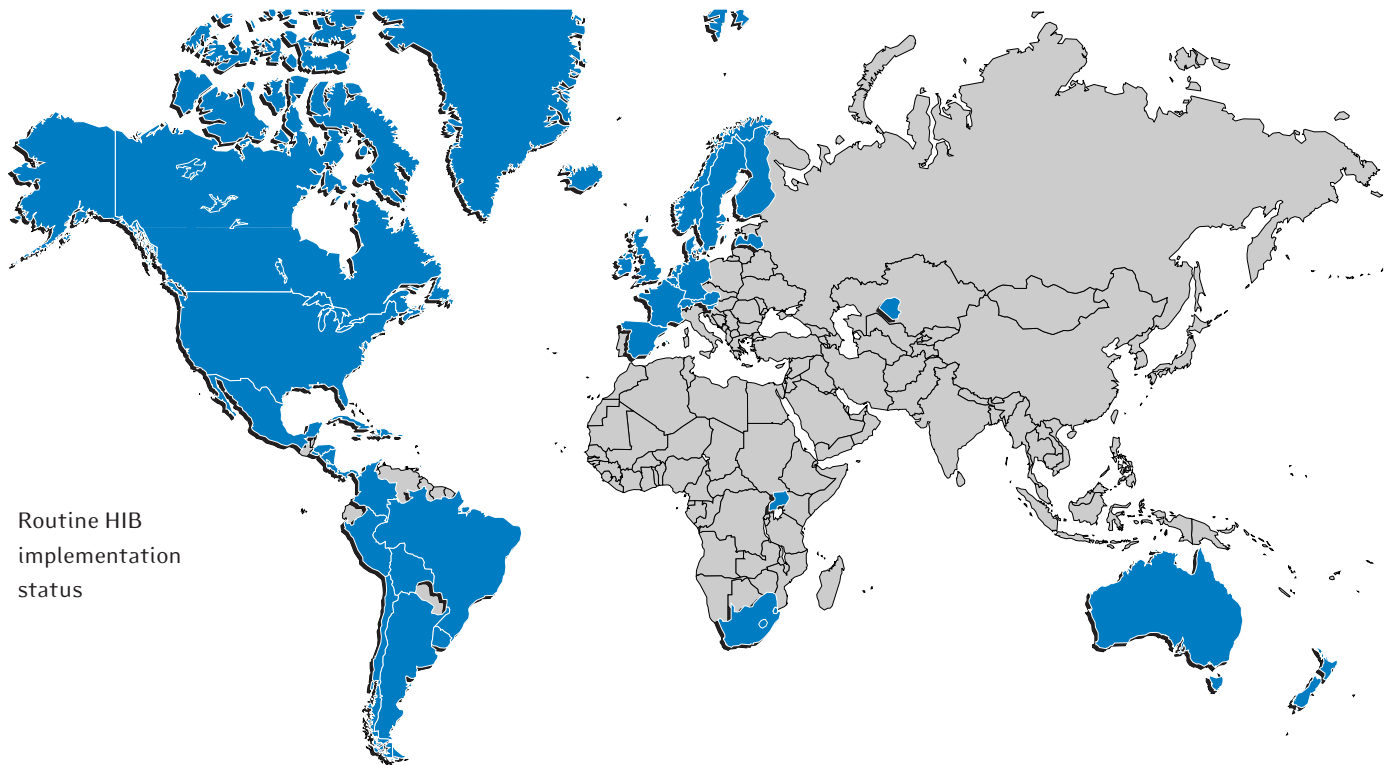
- Vaccine makers usually begin with modest production capacity when approval is imminent—far too late if immediate worldwide access is the goal. Companies delay scaling up for several reasons: They hedge their bets that their particular vaccine will be successful; demand is often uncertain or poorly analyzed; the profits for vaccines tend to be much lower than for therapeutic drugs; and production know-how is often lacking in the early stages of deployment.

- To contribute to R&D costs and to cover ‘overhead,’ makers of a new vaccine initially target industrialized country markets, where consumers and third-party payers have the willingness and ability to pay full price.

- As new vaccines are introduced into richer countries over several years, makers become more adept at manufacturing the vaccines. Production and distribution kinks are worked out; manufacturing costs per unit decline; and efficiency rises, producing increases in yield and supply.

- Over time, the price of the vaccine falls, as supply increases and competing products enter the marketplace. The vaccine is gradually introduced into wealthier developing countries, as delivery mechanisms are established.

FIGURE 1



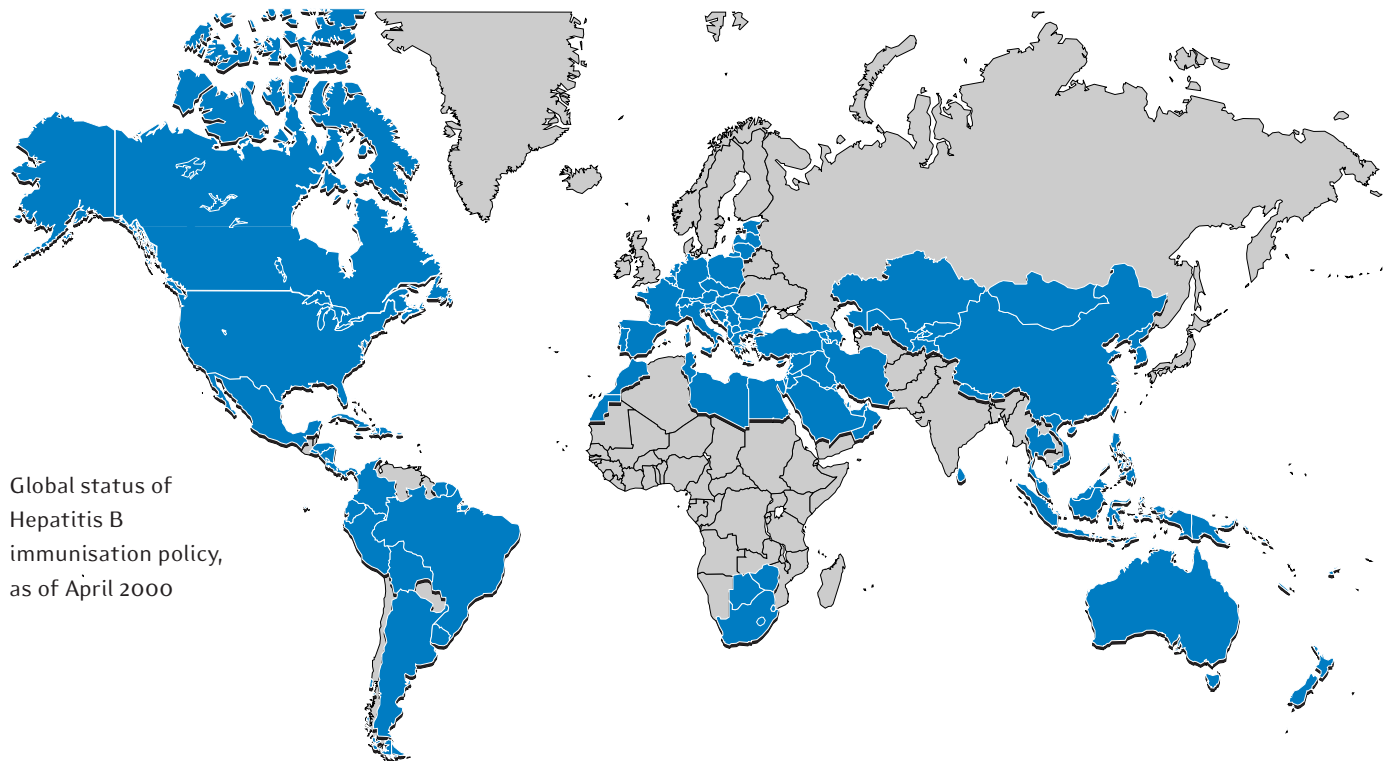
Routine Hib implementation status

Routine Hib implementation status

- No policy
- Routine policy

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers and boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.  
Source: World Health Organization, Department of Vaccines and Biomedicals

FIGURE 2



Global status of  
Hepatitis B  
immunisation policy,  
as of April 2000

Routine HIB implementation status

- No policy
- Routine policy

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers and boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.  
Source: World Health Organization, Department of Vaccines and Biomedicals

Economics alone do not fully explain the delays in deploying new vaccines in developing countries.

- Eventually, when the price is perceived to be low enough, developing country governments and international donor agencies begin purchasing the vaccines. Many years—perhaps as long as a generation—are required before the price declines sufficiently to permit wide-scale vaccination in the world’s poorest regions.

A vaccine maker’s approach to pricing also has a potentially important impact on the pace at which the above-described steps take place.<sup>1</sup> Industrialized countries constitute the global market’s core market because, although these markets only purchase a small number of doses, they do so at full price. Organizations like UNICEF purchase large numbers of doses of vaccine (estimated to be between 20 – 35 % of the total volume produced by the global manufacturers). However, these volumes only account for a small fraction of the manufacturer’s total revenue (less than 5 %) because of special low prices for the poorest developing country markets. Some manufacturers might, in an effort to ensure they can stay in business for the long run, charge a single, average ‘flat’ price worldwide. Such flat prices

would be inevitably beyond the means of most poor countries and international donors. Developing countries and international donors are simply unable to hold their own in the same market with buyers who are both willing and able to pay high prices. Flat pricing, therefore, substantially delays developing countries’ meaningful access to important vaccines.

From a global health standpoint, a far preferable approach is to segment the global market for pricing purposes according to ability to pay. This approach, known as ‘tiered pricing,’ permits a manufacturer to charge different prices in different countries. Companies that offer lower prices to poorer countries typically seek to balance a range of competing concerns, including a country’s need for the product, the certainty that the product will actually be used by the population in need (rather than be diverted for resale in other markets), the purchaser’s ability to pay, and, of course, the company’s own desire to maximize revenues and profits. Political acceptance of tiered pricing is a prerequisite to a company’s willingness to pursue the

practice. Any indication that political support does not exist for differential pricing typically prompts companies to gear pricing strategies exclusively to the needs of the primary market in industrialized countries.

Although tiered pricing generally accelerates the introduction of vaccines in poorer countries by enabling large purchases by international organizations, national governments, or donors, it is normally an available option only many years after initial licensure, as companies typically take years to develop sufficient production capacity to permit such large purchases at low prices (especially in the absence of alternative global mechanisms to subsidize vaccine purchases). In addition, because developing countries have differing levels of resources, deciding how to tier prices can be difficult.<sup>2</sup>

Shifting to a new paradigm that facilitates simultaneous introduction of new vaccines in ‘North’ and ‘South’ will require that global policymakers address pricing and other economic realities of the vaccine world. This will necessitate consideration of alter-

<sup>1</sup> Vaccine production is said to be a ‘fixed cost business,’ i.e., costs, after R & D, are heavily determined by costs of R&D and production plant. The production cost of vaccines is heavily scale-sensitive, i.e., the larger the volume of doses produced, the lower will be the per dose cost. Within the capacity limits of a particular manufacturing plant, the cost of producing a few more doses can be said to be “fully marginal,” i.e., just the costs associated with those doses if the main running costs are assigned to the basic production for sales to affluent markets. If the volume of ‘extra’ doses is more substantial, then some other costs, such as quality control for those doses, are also assigned to their production cost (the term ‘marginal price’ is used to describe this pricing level).

<sup>2</sup> Because there is now a considerable range between richer and poorer developing countries, some agencies, such as the former Children’s Vaccine Initiative (CVI) and its successor Global Alliance for Vaccines and Immunization (GAVI), have proposed a ‘market segment’ solely for the very poorest countries.

## Rapid worldwide introduction of an AIDS vaccine demands advanced planning.

nate economic approaches to vaccine production, possibly including developing country manufacture of vaccines in joint partnership with large pharmaceutical companies. (See appendix 2.)

Economics alone, however, cannot fully explain the unconscionable delays in deploying new vaccines in developing countries. The current approach also reflects the low value placed on disease prevention in developed and developing countries alike, as well as the refusal of Established Market Economies governments to recognize the necessity for global approaches to disease control. To accelerate the actual use of an AIDS vaccine in developing countries, it will be necessary to confront not only the economic realities of the vaccine field but also the political and attitudinal factors that have heretofore precluded worldwide access to safe and effective vaccines.

### **AIDS VACCINATION PRESENTS UNPRECEDENTED CHALLENGES**

Efforts to assure simultaneous, worldwide introduction of a preventive AIDS vaccine must address a daunting array of additional obstacles that are specific to HIV/AIDS. These include:

- The need to formulate policies in the midst of inherent uncertainty and political pressure
- The extraordinarily large number of at-risk individuals who will need immediate vaccination
- The absence of distribution systems for populations who most need a vaccine
- Social and attitudinal barriers to AIDS vaccination
- Special requirements associated with the delivery of AIDS vaccines

### **FORMULATING POLICIES IN THE MIDST OF INHERENT UNCERTAINTY AND POLITICAL PRESSURE**

Under the previously described historical paradigm for new vaccines, formulation of policies to promote vaccination in developing countries begins only after the vaccine has been widely used in industrialized countries. Rapid worldwide introduction of an AIDS vaccine, however, will demand that policies be developed and implemented long before the product is licensed.

The seriousness of HIV/AIDS will cause key decisions regarding potentially effective vaccines to be

subjected to unprecedented global scrutiny. In contrast to the slow pace of vaccination efforts for other diseases, the world's desire to stem the spread of HIV as quickly as possible will necessitate rapid evaluation of the costs, benefits, and risks of candidate vaccines. Decision-making on potential vaccines of limited efficacy will likely be complicated by the possibility that much better vaccines may be around the corner. (See Table 1.)

Moreover, once protection against HIV is first achieved, improved vaccines are likely to follow rapidly, given the range of scientific technologies now available. As these second and third generation vaccines become available, strategies and programs for vaccination against HIV/AIDS will need to evolve rapidly. This contrasts with the typical immunization scenario where the first widely introduced product is rarely replaced.

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**TABLE 1: HYPOTHETICAL SCENARIOS OF AIDS VACCINE AVAILABILITY**


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**Generation 1: Possibly wide availability in 2004-2008**


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- Low (~40 %) protection against infection with closely related strains (such a vaccine may not have wide clade or geographic coverage)
- Moderate (e.g., 10-fold) prolonged reduction in viral load
- Multiple doses, short-lived protection (e.g., 3 doses and 6-monthly boosters)
- Parenteral route of administration

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**Generation 2: Possibly wide availability in 2008-2012**


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- Moderate (~70%) protection against infection, most strains
- Better or substantial (e.g., 100-fold) prolonged reduction in viral load
- Multiple doses but longer-lived protection (e.g., 3 doses and 3-yearly boosters)
- Parenteral route of administration; oral booster

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**Generation 3: Possibly wide availability in 2010-2020**


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- High (~90%) protection against infection, most strains
- Extreme (e.g., 1000-fold) prolonged reduction in viral load
- Simple dosing (e.g., 2 doses, 10 years booster)
- Oral route of administration

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Hypothetical scenarios on vaccine availability become more complex if vaccines must be specific to the locally/geographically prevalent HIVs.

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Existing vaccination services in developing countries are overwhelmingly geared to newborns.

**THE NEED FOR SWIFT VACCINATION OF AN ENORMOUS NUMBER OF AT-RISK INDIVIDUALS**

When introducing vaccines, public health campaigns target those most susceptible to disease. Historically, vaccines have been introduced into annual infant birth cohorts, which are relatively small. In the case of pediatric vaccines, this approach makes some sense, as the risk of pediatric diseases usually extends only a few years after birth and dramatically reduces with age.

With HIV, by contrast, the pool of sexually active persons susceptible to infection spans multiple age groups. Even assuming that sexual risk declines with age, the pool of older susceptibles who warrant protection would be many times greater than the cohort of people entering the at-risk pool in any given year.

Swift, worldwide vaccination of at-risk persons will require a massive volume of new vaccine. As explained above, however, the typical production curve for vaccine makers is to start small, then build capacity over time. An entirely different way of doing business will be needed in the case of HIV/AIDS.

Ensuring sufficient quantity of new vaccine will require sound estimates of the likely demand for the product. Unfortunately, the international agencies through which many developing countries obtain vaccines do not currently possess reliable techniques for assessing new vaccine demand. Estimating demand in time to ensure sufficient production capacity will require the development of sound, new economic models and the implementation of these new approaches well in advance of the actual date for introduction of the vaccine.

**THE PAUCITY OF RELEVANT DISTRIBUTION SYSTEMS**

Initial AIDS vaccination efforts will target adolescents (10–19 years), sexually active adults, and high-risk groups (e.g., sex workers, injection drug users, truck drivers, etc.). After most at-risk individuals have been reached, routine vaccination efforts will likely shift to early adolescents (10–13 years) in order to confer immunity prior to onset of sexual activity.<sup>3</sup>

Existing vaccination services in developing countries, though, tend overwhelmingly to be geared

to newborns. AIDS vaccines, therefore, will require that new delivery systems be developed for groups who need immediate vaccination (including adolescents; sexually active adults, including sex workers and migrant workers; and injection drug users).

Development of delivery mechanisms should build on existing health channels, such as reproductive health centers, HIV prevention programs, STD services, military health services, workplace clinics, and schools. Effective delivery of AIDS vaccines, though, will require substantial enhancement of existing vehicles. Programs to prevent neonatal tetanus, for example, reach only 40% of women of childbearing age, while out-of-school youth are not reachable through school-based programs. Creative solutions will need to be found, and ensuring that such solutions are in place the moment a vaccine is available will necessitate immediate action on the part of the global community.

**SOCIAL AND ATTITUDINAL BARRIERS TO AIDS VACCINATION**

The stigma associated with HIV/AIDS, which has often dis-

<sup>3</sup> The time it will take to adapt AIDS vaccines to infant vaccination makes the 'EPI'/infant system an implausible delivery vehicle for AIDS vaccination at least for the foreseeable future. (For example, a series of trials would be necessary with the promising candidates from adult trials, taking them through population groups of decreasing age, finally to the traditional infant 'EPI' group. If each trial lasted a total of 3 or 4 years and two or three were needed, then about 10 years would be necessary just to see if the vaccine worked in the infant schedule.) If implemented as an infant immunization, 15 to 20 years would elapse before the recipients of AIDS vaccination entered the age group at risk. There would be ethical questions in running the trials arising from the (side-effect) risk/benefit ratio of protecting infants and children against a disease transmitted overwhelmingly by sexual intercourse. The compatibility of AIDS vaccines with other pediatric vaccines would also need to be tested. Booster doses may well be required anyway in early adolescence, mostly negating arguments that utilizing the infant immunization system avoids having to develop a new delivery system.



Health officials will need to partner with affected communities to generate broad support for vaccination.

couraged government leaders and other public figures from acknowledging the seriousness of the disease, could similarly dissuade countries from embracing vaccination programs.

Opposition could arise from the belief that AIDS vaccination would encourage sexual promiscuity or illegal drug use. Individuals at risk of infection might also refrain from seeking vaccination out of a fear of being stigmatized as promiscuous, homosexual, or addicted to drugs.

Special educational efforts will be required to overcome the unique stigma associated with HIV/AIDS. In addition, it may be desirable for vaccination efforts within age cohorts to be universal, rather than selective, to reduce the potentially deterrent impact of HIV-related stigma.

Stigma, though, will not likely be the only attitudinal obstacle to AIDS vaccination. It is quite conceivable that early vaccines will offer lower-than-optimal protection against infection (say, 40%, versus the 70-95% typical for traditional vaccines). While such a vaccine could have an important public health benefit in curtailing the spread of the virus, it might be difficult to convince individuals to accept a vaccine that would leave them at considerable risk of

infection. Policy decisions regarding these vaccines—whether to utilize at all, to mandate or to ‘socially market’—will be difficult and need to be determined by local circumstances.

Addressing these and other social and attitudinal barriers to vaccination will require health officials to partner with affected communities to generate broad support for vaccination efforts. Among those who should be enlisted in these partnerships are non-governmental and community organizations, AIDS service organizations, religious and tribal leaders, mothers’ groups, and civil society institutions.

Here, as in so many other areas, AIDS vaccination contrasts markedly with the typical infant vaccination efforts. In the case of pediatric vaccines, parents act as surrogate decision-makers and broadly accept pediatric vaccination. Efforts expended in education to increase acceptance are relatively simple and non-controversial, and demand can be roughly assumed to equal the birth cohort.

#### **SPECIAL REQUIREMENTS FOR AIDS VACCINATION**

With the exception of adolescent vaccination against hepatitis B, most vaccinations currently pro-

vided do not need to be accompanied by behavioral counseling. AIDS vaccination, by contrast, will require counseling of all potential vaccinees regarding the need to maintain protective behaviors, such as condom use and other practices, to reduce the risk of sexually transmitted diseases. Effective incorporation of behavioral counseling into vaccination efforts will require training of health personnel, as well as ongoing monitoring, and will complicate mass vaccination campaigns. Without effective counseling, vaccination might even have a negative impact, especially with vaccines of lower efficacy, by generating increases in risk behavior that partially or wholly offset the limited protective effect of the vaccine against HIV and also lead to other reproductive tract infections.

In contrast to pediatric vaccines, where mothers make decisions on behalf of their child, the adolescent and young adult targets of AIDS vaccination efforts will need to give informed consent. In light of the well-documented human rights abuses associated with the spread of HIV/AIDS throughout the world, it will be vital to protect the human rights of those who receive AIDS vaccines.

### **WHY ADDRESS USE OF AIDS VACCINES NOW?**

The world's stake in ensuring the soonest-possible use of an AIDS vaccine could not be plainer. Prevention is the only answer for a chronic, devastating disease that for the foreseeable future is likely to remain incurable.

Still, given that an effective vaccine is probably years away, observers might reasonably ask why decision-makers should focus on utilization strategies now. In fact, the reason is clear. If we wait any longer before beginning to build the foundation for a new global vaccine paradigm, we are almost certain to see potentially useful vaccines emerge without the means to get them to those who most need protection against the virus.

Extraordinarily complex planning must be undertaken on a global basis for the evaluation of vaccine candidates and the development of procedures to ensure rapid use. Establishing new production capacity alone normally requires around 5 years and must be geared to accurate estimates of demand. Entirely new distribution strategies must be created for marginalized populations in the world's poorest countries, and a broad range of global players

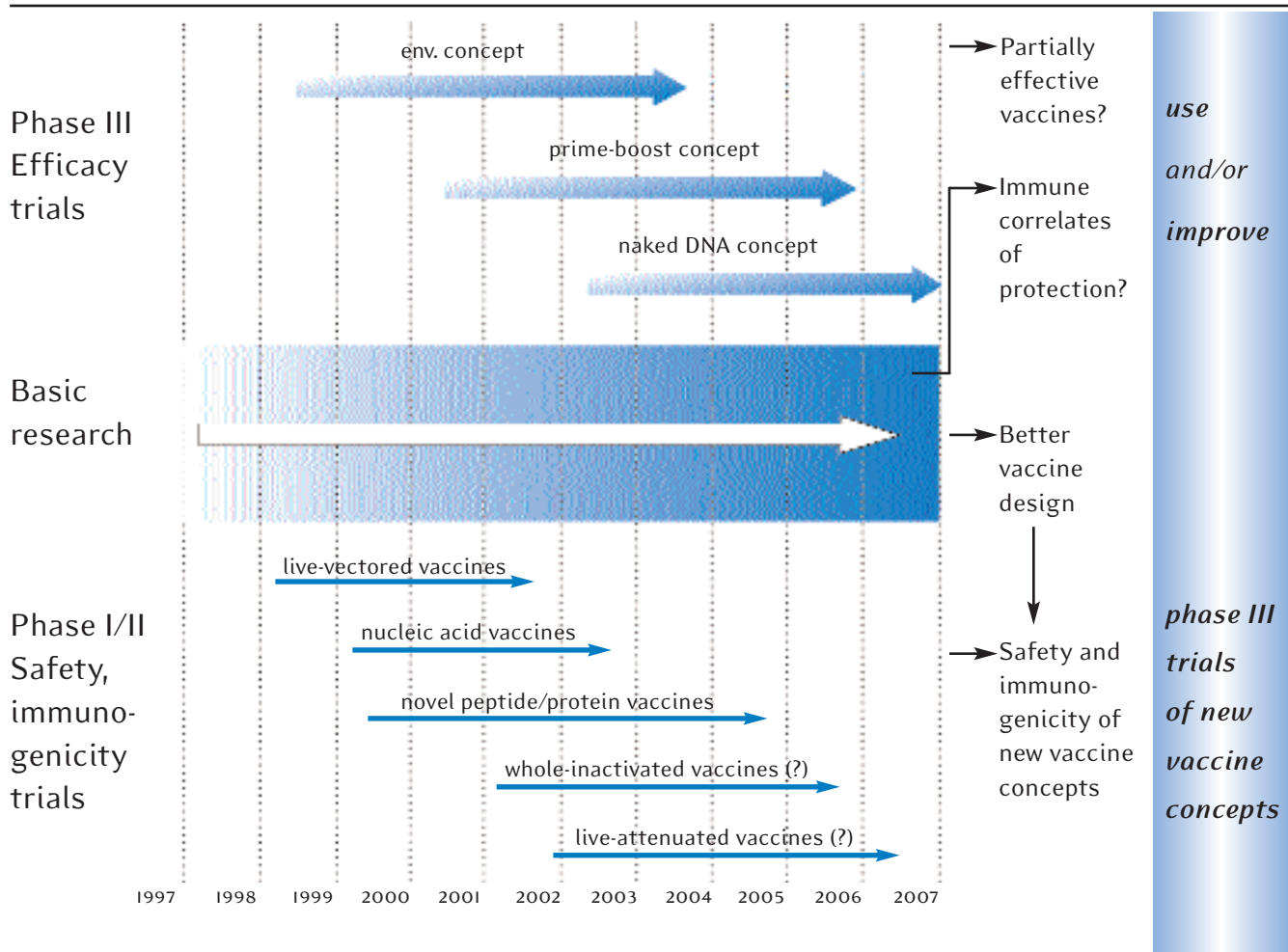
must be mobilized to make the mammoth financial commitments that will be needed to produce, purchase, and distribute vaccines. In short, the world has never attempted for any other disease the effort that will be required to help bring the AIDS pandemic to an end through rapid, large-scale vaccination.

The need for immediate action is underscored by increasingly rapid movement in the field of vaccine science (figure 3). Numerous vaccine approaches are already in various stages of development, and key decisions on candidates currently in trials may need to be made as early as 2002. It is apparent that we have not a moment to waste. While we must move energetically to strengthen HIV behavioral prevention and care initiatives in developing countries, we must also immediately begin addressing the numerous political, financial, and logistical barriers to timely use of a preventive vaccine, our best hope for overcoming HIV/AIDS.<sup>4</sup>

<sup>4</sup> Addressing financing and other mechanisms to ensure worldwide demand for, and access to, AIDS vaccines will also have an important impact on the willingness of private companies to invest in AIDS vaccine research and development. See IAVI's Scientific Blueprint for AIDS Vaccine Development.

FIGURE 3

## HIV vaccine research: What can be accomplished in ten years?



UNAIDS August 1998

**A GLOBAL ACTION PLAN:  
FIVE ESSENTIAL STEPS  
TO ASSURE  
SIMULTANEOUS,  
WORLDWIDE ACCESS**

A single theme—global commitment and collaboration—unites the action steps needed to ensure simultaneous, worldwide access to AIDS vaccines. The public sector must closely collaborate with the private (see figure 4); national governments must work in partnership with multilateral agencies; developed and developing countries must join together in a single global effort to promote AIDS vaccination; and affected communities and non-governmental organizations must finally become true partners in the ownership, development, and implementation of global health strategies.

Although the world has never attempted the ambitious, collaborative approach recommended here, this plan of action is eminently achievable in the presence of vision and will. In contrast to the historical paradigm for vaccination in developing countries—where each step from conception to deployment of a vaccine in the poorest countries is taken sequentially—we must begin moving immediately on each of the following steps to ensure widespread availability of new AIDS vaccines.

**I. Effective pricing and global financing mechanisms must be developed to ensure that vaccines are promptly available for use where they are needed.**

**Key political leaders and institutions should join with the private sector in endorsing the use of a tiered pricing structure for AIDS vaccines that enhances access by permitting poorer countries to pay what they can afford and at the same time permits companies to obtain a satisfactory return on investment.**

In developed countries, richer consumers typically subsidize health care for the less affluent—whether through a commonly financed system of universal health care or via carefully structured relationships between different segments of the health care market. The same general approach makes sense in the case of vaccines. The higher price paid by industrialized countries (normally the primary market served by vaccine makers) enables the manufacturer to cover its R&D and other overhead costs, which in turn allows the company to charge lower prices to poorer countries while still making a small profit on the sale. Consistent with this approach, IAVI's vaccine development partnerships include intellectual property provisions that help ensure that lower prices will be available in developing countries for any successful vaccine.

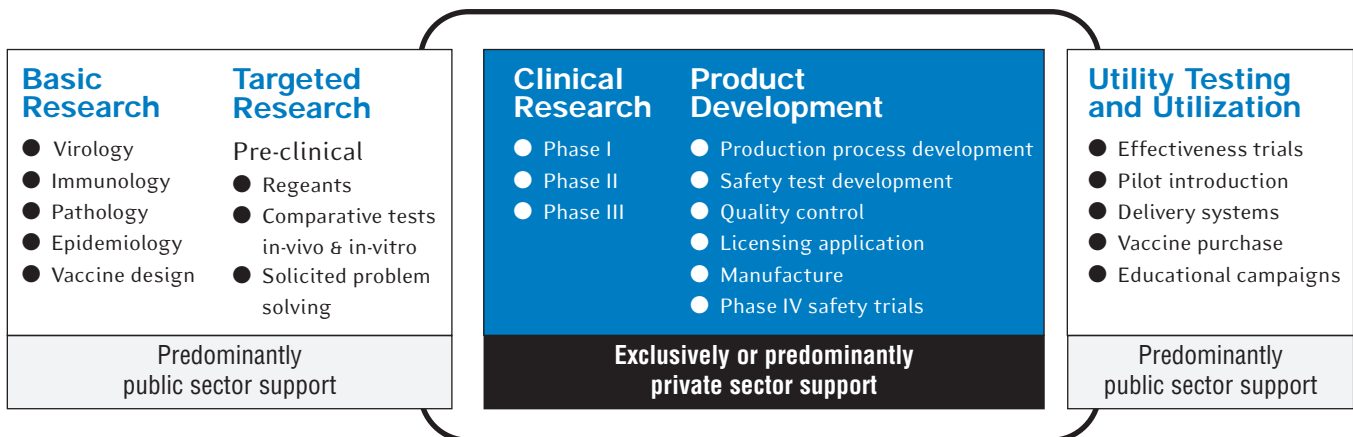
Despite its clear health benefits, tiered pricing is not universally

accepted. Some companies avoid the practice due to concerns about potential political ramifications, and consumers in richer countries sometimes believe they are being gouged when a company offers lower prices for its products in other parts of the world.

Political leadership will be needed to enable both companies and the general public to understand the global imperative for tiered pricing of vaccines. At the national and international levels, leaders must lay the groundwork for tiered pricing through extensive public education. National governments, multilateral agencies, and influential international groups (such as the G-8 and the World Trade Organization) should pass resolutions embracing tiered pricing. Individual companies and industry associations, too, must agree to price vaccine products in a manner that simultaneously generates profit and facilitates swift access for at-risk populations throughout the world.

**Global mechanisms to purchase and deliver vaccines for use in developing countries should be created, and the G-8 nations should immediately make credible financial commitments for the support of such mechanisms.**

## Who pays for vaccine development and utilization?



## Interest in devising purchase mechanisms for AIDS vaccines has recently increased.

It is impossible to estimate with precision the likely cost of worldwide AIDS vaccination. The overall price tag for a global vaccination effort, however, particularly at the outset, will certainly be substantial.<sup>5</sup> The cost per dose of an AIDS vaccine is likely to be considerably higher, at least initially, than the current cost (US\$0.50–\$2.00 per dose to the poorest countries) of relatively new vaccines like HB or Hib. In addition, unlike most pediatric vaccines, where broad coverage is attained over time, AIDS vaccination efforts will need to reach an extraordinarily large group of at-risk individuals in a comparatively short period of time, underscoring the necessity of developing unprecedented financing mechanisms sooner rather than later.

The cost of the vaccine itself may be outweighed by expenses associated with its delivery. This is already the case with traditional vaccines.<sup>6</sup> Thus, financing mechanisms must underwrite both vaccine purchases and the systems that will ensure the vaccine's delivery to those who need it. (The critical need to develop new delivery systems is addressed below in step 3 of the Global Action Plan.)

Even at sharply lower prices, many developing countries will still be unable to afford a new AIDS vaccine. Whereas middle-income countries themselves currently bear the cost of traditional infant vaccination, the poorest countries typically look to international donors for the financing of vaccines, syringes, and (in some cases) delivery. The same result is likely to obtain in the case of AIDS vaccines. While most countries might feasibly cover on their own the costs of AIDS vaccination, especially where they concentrate first on the highest-risk groups, the poorest countries (where HIV is expanding the fastest) will undoubtedly rely primarily on external assistance. Some countries may be eligible for concessional World Bank loans under International Development Association (IDA) conditions, but additional mechanisms will clearly be required to finance a worldwide AIDS vaccination effort.

In a visionary move, the World Bank and others are assessing AIDS vaccine financing mechanisms—both to encourage private industry to increase its involvement in vaccine research and to ensure that the purchasing capacity exists when a safe, effective

vaccine becomes available. The Bank's decisions on such mechanisms were pending in July 2000, when this Blueprint went to press.

The recently created Global Fund for Children's Vaccines (GFCV) seeks to accelerate introduction of 'newer' pediatric vaccines (HB, Hib) in the poorer developing countries (i.e., those with GNP less than US\$1,000 and population under 100 million).<sup>7</sup> Unfortunately, funding for this important new mechanism still comes overwhelmingly from a single source—the Bill and Melinda Gates Foundation. By comparison, industrial country contributions to this and other vaccination vehicles have been badly lacking thus far.

Interest in devising purchase mechanisms for AIDS vaccines has recently increased. U.S. President Bill Clinton, for example, has proposed that companies be given tax credits on the purchase of vaccines for use in developing countries. In the U.S. Congress, Senators John Kerry and Bill Frist and Representative Nancy Pelosi have introduced legislation that, among other things, would authorize annual U.S. Government contributions of US\$1 billion over the next 10 years to a vaccine purchase fund.

<sup>5</sup>The newest pediatric vaccine, the pneumococcal conjugate vaccine, has been marketed in the United States at \$262 for four doses.

<sup>6</sup>The six antigens most currently used in the expanded global immunization program together cost less than US\$1. Delivery costs for these vaccines range upwards from \$15, not including the heavy investments in delivery "infrastructure" in earlier years.

<sup>7</sup>Special arrangements for China, Indonesia, and India are under discussion.

**Private industry must have confidence that the maker of an AIDS vaccine will receive ample recompense.**

Similar discussions are occurring within the European Commission.

**While numerous frameworks are foreseeable in which a purchase fund would be feasible, what is critically missing at the moment is a credible financial commitment from the world's richest countries to ensure global availability of an AIDS vaccine as soon as one becomes available.<sup>8</sup> The G-8 nations must firmly commit to sufficient and timely financial support for an agreed-upon global mechanism to subsidize timely creation of production capacity (see below), purchase AIDS vaccines for poorer countries, and ensure the means to deliver these vaccines to those at risk (see below) if we are to succeed in meeting this challenge.<sup>9</sup>**

As a critical component to a global strategy to accelerate delivery of AIDS vaccines, finance ministries in developing countries must be educated as to the true value of vaccination. Historically, vaccines have been grossly undervalued, as the global community has assumed that vaccines that cost more than 'pennies per dose' are too expensive to be distributed widely. Yet, calculations demonstrate that vaccines for high-burden diseases (such as AIDS) would be cost-effective at

prices 10- to 50-fold higher than vaccines currently used for the EPI infant immunizations.

To encourage enthusiastic industrial involvement in the global search for an AIDS vaccine, private industry must have confidence that the maker of a safe and effective vaccine will receive fair and ample compensation. Consistent with the principle of tiered pricing, global vaccine purchase mechanisms must develop procedures for balancing the global health interests with the financial interests of vaccine manufacturers and their shareholders.

Purchase mechanisms will also need to be carefully coordinated with procedures (described below) for estimating demand, evaluating potential vaccines, and developing new delivery systems.

**II. Mechanisms must be developed to make reliable estimates of demand for specific vaccines and to ensure timely creation of production capacity to permit accelerated worldwide access.**

As noted earlier, manufacturers of new vaccines typically begin with limited production capacity, which is then augmented over time as production efficiency increases and as manufacturing

costs per dose decline. For most vaccines, creating new production capacity requires at least 4–5 years, and significant increases in yield take even longer to develop.

Producing a sharply different result in the case of HIV/AIDS, i.e., having an unprecedented quantity of high-quality vaccine soon after licensure, will require a completely new production paradigm and unprecedented anticipatory collaboration on a global scale. In addition, it will necessitate the forging of entirely new relationships between public and private sectors.

**To ensure appropriate preparation and coordination for the swift introduction of a preventive vaccine, an international body should be convened to monitor and evaluate vaccine candidates undergoing testing.**

Initial efficacy results from the earliest vaccine trials will soon start to become available—possibly as early as in 2001. Future testing of the numerous products currently in various stages of development will similarly generate safety and efficacy data. The needed global mobilization to ensure effective deployment of beneficial vaccines necessarily requires some method to evaluate

<sup>8</sup>Importantly, any commitment by the G-8 must be credible, i.e., it must consist of more than mere words but must instead be tied to meaningful commitments of present and future resources.

<sup>9</sup>Support for the purchase of vaccines for developing countries will likely require pursuit of numerous mechanisms, including a purchase fund for the poorest countries, World Bank loans for IDA-eligible countries, and other incentives for middle-income countries.

**Initial efficacy results from the earliest vaccine trials will soon start to become available.**

candidates, devise AIDS vaccination strategies geared to research findings, and provide information and advice to national authorities.

No such mechanism currently exists. An appropriate international body (such as UNAIDS or WHO) should, following necessary consultation, convene a panel composed of expertise in epidemiology, vaccine development and testing, vaccination logistics, HIV prevention strategies in general, and delivery of health services to likely target populations (adolescents and at-risk sexually active adults). Key stakeholders should be represented, including senior government representatives from both industrial and developing nations.

This panel should meet regularly and be staffed appropriately. It should remain abreast of developments in the vaccine research field and anticipate when key policy decisions will need to be made. The panel will use the information it receives to evaluate potential vaccines, make recommendations to key global entities, and advise national governments. As described below, the panel's recommendations should, where appropriate, trigger a broad range of financial, industrial, research, educational, and public health actions—at national and multi-

national levels—to ensure timely introduction of safe and effective vaccines in developing countries. It is essential that this process be transparent.

**Based on evaluation of available data regarding particular vaccines, appropriate utility studies should be commenced in regions where efficacy trials are not occurring.**

Experience has demonstrated that vaccines do not necessarily produce the same results in all geographical settings. This is particularly true when there is variation between settings in regard to prevalent strains of the pathogen, the nutritional and immunologic status of the recipients, or the prevalence of concomitant infections. Hence, testing of new vaccines for relevance or 'utility' to settings and populations beyond the site of initial trials is—and should be—standard practice.

With HIV/AIDS this need is especially apparent. Not only do different viral clades<sup>10</sup> predominate in different regions, but individual genetic backgrounds differ, potentially affecting immunologic response to antigens. In addition, people become infected with HIV through multiple routes of exposure and may be differently protected by vaccination depending on subsequent exposure modes.

National policy makers will be more comfortable proceeding with introduction of a vaccine if they have evidence that the product is likely to be effective in the populations for which they have responsibility. Theoretically, of course, a full-scale efficacy trial could be conducted in each country and in each at-risk population in which the vaccine might be used. Such an approach is clearly impractical because of time and cost.

Strategies must be developed to test the utility of promising vaccines in a variety of representative settings. A group of experts should be convened to design and oversee strategies for the rapid assessment of the suitability of vaccines in late-stage clinical trials for use in settings beyond their initial testing sites. This working group should include representatives of all relevant organizations, agencies, and potential vaccine users.

**Analytic studies should be undertaken to inform decisions regarding introduction of AIDS vaccines in developing countries.**

Effective policy decisions must be informed not only by accurate data on the safety and efficacy of specific vaccine candidates, but by other forms of essential information. For example, the epidemiol-

<sup>10</sup> Clades are groupings of genetically related viruses that may differ immunologically.



Accurate estimates of private market and public sector demand are urgently needed.

ogy of HIV in different risk groups in each country must be modeled in order to permit assessment of the impact and cost-effectiveness of vaccines with different characteristics and to gear delivery systems to the features of the populations most in need.

Decision-makers will also require information to determine whether to delay use of first-generation vaccines in anticipation of more safety information or more effective second-generation products. Modeling the impact of vaccine use on the overall progression of the epidemic, regionally or globally, will be useful in comparing the benefits of intervention with early generation vaccines versus delay and use of subsequent, possibly more effective or easier-to-use versions. (See appendix 3.)

Multilateral and bilateral donors and national governments should finance analytic studies that are required to mount country-specific vaccination programs.

**A comprehensive effort should be initiated immediately to assess and predict private market and public sector demand for AIDS vaccines.**

Assessments of demand are the foundation upon which key commercial decisions are based in the vaccine field. To pursue product

development efforts in the first place, companies must believe that their efforts will produce sufficient financial return. In addition, companies inevitably consider likely future demand in calibrating production capacity. Accurate predictions of demand are critical to avoid vaccine shortages and to assemble the financing needed to underwrite vaccination programs in poor countries.

Results from the first phase III trials are expected in less than two years. Yet, to date, no authoritative estimates of demand for AIDS vaccines have been developed, and techniques to estimate demand outside industrialized countries are presently lacking. The need for immediate action on this front is apparent.

Because no tested method exists for estimating demand in these circumstances, experts should compare demand estimates using a number of different approaches, including commercial market analysis, approaches based on the delivery of reproductive health services, and approaches based on the number of individuals presently reached (and not reached) by HIV prevention programs. In all such efforts, it will be important to incorporate the likely acceptance of AIDS vaccination, as assessed by community

or non-governmental groups.

Estimation of demand for AIDS vaccines should first be attempted in countries where clinical trials are either planned or underway. These countries have already established some population awareness of the desirability of AIDS vaccination, and therefore may reflect a more accurate reading of ultimate population acceptance.

Because it is impossible to know in advance the results of clinical trials, it will be important to calculate a range of demand estimates based on various assumptions regarding vaccine characteristics, efficacy, and price. The credibility of these estimates will depend on transparency in the assumptions on which estimates are based, as well as the methodology used to determine likely demand.

This access blueprint requires not only accurate assessment of demand but the redefinition of demand consistent with the proposed new paradigm. By developing new financing and delivery mechanisms for poorer countries, the new vaccine paradigm proposed herein will inevitably produce greater demand at an earlier period in the vaccine deployment trajectory, which must be taken into account in the development

**Subsidies may be necessary to accelerate the construction of production capacity.**

of new tools to improve the assessment of global demand.

**Based on sound estimates of demand, appropriate multinational and national financial institutions should collaborate with private industry and/or explore other mechanisms to ensure that sufficient production capacity exists to ensure worldwide introduction of new vaccines.**

The need for unprecedented quantities of vaccine shortly after initial licensure—a radical departure from standard practice in the industry—will make planning production capacity particularly problematic. Additionally, the likelihood that new, improved vaccine generations will displace early products will make potential producers reluctant to invest in production capacity, especially in the face of downward pricing pressures.

The level of needed production capacity will depend on the specific characteristics of individual vaccine candidates. For example, as a vaccine of limited efficacy is likely to generate less demand, it will require a smaller volume production capacity than, say, a highly effective, easy-to-administer vaccine with clear worldwide applicability.

Vaccine production plants generally require four to five years to

commission, design, build, and validate. Construction costs for a large plant may range from US \$100 million to \$200 million, with additional investment required if other support services are needed.

The lead time required to ensure sufficient production capacity to meet worldwide demand necessitates the development of mechanisms to monitor vaccine candidates and anticipate potentially needed production build-up. (See above recommendation on creation of an international vaccine monitoring body.) In addition, since private companies are unlikely to voluntarily incur such costs without certainty that they can be recouped, it is vital to develop financial incentives (e.g., subsidies, World Bank loans and credits, tax incentives from national governments) to encourage and accelerate production capacity that might not otherwise be built. New ways of doing business must be developed to permit honest, meaningful negotiations between public and private sectors regarding steps to ensure sufficient capacity to meet early worldwide demand.

Historically, new vaccines have most consistently emerged from a handful of major pharmaceutical companies or from a small number of specialized commercial or

quasi-public institutions. With AIDS vaccines, it is also possible that effective candidates might come from biotechnology companies, although such companies have less experience with large-scale production. Each of these potential producers, and their possible financial backers, will have different perspectives and inclinations towards investment in large-volume production. Some may be more willing and able to invest if rewards are clear; some may be more willing to consider licensing or transfer of technological know-how for production to reputable partners in developing countries with demonstrated capacity to produce biologics to internationally acceptable quality standards.

If vaccines need to be specifically tailored to developing countries, this demand will be especially acute. For example, there is currently no incentive for a large multinational pharmaceutical company to manufacture a vaccine only for the African market. In this case, public sector intervention—consistent with the protection of intellectual property and assurance of a sufficient return on investment—will be essential. For example, the public sector should consider the potential for developing country manu-

New delivery systems will be needed to reach adolescents and others at high risk.

facturers to produce AIDS vaccines.<sup>11</sup>

Negotiation of investment in production capacity to meet global demand will need to be undertaken with each potential producer in a highly confidential and ‘opportunistic’ fashion, as the scientific picture regarding specific candidates becomes clearer. Monitoring by the international vaccine body should play a key role in identifying appropriate targets for negotiation. Efforts to plan and enhance production capacity must be closely linked with strategies to underwrite the costs of purchasing and delivering vaccines in poor countries. In addition to the companies, key players in these negotiations to enhance production capacity include the World Bank, developing country manufacturers (where appropriate), governments from ‘donor’ and other heavily affected countries, and other interested parties.

With respect to such negotiations, there is considerable potential for suspicion between public sector agencies, hoping to lower costs by driving down prices, and commercial companies seeking what they regard as reasonable compensation for the risks of product development. In these circumstances, interested but impartial

brokers may play a critical role.

Appendix 4 contains relevant information on the economics of vaccine production.

**III. Appropriate delivery systems, policies, and procedures must be developed for vaccination of adolescents, sexually active adults, and other at-risk populations.**

**Developed and developing countries, health experts, multilateral institutions, non-governmental organizations, and other appropriate parties should collaborate to design and establish vaccine delivery systems in developing countries.**

As existing vaccine delivery systems tend not to serve the populations that will initially be targeted by AIDS vaccination efforts (e.g., adolescents, sexually active adults, and other high-risk groups such as injection drug users), work should begin immediately on devising a milestone-driven strategic plan to ensure that such systems are in place when a preventive vaccine is ready for distribution.

Although existing systems have limited relevance to AIDS vaccination, experience nevertheless provides starting points for the development of a strategic delivery plan. For example, recent

experience with vaccination campaigns for polio, measles, and other vaccines should be studied, as some have on occasion targeted adolescents and young adults. In addition, study should be directed toward existing health delivery systems on which vaccination programs are likely to be based (e.g., reproductive health services, HIV prevention/education programs, STD clinics, military health services, services for injection drug users), although AIDS vaccination efforts will need to improve substantially on current coverage rates for basic health services.

Importantly, there are other public health benefits to the creation of comprehensive services to reach populations at high risk of HIV infection. If, for example, schools figure prominently in the delivery of AIDS vaccines, such sites could become key sources for health education on reproductive health and pregnancy, tobacco, safe motherhood, and accident avoidance.

Strategic plans for vaccine delivery must be country-specific (and sometimes community-specific) and informed by in-country research on the epidemiology of HIV and the existing health and social service infrastructure. In especially hard-hit countries, ini-

<sup>11</sup> There are an enormous number of developing country manufacturers. However, most produce only one or more of the traditional and simple-to-produce EPI vaccines, and many have significant problems in quality control. Currently, there are a small number of vaccine producers operating in developing countries that meet global quality standards. With adequate technical and financial support, these and the manufacturers in developed countries could rise to meet the needs associated with AIDS vaccines. (See Appendix 2.)

Vaccination must be accompanied by behavioral counseling and respect for human rights.

tial mass vaccination campaigns may be preferred, whereas other countries might instead focus on systems to deliver vaccines to identified at-risk subpopulations. Economic models will be needed to estimate cost-utility of different delivery approaches. Importantly, while industrialized countries and multilateral institutions may be pivotal in underwriting the development and implementation of new delivery systems, decisions regarding the actual delivery approaches to be pursued in each developing country must be made by the country itself. Countries are, however, likely to need substantial technical assistance in devising and implementing strategic delivery plans, and measures should be taken to ensure availability of such support.

In both planning and actual delivery, it will be essential to include experts in the fields of sex work, injection drug use, out-of-school youth, and men who have sex with men. AIDS vaccination must be accompanied by appropriate behavioral counseling and by a respect for vaccinees' human rights,<sup>12</sup> and strategic planning for delivery of vaccines must take such issues into account.

Key actors to be included as partners in planning for delivery

include representatives of affected and at-risk populations; public health officials; providers of health services; representatives of military health services, where appropriate; representatives of UNAIDS, WHO, UNICEF, the World Bank, UNDP, UNFPA, UNESCO (see appendix 5) and other international humanitarian organizations; bilateral development assistance agencies; regional political and economic bodies; and potential suppliers of vaccines, injection equipment and other materials needed for program implementation.

**Strategic plans should be developed—at international, regional and country levels—to communicate and advocate regarding AIDS vaccines. Such efforts should be directed to policy makers, the general public, and populations most affected by HIV/AIDS.**

Some of the unique features of HIV/AIDS—discrimination, stigmatization, resistance, fear—make communication to achieve understanding and acceptance of vaccination perhaps the most difficult aspect in preparing for vaccine utilization. The range of target audiences is wide: politicians, policy makers, health care providers, potential recipients, and affected communities.

Accordingly, communications strategies—including choice of message(s) and communications channels—will need to be carefully tailored to specific audiences. Without considerable expenditures to promote public acceptance of AIDS vaccination, the many other investments called for in this Blueprint may be wasted.

The success of AIDS vaccination efforts will depend on support from, and sound decision-making by, key policy makers.

Uncertainty regarding safety or efficacy of vaccine candidates, or opposition from certain groups to AIDS vaccination, may incline decision-makers to delay or even deny access to preventive vaccines. Thus, systematic efforts on the part of one or more disinterested, recognized bodies will be needed to communicate up-to-date, accurate, and consistent information to policy makers regarding the development, safety, efficacy, and potential public health impact of specific vaccine candidates.

Within countries, this dissemination of information to policy makers must extend beyond the top layers of the ministry of health. It should also target ministries of finance, which set national budgets, and regional

<sup>12</sup>Areas that must be addressed to ensure protection of human rights for vaccinees include non-discrimination, privacy, community involvement, non-coerced participation, and informed consent.

**Regulatory requirements  
should be harmonized as  
quickly as possible.**

and district level managers who, in decentralized health systems, also need to understand the reasons early use of AIDS vaccines is desirable. These groups (in addition to national health policy makers) must understand the importance of allocating adequate resources to HIV prevention.

Policy makers, however, will constitute only one of many groups that must be targeted by sound communications strategies. The general public's view of AIDS vaccination may affect not only politicians' decisions but also the willingness of individuals to take the vaccine. Country-wide communication strategies must, therefore, be developed. (This will be needed not only in the developing countries where vaccination efforts will be centered, but in industrialized countries, where public support will be needed for the considerable financial contributions that will be required.)

Of course, special communications efforts must target populations at highest risk. Not only will the need for accuracy be paramount with respect to information supplied to marginalized and/or stigmatized groups, but communications efforts toward such populations must also recognize the human rights implications of vaccination programs.

HIV vaccination programs will be optimally effective if they are based on voluntary acceptance—by countries, communities, and individuals. Persuasion, not coercive promotion, must guide communications strategies to enhance acceptance of vaccination. The global desire for rapid uptake of new AIDS vaccines must not override the essential need for careful, respectful community and individual education. For example, for vaccines with more limited efficacy, it may be desirable to promote their public health benefits (e.g., reduction of viral load and associated transmission) rather than market them as individual protection against infection.

**Model approaches to individual education, counseling and informed consent should be developed, piloted and evaluated.**

The hoped-for end result of all vaccine-related communications efforts is widespread, genuine, informed acceptance of the vaccine by appropriate vaccinees. Model approaches for individual education and informed consent should be developed and pilot-tested, for subsequent adaptation to specific country and risk-group circumstances. A key element to such a model approach must be education and counseling of vac-

cinees to maintain behaviors to reduce the risk of HIV infection.

All agencies and institutions involved in AIDS vaccine delivery should adopt common principles and standards for informed consent and risk-behavior counseling. Reaching such an outcome will require that discussions begin long before a vaccine is available for use.

**IV. National regulations and international guidelines governing vaccine approval and use must be harmonized.**

Individual countries license vaccines for use within their borders, and national approaches to market approval often vary widely. In all countries, ensuring the safety of approved vaccines is an overriding concern, although no consensus currently exists on how the safety of candidate AIDS vaccines should be evaluated.<sup>13</sup> (See appendix 6.) Unless variations in national regulatory approaches are addressed prior to emergence of a useful vaccine, access could be substantially delayed while manufacturers perform additional studies or 'repackage' technical material to meet the demands of diverse regulatory schemes.

The relevant regulatory agencies, technical organizations and potential producers should initiate a

<sup>13</sup> Existing candidates employ a broad range of approaches, complicating the development of standards to assess vaccine safety. In addition, risk-benefit tolerance varies from country to country, depending especially on the severity of the epidemic and the availability (or lack thereof) of alternative disease-control strategies. See appendix 5.

**Efforts should be undertaken to educate decision makers about the cost-effectiveness of vaccines.**

process to clarify issues of vaccine safety, reach consensus on approaches to measuring safety, and harmonize regulatory requirements as soon as possible. In formulating requirements and in assessing vaccines, regulatory agencies should, in light of the expanding epidemic, carefully weigh the incremental value of additional requirements against the delays to introduction and their consequences in terms of new infections. The ‘fast-track’ approval and post-licensure monitoring mechanisms adopted for AIDS drugs should be reviewed for lessons.

Additionally, it will be necessary to address potential liability concerns associated with vaccines. Leading experts believe that liability concerns currently discourage some companies from entering the vaccine field; similar worries might dissuade manufacturers from introducing vaccines in key markets or under particular circumstances. These potential problems should be addressed well in advance of the availability of a safe and effective vaccine, and efforts should be made to harmonize competing national liability approaches to the greatest extent possible.

**V. To demonstrate global commitment to effective worldwide deployment of**

**important vaccines, immediate efforts should be undertaken—using the approach articulated in this document, and building on existing mechanisms, such as the Global Alliance for Vaccines and Immunization (GAVI) and the Global Fund for Children’s Vaccines (GFCV)—to achieve maximum use in developing countries of one or more currently underutilized non-AIDS vaccines.**

**Efforts should be undertaken to educate decision-makers and finance personnel about the cost-effectiveness of vaccines.**

Although vaccines are among the most cost-effective medical interventions available, they have historically been grossly undervalued. Notwithstanding the worldwide ravages of various infectious agents, the global community has repeatedly concluded that vaccines that cost more than pennies per dose are too expensive for widespread use. According to studies, however, existing vaccines would remain cost-effective even if their per-dose prices were 10–50 times higher than they are now.

To reverse the historic undervaluation of vaccines, it will be necessary to alter global attitudes about this critical preventive approach. Although lower prices

are critical to purchasing as many doses as possible in a resource-constrained environment, those responsible for allocating resources—finance and health ministers, insurance companies, consumers, and donors—must also be educated as to the value of immunization. They must be convinced to provide at least partial or even complete financing of these cost-effective efforts.

**Existing vaccines that are safe, effective, approved, and used in developed countries should, where needed, be supplied to the poorer developing countries.**

For nearly two decades, the global community has failed to make vaccines for serious diseases (HB, Hib) available in developing countries. Not surprisingly, industry declines to take seriously occasional pronouncements by the public sector regarding the importance of immunization. When it comes to the mammoth investment required to produce vaccines for global distribution, actions mean more than words.

On the other hand, public sector suspicions regarding the motivations of private industry have led to a less-than-ideal degree of communication between these worlds. Through new initiatives—such as GAVI, IAVI, and the former Children’s Vaccine Initiative—this communication breakdown is

GAVI and IAVI are helping to  
heal the communications  
breakdown between the public  
and private sectors.

beginning to heal. The public sector must understand industry's needs and motivations, as well as the enormous pressures placed on corporate management by their shareholders and capital markets. Ways for public and private sectors to work together must be defined and tested until both sides are comfortable in a new working relationship.

GAVI and GFCV represent such an attempt with regard to existing vaccines. GAVI, for example, is an alliance of public and private groups, with a shared mission to increase the immunization of children throughout the world. Partners in GAVI share the situation analysis, vision and strategic objectives of the alliance, but each implements its own activities. To demonstrate the seriousness of global resolve to increase childhood immunization, GAVI, GFCV, and other key actors should demonstrate not only that an existing, high-priority new vaccine can effectively be delivered, but also that the necessary political will and commitment can be mobilized to make use of the vaccine sustainable. Although such success will not obviate the immediate need for effective pricing and purchase mechanisms for an AIDS vaccine, it will give those in company board rooms the confidence to move ahead in partnership with the public sector.

Scientific experts now believe that a safe, effective AIDS vaccine is feasible. Numerous candidate vaccines are entering the development pipeline, and one is already in phase III testing. Such development efforts need acceleration (as explained in *IAVI's Scientific Blueprint for AIDS Vaccine Development*), but political and financial support on the scientific front is clearly on the rise.

Success in creating a vaccine—wonderful as that would be—might nevertheless be a public health disaster if we refuse to plan for its arrival. Already, drugs and vaccines too numerous to count exist to treat or prevent global killers, yet many such products are unused where they are needed because the world assumed—wrongly—that ‘someone’ would provide for their distribution.

With an AIDS vaccine, we will finally have the tool needed to bring to an end the worst health catastrophe of the modern era—a pandemic that is causing unprecedented misery and social disruption. If we act now, the development and deployment of future AIDS vaccines could help forge a new model for dealing with other emerging infections and global public goods.

If we wait until such a product is available before making concrete plans for its distribution, those in need will wait years, perhaps decades, before obtaining access. The greatest scientific triumph of our era might well turn into its worst, most condemnable humanitarian disaster.

The world has the power to accomplish every step set forth in this Access Blueprint. IAVI, for one, is prepared to help with any and all of the strategies identified herein. The vision of worldwide access described in this access blueprint, however, can be achieved only through a global mobilization and the participation of all key stakeholders.

History is watching. It will judge how we respond to this challenge.



## APPENDIX I INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

In general, the elements contributing to ultimate utilization of vaccines are as follows:

### Pre-Licensure

- Understanding of the disease epidemiology, the pathogen, and the responses to infection, sufficient to develop vaccine concepts
- Testing/validation of vaccine concept(s), in animal models if appropriate
- Anticipation of commercial viability of potential products, and assessment of potential deterrents to development, such as litigation/liability and ethical constraints
- Product definition and production process development, often dependent on guidance from regulatory agencies
- Initial establishment of manufacturing capacity
- Clinical testing of product(s)
  - Phases I, II, and III in one or more of the intended target populations
- Application and regulatory approval for at least one of the intended target populations, based on evidence of efficacy, safety, duration of protection, and consistency of production methods

### Post-Initial Licensure

- Adaptation or (re-)design of vaccine to make suitable for use in developing countries and testing in such settings
- Decision processes for national policies on use (which must have credence with anticipated implementers and intended target populations) and international guidance or recommendations from

international bodies

- Establishment of effectiveness/utility in other intended target populations, as necessary
- Regulatory approval in other jurisdictions of intended use
- Demonstration projects before wide-scale introduction
- Communication of the scientific rationale for recommended vaccination strategies to policy makers and health care providers, and achievement of their acceptance by target groups and the general public
- Supply, i.e., sufficient initial or expanded production capacity (dependent on estimates of demand and uptake), including consideration of "supply management" in shortages and local production/technology transfer as long-term means of capacity expansion
- Financing mechanism and adequate resource allocation for all intended recipients (including the poorest countries/populations) for:
  - Vaccines (and syringes, if needed)
  - Delivery of vaccination, e.g., provider training, record keeping, distribution, cold chain expansion, recipient education, etc.
- Negotiation of pricing strategies, to facilitate access for the neediest populations/countries
- Establishment of effective delivery systems to reach intended target populations (In the case of AIDS vaccines, these are assumed, at least initially, to be adolescents and sexually active adults, intravenous drug users (IDUs), sex workers, migrant workers et al.—see discussion.)

- Systems to monitor vaccination safety, effectiveness, and impact, as a basis for strategy improvement

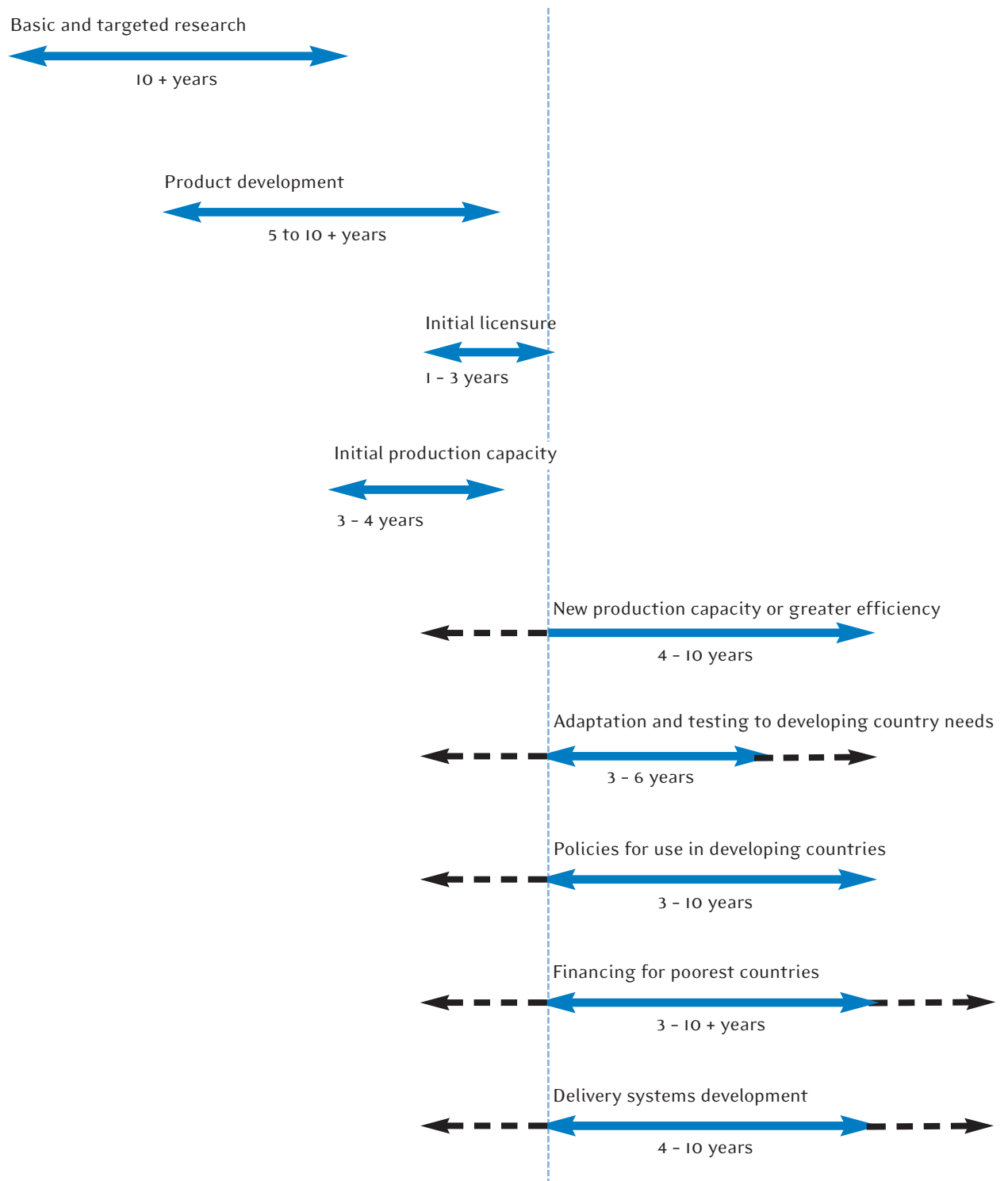
The time line for these steps is shown in figure A1.1.

For each of these general elements, a preliminary analysis was conducted which identified:

- General requirements for vaccine development and/or utilization
- Current status for vaccines against AIDS
- What more needs doing for vaccines against AIDS
- Major interest groups needing to be engaged in discussions

The analysis is presented below, in tabular form.

## Illustrative timelines for steps in achieving wide vaccination utilization



In the historical paradigm, these steps are mostly addressed sequentially. Under a new paradigm many could be attempted sooner and in parallel, significantly reducing delays, and protecting millions earlier.

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**INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION**

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Understanding of disease epidemiology, pathogen and human response</b>			
Basic research	<ul style="list-style-type: none"> <li>- Sub-optimal attention to ‘global’ issues, e.g., effect of ‘genotype’ on infection and vaccine responses</li> <li>- Need to define ‘immunotypes’</li> <li>- Need to identify correlates of protection</li> </ul>	<ul style="list-style-type: none"> <li>- Promote resources for strengthening R &amp; D capacity (e.g., via NIH/FIC; EU; ANRS/France)</li> </ul>	Academia; biotechs; ‘big pharma’; research funders
<b>Testing/Validation of vaccine candidate concepts</b>			
Many candidates need to enter ‘pipeline’	<ul style="list-style-type: none"> <li>- IAVI has already broadened pipeline</li> <li>- Few candidates will enter phase III in the next 5 years, so continued efforts needed</li> </ul>	<ul style="list-style-type: none"> <li>- Expand range of product development partnerships</li> <li>- Promote similar funding by other agencies</li> </ul>	Academia; biotechs; ‘big pharma’; research funders; venture capital investors, both commercial and ‘social’

\*Groups desiring products become available for public health use, i.e., potential recipients and public health officials, are covered by the term "vaccine access stakeholders" which include: NGOs, etc.

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INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Anticipation of commercial viability of product(s) and potential deterrents</b>			
<p>Balance of risks, costs, and potential revenues and profitability must become sufficiently attractive to those with product development expertise</p> <p>The prospect of litigation/liability for suspected vaccine-adverse events must be judged manageable</p> <p>Product development must not entail insurmountable or very costly barriers arising from ethical constraints</p>	<ul style="list-style-type: none"> <li>- Few of current candidates yet believed to be commercially viable, at least by 'big pharma'</li> <li>- Some uncertainty and apprehension exists regarding AIDS vaccines, but it does not appear to be a major deterrent. AIDS vaccines could be included in other schemes to limit litigation/liability, e.g., US National Vaccine Injury Compensation Program (NVICP)</li> <li>- Revision of Helsinki, CIOMS and WHO guidelines on the ethical conduct of research involving human subjects is underway</li> <li>- UNAIDS has issued guidance on Ethical considerations in HIV preventive vaccine research, in May 2000</li> <li>- Clinical testing of products in developing countries continues to be a sensitive issue</li> <li>- Some proposals regarding trials in developing countries (state-of-the-art care; 'free' product) would dramatically raise costs and constitute commercial disincentives</li> </ul>	<ul style="list-style-type: none"> <li>- Balance of risks, costs potential revenues and profitability needs to be made more attractive by action on other determinants or alternative mechanisms</li> <li>- Mechanisms to include AIDS vaccines in vaccine injury compensation schemes should be investigated</li> <li>- All stakeholders should participate in these discussions and meet all international and national guidelines in their activities</li> <li>- Full involvement of developing country representatives is essential to make such discussions and consensus relevant</li> </ul>	<p>Biotechs; 'big pharma'; AIDS vaccine access stakeholder</p> <p>Policy makers in US, Europe, Japan and developing countries, where relevant</p> <p>Academia; biotechs; 'big pharma'; research funders; AIDS vaccine access stakeholders, in particular UNAIDS and WHO</p>

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**INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION**

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Product definition and production process development</b>			
<p>For entry into clinical testing, especially phase III trials, candidate vaccines must derive from reliable production processes and substrates, judged acceptable by national regulatory agencies</p>	<ul style="list-style-type: none"> <li>- Many concepts for AIDS vaccines entail new technologies or agents previously not the subject of guidance from regulatory agencies</li> <li>- Guidance/requirements on specific products may vary among different regulatory agencies</li> <li>- Differing requirements in product development among national agencies may ultimately delay or complicate ‘cross-licensing’ of products</li> <li>- End points for pivotal clinical trials have been defined for some candidate vaccines guidance</li> </ul>	<ul style="list-style-type: none"> <li>- Encouraging relevant national and supra-national regulatory agencies adopt consistent and timely approaches to product development</li> <li>- Analytical studies and consensus development process (see also Regulatory Approval)</li> </ul>	<p>National regulatory agencies of countries where vaccines are being developed including countries hosting trials; European Medicines Evaluation Agency (EMA); UNAIDS; WHO; International Association for Biological Standardization (IABS); International Federation of Pharmaceutical Manufacturers (IFPMA); potential producers; AIDS vaccine access stakeholders</p>
<b>Preliminary establishment of manufacturing capacity</b>			
<p>To obtain material for clinical studies, especially phase III trials, some GLP/GMP production capacity needs to be put into place by product sponsors</p>	<ul style="list-style-type: none"> <li>- Potential manufacturers will keep investment in new production capacity (dedicated to AIDS) to a minimum in light of uncertainty in outcome of clinical trials</li> <li>- Options for increase in production capacity may be discussed as phase II/III trials show promise</li> <li>- As potential of different approaches becomes clearer, producers may be less averse to production capacity investment</li> <li>- Investment risk is lower for products with ‘common’ production technologies</li> </ul>	<ul style="list-style-type: none"> <li>- This commercial decision is reasonably justified in present circumstances</li> <li>- Encourage consideration of global demand as discussions occur later on production capacity enlargement (see supply): options to be raised could include technology transfer for local production</li> <li>- Encourage investment in larger capacity production as early as realistic</li> <li>- Consider mechanisms for public sector sharing of production capacity costs</li> <li>- Prioritize products having ‘common’ production technologies, other considerations being equal</li> </ul>	<p>Biotechs; ‘big pharma’; local producers; potential funders of production plant; AIDS vaccine access stakeholders</p>

INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Testing/Validation of candidate product(s)</b>			
<p>Because no ‘perfect’ animal models or known correlates of protection exist, many candidate products need to be tested in humans</p> <p>Pharmaceutical company’s expertise in producing products suitable for clinical testing need to be engaged more widely</p>	<ul style="list-style-type: none"> <li>- More candidates need to be pursued through phase III trials, including pertinent formulations For all potential target populations</li> <li>- R &amp; D for combating clades not yet circulating in the US and other developed countries can be done efficiently only in LDC settings where they now occur</li> <li>- Support for R &amp; D on AIDS vaccine needs of LDCs should be expanded</li> </ul>	<ul style="list-style-type: none"> <li>- Continue and expand product development partnerships</li> <li>- Continue to promote two-pronged approach to vaccine development, namely clinical investigation/trials, as well as ‘basic research’</li> <li>- Educate ‘funders’ on need for clinical/ phase III aspect of AIDS vaccine development</li> <li>- Mobilize extensive resources for phase III trials, especially those in LDCs, including from novel sources such as World Bank loans, and multilateral development banks, e.g., those for Asia, Africa and Latin America</li> </ul>	<p>Academia; biotechs; ‘big pharma’; research funders; AIDS vaccine access stakeholders</p>

INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Regulatory Approval</b>			
<p>Manufacturers need to prepare dossiers for regulatory approval in each ‘jurisdiction’</p> <p>National agencies (or supra-national groups, e.g., EU/EMEA) assess safety and efficacy</p> <p>Each subsequent jurisdiction will also review according to their procedures, including LDCs</p> <p>WHO needs to develop guidance on AIDS vaccine production requirements, which will be used by agencies (e.g., LDCs) without this expertise</p>	<ul style="list-style-type: none"> <li>- Presently dossier format varies between major regulatory jurisdiction, i.e., US/FDA vs. EU/EMEA, etc., entailing additional costs/work/trials for producers</li> <li>- Discussions among agencies could facilitate consistent and timely approvals</li> <li>- In some LDCs NRAs may need technical assistance to process regulatory approval in timely manner</li> <li>- This may be useful if production methods are made ‘public domain’</li> </ul>	<ul style="list-style-type: none"> <li>- Immediately initiate discussions among national regulatory agencies (incl. US/FDA &amp; EU/EMEA, IFPMA, potential producers, Int. Assn. for Biological Standardization, Int. Commission on Harmonization) on expedited handling of AIDS vaccine licensing</li> <li>- Initiate discussions with WHO and LDC NRAs where trials ongoing, on regulatory issues</li> <li>- No immediate action—depends on what emerges as useful products</li> </ul>	<p>Nat Reg. Agencies including those in countries hosting trials, as well as those developing products; IABS; EMEA; WHO, etc.; AIDS vaccine access stakeholders</p>
<b>Decision processes for international recommendation and national policies</b>			
<p>Use of AIDS vaccines needs to be developed from the scientific information that will result from vaccine efficacy trials tailored to local/national situations, but guided by international recommendations and national policies</p>	<ul style="list-style-type: none"> <li>- Early international recommendations on use could accelerate vaccine adoption</li> </ul>	<ul style="list-style-type: none"> <li>- Accelerate development of national AIDS vaccination policy through commissioning papers on vaccine/vaccination impact scenarios, cost-effectiveness of AIDS vaccination, and other aspects</li> <li>- Creation of a body (incorporating all relevant expertise) to develop guidance on AIDS vaccination in various risk- group/national circumstances</li> </ul>	<p>AIDS vaccine access stakeholders, in particular National AIDS Control Programmes, UNAIDS, and WHO; Biotechs; ‘big pharma’</p>

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INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
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Decision processes for international recommendation and national policies (cont'd.)

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- There is not yet in place an appropriately constituted body charged with translating vaccine trial results into AIDS vaccination strategies. Such a body would include experts in epidemiology, vaccine development, vaccination logistics and provision of health services to the relevant target populations (adolescents and adults) through the likely delivery channels (schools, reproductive health services, sexually transmitted disease services etc.); vaccination financing; and cost/effectiveness analysis

- At the national level, policy setting for and implementation of AIDS vaccination is likely to require broad consultation among the same groups. Responsibility for development of AIDS vaccination policy, in HIV prevention, needs to be clearly assigned in each country

- Initiate discussion on the setting of AIDS vaccination policy in countries where trials are being conducted



INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<p>Testing/Validation of effectiveness in wider population groups</p> <p>Effectiveness and safety of licensed vaccine(s) may need testing/verification in target populations other than those for which it is initially licensed</p> <p>Trials in larger numbers in same target population mostly assess safety</p>	<p>Trials in larger numbers in same</p> <ul style="list-style-type: none"> <li>- Given clade variation with different geographic target populations, possible genetic variations in response and historical experience with variations in vaccine effectiveness, those charged with recommending policy will likely want evidence relevant to 'new' target populations</li> <li>- Initial VaxGen trial is to be followed by trials on other clades and by larger effectiveness trial, if sufficient efficacy is demonstrated</li> <li>- Number and extent of effectiveness trials required by policy makers cannot be predicted at present. Balance between less or more may affect timing of access to some populations, depending on which candidates initially tested where</li> <li>- Logical schemes for required effectiveness trials could be developed based on planned efficacy trials and clade coverage, etc.</li> <li>- No group presently has responsibility for evaluating transition from efficacy trials to use in likely target populations</li> </ul>	<p>Trials in larger numbers in same</p> <ul style="list-style-type: none"> <li>- Creation of a scientific/public health group responsible for eventually developing recommendations for use. Group should include scientists, public health officials and the wide range of groups that can address feasibility of reaching target populations (which are not typical infant/child [EPI] immunization targets)</li> <li>- Mobilize resources for earliest possible (pilot?) testing of vaccines in new populations. Sources could include development assistance agencies and EU, since such studies may qualify as 'application,' not basic research</li> <li>- Rapid sharing of successful trial results will increase interest in vaccine adoption</li> <li>- Conduct parallel trials of AIDS vaccine candidates to assess clade specificity and cross protection</li> </ul>	<p>Potential producers; AIDS vaccine access stakeholders, in particular National AIDS Control Programmes, UNAIDS and WHO</p>

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**INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION**

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Demonstration projects before widespread introductions</b>			
<p>Logistical feasibility of vaccine delivery may need to be assessed prior to wide introduction, in some countries. Such studies may also add to confidence regarding absence of side effects</p>	<ul style="list-style-type: none"> <li>- National implementers may feel the need for phased AIDS vaccine introduction, to assess delivery systems functioning, especially since new delivery systems will need to be developed and recordkeeping may be complex (e.g., for prime-boost approaches)</li> <li>- Extended phasing of pilot studies could delay wide adoption (for example, pilot studies of HB vaccine delivery in 'EPI' in Thailand lasted many years)</li> <li>- Demonstration projects/pilot introduction may be controversial for some groups that are marginalized or practice illegal behaviors (e.g., commercial sex workers; IDUs)</li> </ul>	<ul style="list-style-type: none"> <li>- Reduce the delay that too many pilot studies might impose by encouraging early planning for new delivery systems for adolescents/HRGs (see below: Delivery Systems)</li> <li>- Early sharing of experience in AIDS vaccine adoption might also reduce the desire to conduct phased introduction</li> <li>- Educational efforts on necessity to address prevention in groups at highest risk</li> </ul>	<p>Potential producers; AIDS vaccine access stakeholders</p>

INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Communication (pre- and post-licensure)</b>			
<p>Expectations for speed of vaccine development and availability need to be managed to avoid unjustified optimism or doubt</p> <p>Politicians and policy makers need to be informed of rationale for vaccine use</p> <p>Health care providers (for target populations) need to be informed of vaccine issues and trained to communicate effectively with potential recipients</p> <p>Potential recipients need to be counseled effectively on vaccine efficacy to maintain other protective behaviors</p>	<ul style="list-style-type: none"> <li>- Some activities underway, but the need to manage expectations will become greater as trial results emerge</li> <li>- Effectiveness of such efforts critical to sustained political support (especially if problems occur)</li> <li>- Provider/recipient communication is generally poor in public settings; ‘providers’ for target populations (schools, adolescents, HRGs) not familiar with vaccines</li> <li>- Long recognized as a new challenge, unique to AIDS/STD vaccines. This will be especially difficult if vaccine is delivered in mass campaigns, e.g., in schools</li> </ul>	<ul style="list-style-type: none"> <li>- Expand communication as release of trial results is anticipated</li> <li>- Expand efforts as vaccines proceed through licensure</li> <li>- Ensure issue is addressed as discussions on delivery system development (below) are started</li> <li>- Analysis could be initiated on how vaccine recipient education could best be done</li> </ul>	<p>AIDS vaccine access stakeholders; potential producers; political appointees and elected officials</p>

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INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<p><b>Supply</b></p> <p>New approaches to production capacity planning (and financing) are needed to avoid delays (inherent in historical approaches) in access for poorer countries</p> <p>Public sector needs to improve ways of forecasting demand, and uptake, for industry decisions on production capacity</p>	<ul style="list-style-type: none"> <li>- Supply and financing issues are inextricably linked. Discussions have been conducted over the last 5 years on accelerating new vaccine introduction in general. The key issues have been identified, and some options identified, but no general strategy has been agreed upon</li> <li>- Demand estimation for new vaccines, and AIDS vaccines in particular, is at present rudimentary. AIDS vaccine demand studies to date (Bishai, et al.) are somewhat theoretical, not based on validated decision rules</li> <li>- Studies by UNAIDS, WHO, World Bank and academia are underway to evaluate various vaccination strategies, but these need to be linked to the discussion of delivery, supply and financing strategies</li> </ul>	<ul style="list-style-type: none"> <li>- Through early discussion with potential manufacturers, encourage them to consider approaches to meeting global supply needs</li> <li>- Provide information to developed country manufacturers about potential manufacturing partners in developing countries</li> <li>- For AIDS vaccines, commission further analysis of supply/financing options, and engage relevant players/producers in planning to fully meet anticipated supply needs</li> </ul>	<p>Potential producers; AIDS vaccine access stakeholders</p>

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INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
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Supply (cont'd.)

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- The ultimate strategies to meet global demand will probably depend on (a) the technology used to manufacture the vaccine, e.g., rDNA, cell culture, fermentation, etc.; and (b) 'ownership' of the technologies for manufacture of successful vaccine candidates, e.g., big pharma versus small biotech, and their commercial philosophies for supply (i.e., in-house versus technology transfer; developed country versus global market orientations)

INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Financing mechanisms and adequate resource allocation</b>			
<p>Adequate resources through appropriate financing mechanisms need to be put in place, so that all populations at risk have access to vaccine irrespective of individual (or national) capacity to pay</p> <p>Financing is also needed for vaccination delivery (training, communication, distributions system/cold-chain expansion/ storage); this cost may be greater than vaccine cost</p> <p>The poorest countries may need to rely on external sources ('donors') to cover the cost of vaccine and its delivery</p>	<ul style="list-style-type: none"> <li>- Complex area, linked with supply/capacity decisions and pricing policies</li> <li>- Historical approaches (waiting for excess capacities and marginal pricing) will meet public health needs only after considerable delay (decades), or maybe not at all</li> <li>- Decisions on which countries should receive external 'subsidy' for vaccine/vaccination cost (in grant or most favorable price) are politically difficult</li> <li>- Discussions are advanced under the Global Fund for Children's Vaccines for mechanisms to subsidize the poorest smaller countries (&lt; \$1,000GNP, &lt;150 million population) for existing pediatric vaccines and service delivery; discussions for larger poor countries (China, India, Indonesia) are underway. AIDS not included in present discussions</li> </ul>	<ul style="list-style-type: none"> <li>- Promote political support for full and rapid financing of AIDS vaccinations, throughout the world</li> <li>- Foster discussions on mechanisms for financing vaccines and vaccination delivery in general</li> <li>- Commission paper(s) on application of evolving ideas (GFCV, WB options, EU and other options) to AIDS vaccines</li> <li>- Engage potential producers of AIDS vaccines in discussion on mechanisms by which supply for all populations could be ensured</li> <li>- Work with EU to assess applicability of such mechanisms to AIDS vaccines</li> <li>- Continue to develop concepts of World Bank</li> </ul>	<p>Potential producers; AIDS vaccine access stakeholders; potential funders of utilization</p>

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INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

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Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
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Financing mechanisms and adequate resource allocation (cont'd.)

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- European Union has developed financing options for those vaccine/vaccination programs that (poor) W. African countries put as national priorities

- World Bank has considered various market mechanisms to raise commercial interest in AIDS vaccine development including:

- vaccine purchase fund(s); and
- contingent loans and credits

but has not defined which countries might be eligible or decided on a final mechanism if it commits to this approach

- World Bank loans (IDA/IBRD) could be used for AIDS vaccination financing at present; a new credit mechanism for communicable disease control is under consideration as of July 2000

INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
<b>Negotiations of procurement and/or pricing strategies</b>			
<p>Procurement/pricing strategies need to be ‘managed’ to balance commercial incentives and access</p> <p>The case for differential pricing (through market segmentation in procurement) or for price subsidy for the poorest countries needs to be promoted as a tool that will enhance access and lower overall development aid provided by developed countries</p>	<ul style="list-style-type: none"> <li>- Complex issue, related to supply/production capacity and financing</li> <li>- Market segmentation (for poorest) and price subsidy not universally accepted in political or vaccine procurement circles</li> <li>- No overall agreement between public/private sectors on market segmentations or pricing policies; possibility of US FTC issues in this area</li> <li>- Where monopoly suppliers occur, pricing becomes very sensitive issue</li> <li>- Willingness of public sector agencies to establish market segmentation for poorest countries (and defend lower prices against criticism of middle-income countries) not yet established</li> </ul>	<ul style="list-style-type: none"> <li>- General discussions of supply/financing for vaccines need to be promoted</li> <li>- Impact of general proposals for AIDS vaccines needs to be assessed</li> <li>- Assessment of technology transfer as a mechanism for meeting supply/capacity needs and avoidance of negative reaction to lower prices for poorer countries needs to be conducted by competent, impartial body</li> </ul>	<p>Potential producers; potential purchasers/funders; AIDS vaccine access stakeholders</p>



INFLUENCING THE DETERMINANTS OF AIDS VACCINE UTILIZATION

Requirements for ultimate vaccine development and utilization	Current status for AIDS vaccines	What more needs doing for AIDS vaccine	Major interest groups needing to be engaged in discussions*
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Development of delivery systems

<p>Vaccine needs to reach individuals/groups at risk of Infection</p>	<ul style="list-style-type: none"> <li>- HIV infection risk is overwhelmingly sexual activity; infection rates highest in developing countries, and among certain groups, including commercial sex workers, IDUs, migrant workers</li> <li>- At start of vaccination the vaccine's duration of protection will not be known</li> <li>- Early adolescents and sexually active adults at high risk will be target groups</li> <li>- In poorer countries, vaccination systems now mostly reach only infants/young children</li> <li>- HIV prevention programs and other health services (reproductive health, family planning, STD services, etc.) reach groups that are potential recipients of vaccines</li> <li>- Transition to pediatric administration may be possible over time, if vaccines of long duration (or 'booster' systems) are developed</li> </ul>	<ul style="list-style-type: none"> <li>- Promotion of early consideration of delivery of vaccination to target populations (adolescents, at-risk sexually active adults) through likely contacts (schools, reproductive health services, STD services, military clinics, etc.)</li> </ul>	<p>AIDS vaccine access stakeholders; potential funders of delivery systems strengthening; technical agencies in health services delivery; NGOs involved in health services delivery</p>
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## APPENDIX 2 AN OVERVIEW OF GLOBAL VACCINE MANUFACTURING CAPACITY

What now exists?

Vaccines are manufactured by many different types of producers around the world—over 100 facilities in over 40 countries report they produce vaccines. Some are private, others public. Some have a strong research and development base and invest large amounts of money into new products; others do no research and development and choose to produce what is already available and technologically well known. Due to the nature of vaccines, regardless of which one is being discussed, it is critical to know any vaccine being used around the world meets a certain standard of quality, and this is not always the case (see footnote at the end of this appendix). Volume and range of production are also considerations when contemplating vaccine production possibilities.

The types of producers manufacturing vaccines globally fall into four basic categories. For the purpose of this breakdown, the primary focus is on the level of research and development and known quality of the vaccines produced.

**Category 1:** Vaccine divisions of major multinational pharmaceutical companies

These generally offer a wide range of vaccines that meet international quality specifications. Manufacturers in this category invest significantly in research and development of new products, and these companies have large capacity potential. These five major vaccine manufacturers produce most of the newer vaccines and are part of larger pharmaceutical firms. These companies include Aventis-Pasteur, Glaxo SmithKline, Chiron, Merck, and Wyeth Vaccines and Pediatrics. These companies are multinational in nature but have manufacturing sites in the United States, France, Italy, Canada, Belgium, and Germany.

**Category 2:** Manufacturers that produce a significant quantity of vaccine that meets international quality specifications

These manufacturers produce vaccine for export. Some export only one product, while others produce and export multiple vaccines. In addition, they vary in their amount of research and development-based activity. Some are private firms, others are public in nature. Some limit their production to some or all of the basic EPI vaccines (DTP, OPV, BCG, Measles); others produce "niche" vaccines. These manufacturers can be found in Korea, India, Japan, Switzerland, the United Kingdom, Australia (all of which have substantial biotechnological bases), Indonesia, Hungary, Bulgaria, Denmark, and Senegal.

**Category 3:** Manufacturers with some research and development base but whose vaccines have not yet been evaluated for their ability to meet international quality standards

These manufacturers may or may not produce EPI vaccines in addition to other vaccines necessary to their country or region, or lucrative for export (for example Japanese encephalitis, hep B, influenza). These are generally public sector manufacturers and include China, Iran, the Netherlands, Norway, Brazil, Cuba, and Sweden, most of which have established or growing capacity for biotechnology.

**Category 4:** Other vaccine manufacturers that lack the research and development base and do not meet international quality standards, thus are not reliable suppliers

These are generally public sector manufacturers in developing countries, producing a limited range of products that may not meet their national needs.

There are many of these manufacturers around the world.

Who could contribute to AIDS vaccine supply?

Current vaccine manufacturers in Categories 1 and 2 could, under certain circumstances, contribute to AIDS vaccine supply. Manufacturers in Category 3 might also contribute since they may be able to demonstrate production of AIDS vaccine to acceptable international standards even if they have not yet been assessed for production quality of their current products.

Which current manufacturers are realistically likely to be able to contribute to production of AIDS vaccines depends on a number of factors:

- The degree of complexity of the production methods;
- Who holds the intellectual property (patents and know-how) and whether they are willing to license or otherwise transfer it to other parties; and
- Whether the recipient of the production information can implement it consistently, to the satisfaction of their national regulatory agency, and in the case of international supply through UN agencies, to the criteria elaborated by WHO.<sup>1</sup>

Whether production should be encouraged in a wide range of institutions will depend on:

- Whether it is needed for the volume of supply needed;
- Whether the production economics make sense (versus other approaches such as underwriting production capacity in one or a few locations) (Contrary to a wide misperception, CVI/WHO studies have shown that production in develop-

ing countries is not always lower cost);

- The investment in capital equipment and training, and the time needed to establish production; and
- The long-term plans for use of the plant capacity

TABLE A2.1

	Level of R&D	Meets international quality standards	Product range	Production volume
Category 1	High	Yes	Very wide	Large
Category 2	Variable (some emerging)	Yes	Variable	Large
Category 3	Variable (some emerging)	Unknown	Variable	Variable
Category 4	None or	No	Limited	Low

## APPENDIX 3 ILLUSTRATIONS OF THE IMPACT OF VAC- CINE UTILIZATION ON PROGRESSION OF THE HIV/AIDS EPIDEMIC

Analysis of the likely impact of different vaccine usage will assist policy makers in selecting among options. It will also be useful in illustrating simply to policy makers the benefits of particular courses of action.

Modeling can, for example, predict the relative benefits of preparatory activities and intense early promotion of vaccine use versus a more passive uptake of vaccines. As illustrated by the extra lives saved in scenario 3 versus 2 in Figure A53 below.

Once basis models and assumptions have been elaborated, it is relatively simple to refine them, to tackle more complex questions such as scenarios entailing successive generations of hypothetical vaccines, such as those outlined in Table 1 (page 17). Scenario 5 versus 4 shows the relative benefits of anticipatory activities and early promotion, versus passive adoption.

The exercise shown below is to illustrate how the outcome of complex calculations can in fact be simply compared in terms of final impact. This is undoubtedly preferable to ‘gut’ intuition on preferable strategies.

The three figures represent calculations based on some simple (easily modified) assumptions and five different scenarios.

- Assumptions:
  - A constant 5 million new infections per year, and 10 years to death after infection
  - No effect of vaccine on infectivity

### Appendix 3

Illustrations of the impact of vaccine utilization on progression of the HIV/AIDS epidemic Scenarios:

- (1) No vaccine use
- (2) A vaccine with 90% efficacy is put

into wide use (100%) immediately in 2004

- (3) A vaccine with 90% efficacy is introduced progressively (10% coverage increment annually) between 2004 and 2014
- (4) Three successive vaccines with 40%, 70%, and 90% efficacy are put into use (100% coverage) immediately
- (5) Three successive vaccines with 40%, 70%, and 90% efficacy are introduced progressively (10% coverage increments annually)
- (6) The comparative benefit of using 40% and 70% efficacy vaccines as they become available, versus decisions to forgo these and use only the one with 90% efficacy when it becomes available

Figure A3.1 shows the effects of these scenarios on incidence of HIV infection

Figure A3.2 shows the effects of these scenarios on AIDS deaths

Figure A3.3 shows their relative impact in reductions of HIV infections

**Figure A3.1**  
Global HIV Incidence: Vaccine Deployment Scenarios

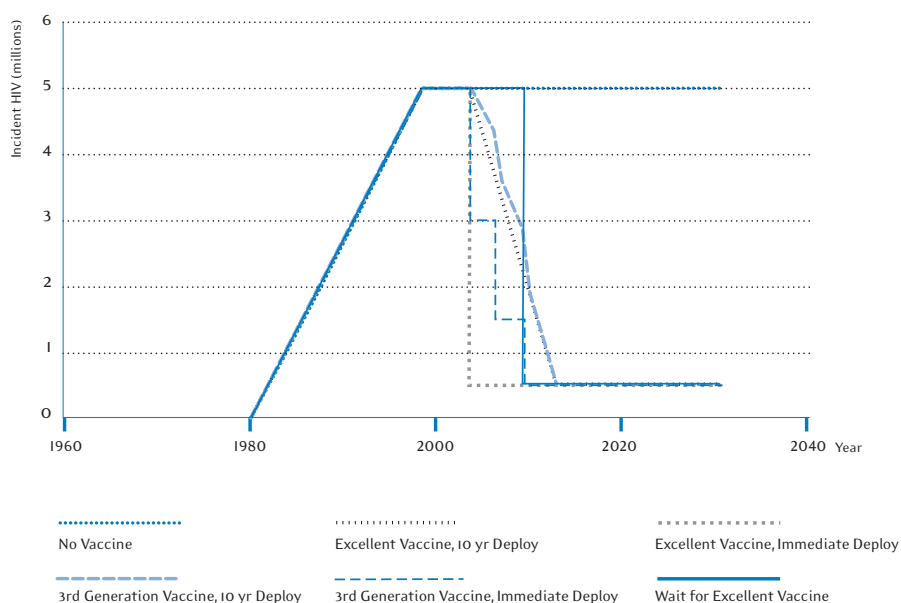
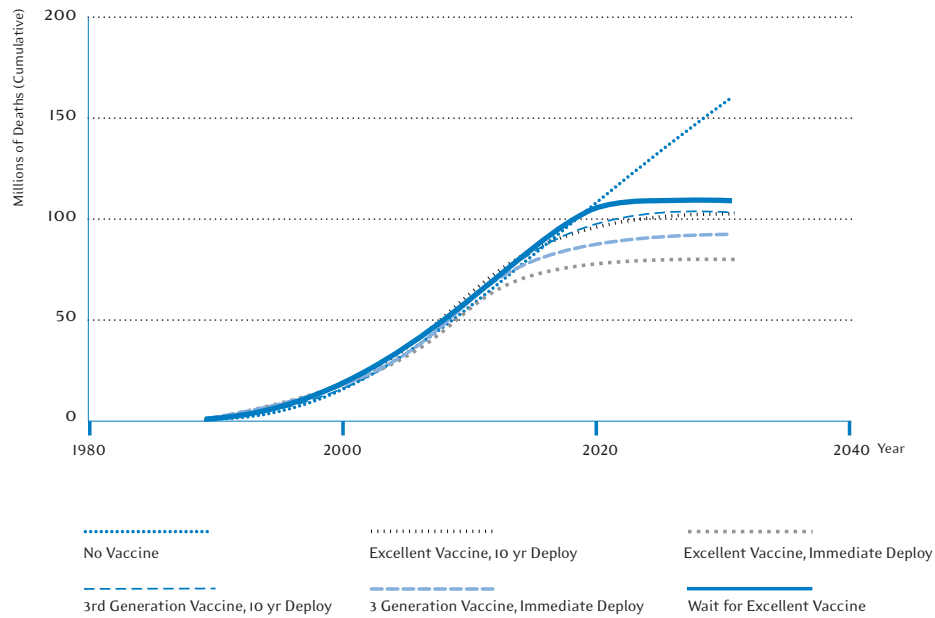
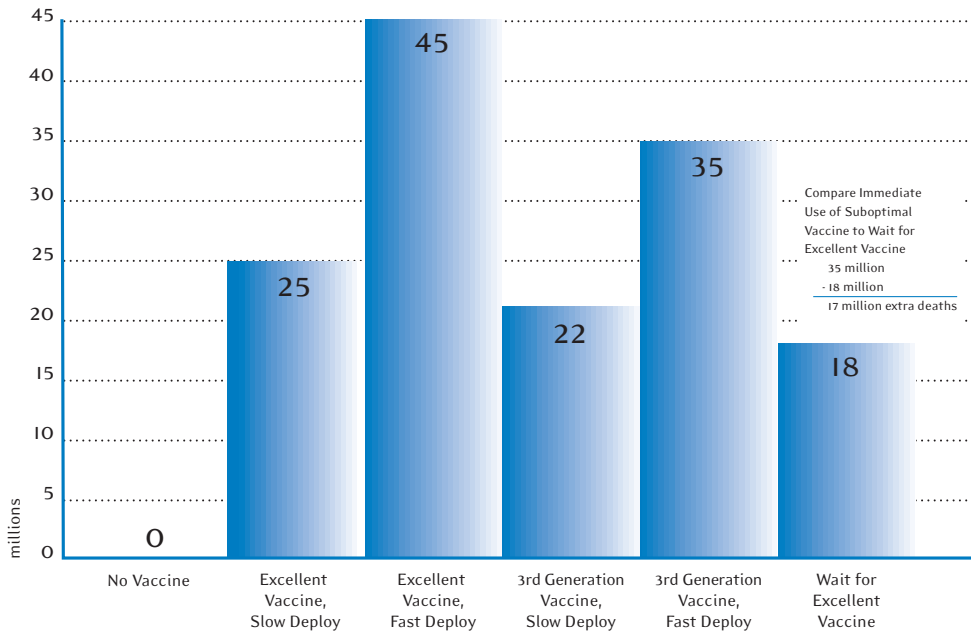


FIGURE A3.2 AND  
FIGURE A3.3

Global AIDS Deaths: Vaccine Deployment Scenarios



Lives Saved with Different Vaccination Strategies



## APPENDIX 4 THE ECONOMICS OF VACCINE PRODUCTION, COST AND PRICING

With traditional vaccines\* major producers can offer, for the poorer developing countries, prices for large purchases that are considerably lower than the prices charged in industrialized countries. But an adequate supply, and affordable prices for the poorer developing countries (usually through UNICEF) with the traditional vaccines took many decades to emerge. This is the result of a number of factors, the most important of which is a learning curve in manufacturing. Time is obviously a factor in learning, but by understanding the realities and economics of vaccine production, it may be possible to develop new ways of collaboration with the potential producers of AIDS vaccines to accelerate the supply to all countries needing to use the vaccine.

Vaccines have typically been developed for and manufactured first in the advanced industrialized countries. Production processes are relatively inefficient initially. Manufacturers build their production capacity to supply the market that they know can pay. They are averse to "excess" production capacity as this represents wasted investment if no one will buy the product. Prices are set in order to contribute to overall company business needs to cover costs, including R & D on future products, of production plant, and return to investors. This supply to more affluent markets is at full-cost; i.e., they essentially pay for getting the vaccines earlier, and for the R & D that brings new products.

As a product matures, a learning curve leads to more efficient production. This is faster the greater the volume produced and if the producer invests actively in improving efficiency. (Fig. A 4.1) Supply also increases because new producers enter the market.

Supply increases, production costs per dose drop progressively because of efficiency and competition, and this can be reflected in prices charged to new markets if a policy of different prices for different markets (price-tiering) is adopted. Thus a large volume of supply becomes available,

and more countries can adopt the vaccine at a price they are willing to pay.

While initially a new vaccine may be available from only one producer, there are often competing products after a few years. As producers generally operate in a commercially competitive environment, they manage supply and pricing to maximize revenues and profitability, but also to maintain market share and enter new markets.

A progressive increase in supply through higher production efficiency and additional suppliers occurs over time. This leads to a gradual adoption of vaccines into new markets/countries, usually at progressively lower prices. This is shown in Figure A4.2. For recent 'new' vaccines such as hepatitis B and Hib, the average time to adoption (peak in Figure A4.2) appears to be at least 15 years. This generalized description of events is born out by the picture of supply volume and price for polio vaccine – a mature product (Figure A4.3).

Another factor comes into play in the supply of vaccines to the poorer countries, which is usually achieved through large volume purchase. Purchase of pediatric vaccines for developing countries has typically been by arrangements with UNICEF or the Pan American Health organization, but other agencies, such as the World Bank, could play such a role.

Vaccine production is said to be a "fixed cost business"; i.e., costs are mainly determined by production plant. The production cost of vaccines is heavily scale-sensitive; i.e., the larger the volume of doses produced, the lower will be the per dose cost. Within the capacity limits of a particular manufacturing plant, the cost of producing a few more doses can be said to be "fully marginal," i.e., just the costs associated with those doses, e.g., vial costs, if the main running costs are assigned to the basic production for sales to affluent markets. If the volume of 'extra' doses is more substantial, then some other costs, such as quality control for those doses, are also assigned to their

production cost (and the term 'marginal price' is used to describe their pricing) as seen in Figure A4.4.

Manufacturers can assign their operating and production costs for core (industrialized) and 'additional' (developing) country markets in various ways. Even though the volume of doses of the traditional vaccines supplied for developing countries is now very large, the core market is more important to the large producers as that is where they derive the revenues to cover most costs.

Thus when the manufacturing capacity exists, marginal (lower) pricing (tiered pricing) is possible. This extra capacity usually exists only many years, even decades, after initial introduction. The practice of 'price-tiering' (offering different prices to different markets) is based on a number of considerations:

- The market's need for and capacity to pay for the product balanced with the need to maximize revenues generally;
- The volume of the purchase (bigger volumes get bigger discounts);
- The certainty that the proposed purchase will be actually paid for;
- The nature of the product sold (e.g., vaccine cost per dose in multi-dose vials is less than that in single-dose vials);
- The desire to penetrate new markets or maintain market share;
- The level of marketing expenses or distribution costs;
- The degree of confidence that the product will be used in the population for which the concession on price was made, not be diverted for resale and intermediary profit, into markets for which the concession was not intended.

The counterpart of price-tiering, by manufacturers, is 'market segmentation.' Under this concept different markets (or potential purchasers) are identified for which purchasing arrangements will be made independently. In pricing products

to what a market can afford, industry generally utilizes market segmentation. In establishing large aggregated purchase mechanisms, UNICEF (for all developing countries) and PAHO (for developing countries in the Americas) use market segmentation. Because there is now a considerable range between richer and poorer developing countries, some agencies such as the former Children's Vaccine Initiative (CVI) and the successor Global Alliance for Vaccines and Immunization (GAVI) have proposed a 'market segment' just for the poorest countries.

As envisioned by the entities that have considered market segmentation and price-tiering (including CVI, WHO, UNICEF, and PAHO), it would operate with competition among potential suppliers on price and other characteristics such as reliability. Advocates for market segmentation and price-tiering for vaccines are utilizing usual commercial practices to achieve a public health goal.

Market segmentation to get a special, lowest price for the poorest obviously entails deciding which countries would be eligible, which is politically difficult.

The alternative to market segmentation, with its implied price-tiering, is the establishment of a 'flat' pricing structure, i.e., a similar price for all purchases. Since commercial manufacturers would not let profitability suffer, a 'global price' (including contributions to R & D and other business expenses) would be higher than many poorer countries or donors could afford. (If an unattractive price were enforced by price controls [or coercion through adverse publicity] potential producers would forsake the market.)

Flat-rate pricing generally works against the long-term interests of public health. As the flat-rate goes down, attractive to richer countries in the short-term, funds available to industry to support R & D are diminished and innovations would probably decline.

Market segmentation and tiered pricing allow the poorest to have access and all to

benefit from R & D. The more affluent purchasers contribute to research and development.

The investment required in production capacity is already very high (US\$100 million to \$200 million for a new plant). The larger the plant capacity, the higher the investment. Manufacturers are averse to investing initially in production plant big enough to supply the whole (global) need, when some of this may not be able to pay the initial higher price. Hence, for a partnership between the potential producers and the stakeholders in AIDS vaccine access, several issues become central:

- Early estimates of the demand since building and validating production capacity takes a minimum of 3–4 years; and
- Identifying ways to ensure the financing of the vaccine for all who need it, irrespective of the individuals or their countries' capacity to pay directly
- The extent to which the product derives from research and development supported by 'public sector social venture capital,' i.e., the support of product development with the return on investment geared towards access of poorer countries rather than financial rewards; and
- The extent to which the product's characteristics make it suitable for use under the constraints that are imposed by health systems in developing countries.

While the general principles of market segmentation and price-tiering are fairly well-accepted practice in vaccine supply, there is considerable debate on the details. This debate generally centers on how the markets should be segmented. Some middle-income countries feeling entitled to the lowest possible price suggest they should be grouped with the poorest.

While market segmentation and price-tiering are a practical way of enhancing access to and affordability of new vaccines for the poorest countries, there is a lack of understanding of their potential benefits. Extensive educational efforts are

needed to achieve better acceptance of the practice.

Meeting demand for AIDS vaccines: A new paradigm needed

Under normal circumstances, price-tiering by manufacturers to different markets is unlikely early in a product's life cycle for a number of reasons:

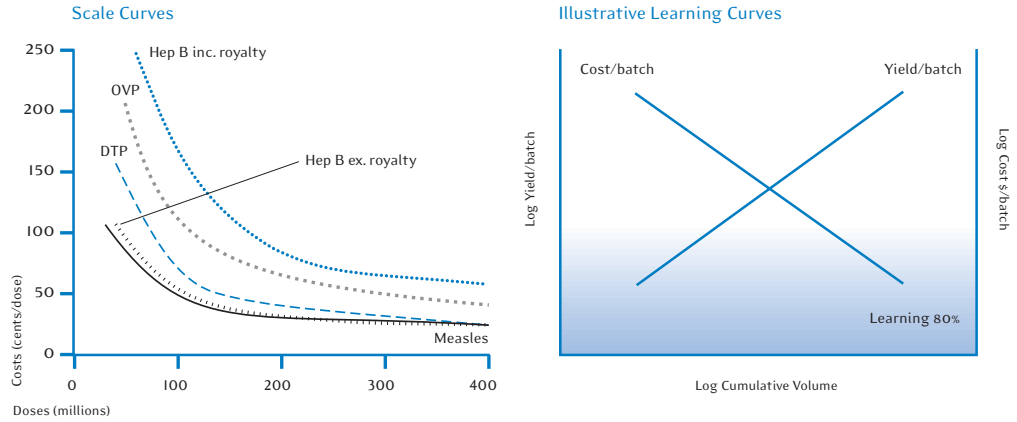
- The full production capacity can probably be sold at full price in markets able to pay;
- Early differential pricing would call into question pricing to initial core markets (i.e., accusations of price-gouging); and
- Production efficiency is relatively low so production costs per dose are higher, relative to what can be expected after the learning curve.

Hence, a new paradigm is needed that avoids the delays inherent in 'trickle-down supply.' Designing new approaches for AIDS vaccines must take into account:

- The basic economies of vaccine production, supply and efficiency;
- The fact that production plants are expensive (US\$100 million–\$200 million) and take a minimum of 4–5 years to build and validate;
- Commercial industry will only invest in capacity to meet developing country needs if the market demand (volume of product needed and its financing) is predictable and secure;
- The demand curve for AIDS vaccines will have a high peak of the pool susceptibles followed by lower routine immunization of the new at-risk cohorts;
- First generation vaccines, and production plants, may be rapidly superseded by improved versions from competitors;
- The political environment regarding AIDS vaccines is likely to remain unpredictable, in terms of both consumer attitudes and international relations.

FIGURE A4.1 AND  
FIGURE A4.2

How the 'learning-curve' affects vaccine production costs and supply.  
The cost benefits of scale and learning are potentially very important for new vaccines.



- The production of large volumes to serve the demands of the whole global market will provide maximum profitability because of manufacturing scale efficiencies, rapid 'learning' to provide higher yield giving a rapid decline in production costs per dose and greater supply for poorer countries.
- This strategy reduces competitive/piracy threats since there is no unmet demand and has the value of marginal revenue.
- Historically this strategy has not been adopted because of the uncertainty of biological scale-up and investment in larger capacity plant; unpredictable demand and because early tiered-pricing is a threat to pricing in 'core' markets.

Source: Mercer Management Consulting: Study for Children's Vaccine Initiative, 1997.

Representation of relationship of time of adoption of vaccine innovations to price.

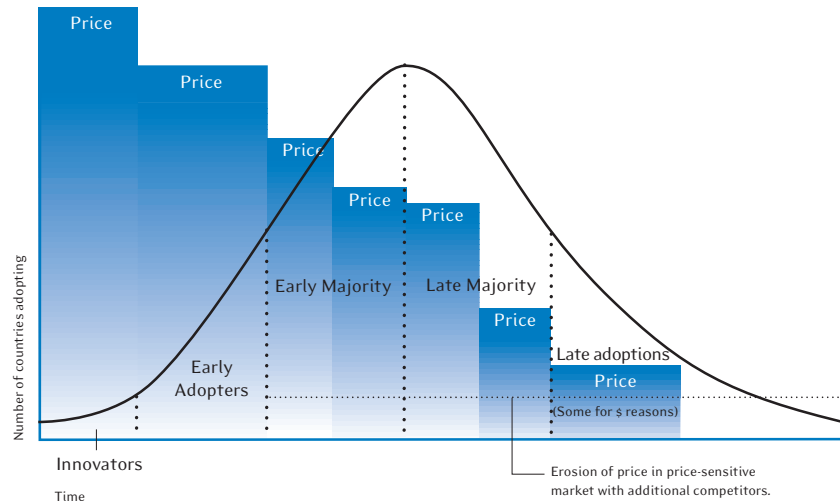
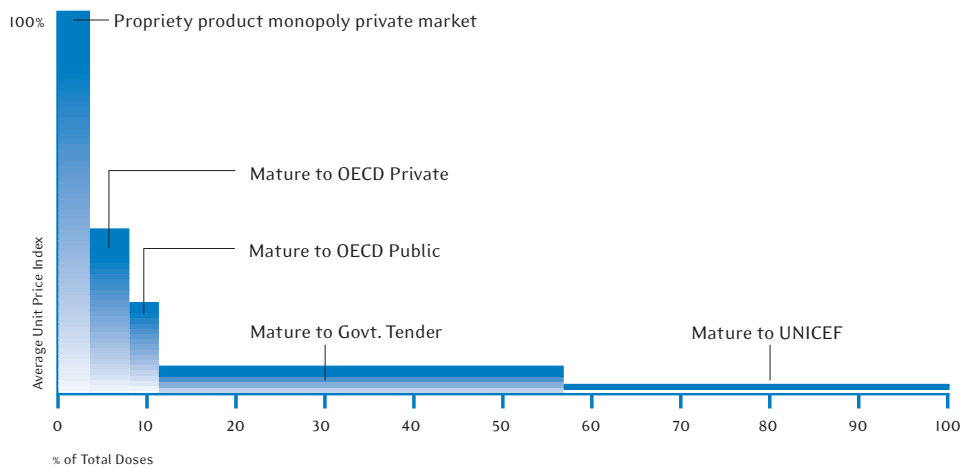




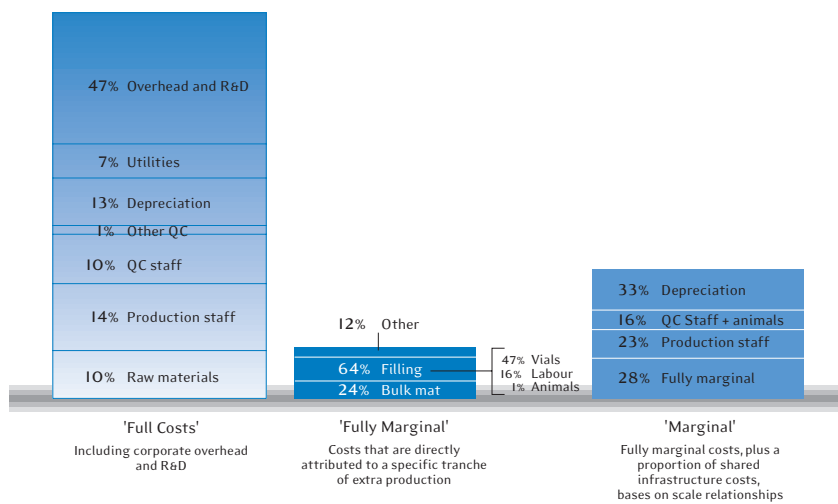
FIGURE A4.3 AND  
FIGURE A4.4

Price/Volume relationships for supply of a 'mature' vaccine.\*



\* >30 years after first marketing approval.  
Source: Mercer Management Consulting, Study for UNICEF, 1994.

Price differentials between markets can exist because of marginal costing



Source: Mercer Management Consulting, Study for US DHHS, 1995.

## Appendix 5

### Major inter-governmental organizations relevant to development and utilization of vaccines against AIDS

The following material on international agencies relevant to development or utilization of vaccines against AIDS is taken from the UNAIDS Website.

#### UNAIDS: The Joint United Nations Programme on HIV/AIDS

As the leading advocate for worldwide action against HIV/AIDS, the global mission of UNAIDS is to lead, strengthen, and support an expanded response to the epidemic that will:

- Prevent the spread of HIV
- Provide care and support for those infected and affected by the disease
- Reduce the vulnerability of individuals and communities to HIV/AIDS
- Alleviate the socioeconomic and human impact of the epidemic.

#### Why UNAIDS?

From 1986, the World Health Organization (WHO) had the lead responsibility on AIDS in the United Nations, helping countries to set up much-needed national AIDS programs. But by the mid-1990s, it became clear that the relentless spread of HIV, and the epidemic's devastating impact on all aspects of human lives and on social and economic development, were creating an emergency that would require a greatly expanded United Nations effort. Nor could any single United Nations organization provide the coordinated level of assistance needed to address the many factors driving the HIV epidemic, or help countries deal with the impact of HIV/AIDS on households, communities, and local economies. Greater coordination would be needed to maximize the impact of UN efforts.

Addressing these challenges head-on, the United Nations took an innovative approach in 1996, drawing six organizations together in a joint and cosponsored program—the Joint United Nations Programme on HIV/AIDS (UNAIDS). The six original Cosponsors of UNAIDS—UNICEF, UNDP, UNFPA,

UNESCO, WHO, and the World Bank—were joined in April 1999 by UNDCP.

The goal of UNAIDS is to catalyze, strengthen, and orchestrate the unique expertise, resources, and networks of influence that each of these organizations offers. Working together through UNAIDS, the Cosponsors expand their outreach through strategic alliances with other United Nations agencies, national governments, corporations, media, religious organizations, community-based groups, regional and country networks of people living with HIV/AIDS, and other non-governmental organizations.

#### How UNAIDS works

With an annual budget of US\$60 million and a staff of 129 professionals, UNAIDS is a modest-sized program with a substantial impact. The UNAIDS Secretariat operates as a catalyst and coordinator of action on AIDS, rather than as a direct funding or implementing agency.

The largest donors to UNAIDS in 1998 were the United States Government, which contributed US\$15 million, followed by the Governments of the Netherlands, the United Kingdom, Sweden, Norway, and Denmark. UNAIDS also receives funds from non-traditional donors such as China, Thailand and South Africa.

UNAIDS is guided by a Programme Coordinating Board with representatives of 22 governments from all parts of the world, representatives of the 7 UNAIDS Cosponsors, and 5 representatives of nongovernmental organizations (NGOs), including associations of people living with HIV/AIDS. UNAIDS is the first United Nations program to include NGOs in its governing body. The Cosponsors and Secretariat also meet several times a year as the Committee of Cosponsoring Organizations (CCO).

The Secretariat of UNAIDS is based in Geneva, Switzerland. Current priority areas for the Secretariat include:

- Young people
- Highly vulnerable populations
- Prevention of mother-to-child HIV transmission
- Developing and implementing community standards of AIDS care
- Vaccine development
- Special initiatives for hard-hit regions, including sub-Saharan Africa.

In January 2000, UNAIDS and WHO agreed to jointly undertake a range of activities related to AIDS vaccines. These will be managed under the WHO-UNAIDS HIV Vaccine Initiative.

#### UNAIDS at country level

In developing countries, UNAIDS operates mainly through the country-based staff of its seven Cosponsors. Meeting as the host country's United Nations Theme Group on HIV/AIDS, representatives of the Cosponsoring organizations share information, plan and monitor coordinated action between themselves and with other partners, and decide on joint financing of major AIDS activities in support of the country's government and other national partners. The principal objective of the Theme Group is to support the host country's efforts to mount an effective and comprehensive response to HIV/AIDS.

In most cases, the host government is invited to be part of the Theme Group. Increasingly, other partners such as representatives of other United Nations agencies and bilateral organizations working in the country are also included.

In priority countries the Theme Group has the support of a UNAIDS staff member, called a Country Programme Adviser (CPA). Elsewhere, a staff member of one of the seven Cosponsors serves as the UNAIDS focal point for the country. In addition to supporting the UN system, these staff endeavour to build national commitment to AIDS action and provide information and guidance to a range of

host country partners, including government departments and groups and organizations from civil society, such as people living with HIV/AIDS.

The UNAIDS Secretariat makes catalytic funding available for selected AIDS initiatives. Between January 1998 and May 1999, proposals were received and approved for projects in a total of 87 countries.

As of April 1999, the UNAIDS Cosponsors had established 132 United Nations Theme Groups on HIV/AIDS covering 155 countries. For their day-to-day operations, most Theme Groups have set up special working groups that involve donors, NGOs and groups of people living with HIV/AIDS.

Information on UNAIDS and links to its cosponsors can be found at—  
<http://www.unaids.org>

Cosponsors of UNAIDS

UNICEF

Mandated to advocate for the protection of the rights of children to help meet their needs and expand their life choices, the United Nations Children's Fund (UNICEF) is their chief advocate, acting within the framework of the Convention on Rights of the Child. UNICEF, its national committees and allies mobilize the moral and material support of governments, organizations and individuals worldwide in a partnership committed to giving children a first call on societies' resources in both good times and bad.

A decentralized operational agency, UNICEF works with governments and NGOs in the fields of health, nutrition, basic education, safer water, and sanitation to improve the lives of children, youth, and women. It helps build national and local capacities to provide, maintain, and expand necessary services, and to empower families and communities with the knowledge and means for self-reliance.

The rapid spread of HIV/AIDS is threatening the gains made in child health over the past two decades. The epidemic has a significant impact on adolescents, as adolescence is both a period of increased risk and a window of opportunity to develop the skills, attitudes and behavior necessary to prevent HIV infection in adulthood. The epidemic affects children and families, leaving many without protection, care, or income.

UNICEF brings to UNAIDS its operational field capacity in over 160 countries. It brings demonstrated effectiveness in communication and advocacy and a network of national committees. UNICEF's priority program areas include youth health, school AIDS education, program communication, children and families affected by AIDS, and mother-to-child HIV transmission. UNICEF's particular strength in meeting the needs of especially vulnerable families and children will assume greater importance in the coming years.

UNDP

An important objective of the HIV/AIDS-related activities of the United Nations Development Programme (UNDP) is to support countries to strengthen and expand their capacity to respond to the development implications of the epidemic. Activities are focused on identifying effective and sustainable policy and program responses surrounding the epidemic's social and economic implications. The aim is to strengthen capacity for an effective response within governments and civil society as well as within UNDP itself.

In partnership with many organizations, UNDP emphasizes support to initiatives which catalyze community and national mobilization; create a supportive ethical, legal and human rights framework; are

gender sensitive; empower people to take charge of their own well-being, drawing on local resources and building on local knowledge and values; and foster an enabling political, economic, and social environment.

Through its network of over 130 country offices serving over 150 nations, UNDP plays an important complementary role to that of other UN organizations; within the operational activities of development cooperation through a system of UN, national and other executing agencies; it provides technical support in cross-sectoral, multidisciplinary area of technical assistance relating to sustainable human development; and it has overall responsibility for assisting the Secretary-General in improving the coordination of operational activities for development, including strengthening the Resident Coordinator System.

UNDP's regional programs provide an important mechanism for fostering inter-country collaboration and helping regional institutions and networks to strengthen their capacity to respond effectively to the epidemic.

UNFPA

The mandate of the United Nations Population Fund (UNFPA) is, inter alia, to build the knowledge and capacity of countries to respond to needs in the area of population.

A major focus of UNFPA support at the country level is reproductive health, including family planning and sexual health. UNFPA considers prevention and management of sexually transmitted diseases (STDs) and prevention of HIV/AIDS to be integral components of reproductive health. In the context of

reproductive health, the preventive interventions include appropriate and effective information, education and communication (IEC) in support of safe sexual behavior; interpersonal counselling (for both sexual and mother-to-child transmission); improved access to and provision of condoms; and good clinical practices to prevent through exposure to HIV-infected blood.

UNFPA contributes to overall UNAIDS work by providing access to its worldwide network of country offices which support national reproductive health programs; its accumulated expertise in reproductive health promotion and service delivery, with a special focus on the needs of women and adolescents, and on male responsibility; its experience in logistics management of reproductive health commodities, including condoms; its experience in working with non-governmental organizations; and its experience in organizing technical assistance and strengthening national capacity-building through UNFPA Country Support Teams.

#### UNDCP

The United Nations International Drug Control Programme (UNDCP) is entrusted with exclusive responsibility for coordinating and providing effective leadership for all United Nations drug control activities. UNDCP addresses all aspects of the drug problem, including such wide-ranging activities as demand reduction, comprising prevention, treatment, and rehabilitation; supply reduction, including alternative development and law enforcement; and legislative and institutional advisory services to enhance government's capacity to implement the international drug control conventions. UNDCP is assisting governments in the implementation of action plans, including the Declaration on Drug Demand Reduction, adopted at the special session

of the General Assembly devoted to countering the world drug problem, held in June 1998.

The use of psychoactive drugs has facilitated the spread of HIV infection in several ways. The most direct is by HIV transmission through needles shared by injecting drug users. The disinhibiting properties of psychoactive substances also lead to sexual and other high-risk behaviors that individuals might otherwise avoid. Through sexual contacts, HIV infection is spread from the drug-using community to others. International drug control is therefore a vital tool for HIV prevention. In this context UNDCP is active in supporting HIV/AIDS prevention in programs to reduce the demand for illicit drugs. Youth and high-risk groups are particularly targeted. Coordination within the UN system has resulted in more effective programming responses to drug use and the AIDS epidemic in a number of countries.

UNDCP operates from its headquarters in Vienna, Austria, as well as from a field network currently comprising ten subregional offices and nine country offices. Liaison offices are maintained in New York and Brussels.

#### UNESCO

The mandate of the United Nations Educational, Scientific and Cultural Organization (UNESCO) is to foster international cooperation in intellectual activities designed to promote human rights, help establish just and lasting peace, and further the general welfare of mankind. Thus, the ethical imperative is central to UNESCO's mandate and its task of contributing in all fields of intellectual endeavor to human development and the building of a culture of peace based on respect for human rights, tolerance, and democratic principles. In its

fields of competence—education, science, culture, and communication—UNESCO has both technical responsibilities as regarded in programs and projects, and 'political' responsibilities, in the sense of public and social morality, in the general approaches and broad principles governing its efforts.

UNESCO's cosponsorship of UNAIDS is based on the conviction that isolated actions against AIDS that are not developed in an integrated, cross-disciplinary manner may be doomed to failure.

Although not a funding agency, UNESCO can make a contribution to UNAIDS by virtue of the scope of its fields of competence, its interdisciplinary and cross-disciplinary approaches combining technical skills and ethical requirements, and its experience acquired over 50 years of intellectual cooperation. It can bring the vast network of institutions with which it collaborates into the fight against AIDS, in the short-term to meet the most urgent prevention and care needs, and in the medium-term to remedy or offset the foreseeable effects of the epidemic.

#### WHO

The World Health Organization (WHO) is the directing and coordinating authority on international health work. Its objective is "the attainment by all peoples of the highest possible level of health," health being defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO Constitution, 1948).

WHO established the Special Programme on AIDS in 1986 in order to respond to the emerging HIV/AIDS epidemic. In 1987 the program became the Global Programme on AIDS (GPA), which was

ultimately dismantled in 1996 with the creation of UNAIDS. Throughout its 10-year existence, GPA advocated the need for multisectoral response to the epidemic, which WHO still advocates today.

Through its new Initiative on HIV/AIDS and sexually transmitted infections (HSI), WHO as a Cosponsor of UNAIDS strengthens the response of the health sector through the development of norms, standards, and guidelines; research; advocacy; technology development; and technical cooperation with countries. The areas covered include: prevention of HIV and sexually transmitted infections (STIs), particularly for those vulnerable and/or at increased risk; ensuring safe blood supplies; vaccine development; surveillance of HIV, AIDS, and STIs; and the development and evaluation of STI/HIV policies and programs. In the area of care for people with HIV or AIDS, WHO's activities include strengthening the capacity of health systems to provide a continuum of comprehensive care involving referral site, hospitals, home, and care and support initiatives in the community; ensuring access to essential drugs; and improving access to other relevant drugs through negotiations with the pharmaceutical industry and other channels.

#### World Bank

The mandate of the World Bank is to alleviate poverty and improve the quality of life. HIV/AIDS entails an enormous loss of human and economic resources and poses a substantial threat to the economic and social growth of many nations in the developing world. HIV/AIDS requires expensive and long-term health care; it mainly affects adults in the most productive years; it raises complex legal and ethical issues; it reaches all segments of society; and it is growing rapidly.

Between 1986 and early 1999, the World Bank committed over US\$750 million for more than 75 HIV/AIDS projects worldwide. Most of the resources were provided on highly concessional terms through the International Development Association. To more effectively address the devastating consequences of HIV/AIDS on development, the Bank is undertaking a new response to the epidemic, working partnerships with UNAIDS, donor agencies, and governments. The strategic plan for the Intensifying Action against AIDS builds upon the strong comparative advantages possessed by the partners to rapidly increase the level of action and available resources and to bring to scale the interventions needed for prevention and impact mitigation.

In its policy dialogue with borrowing countries, the Bank stresses that HIV/AIDS is a development priority and highlights the need for top-level political commitment, systematic health care reforms, human rights protection, and a range of multisectoral reforms to help reduce the factors contributing to HIV spread. Whenever possible, Bank-assisted activities are advised technically by the other Cosponsors or the UNAIDS Secretariat and are planned and executed by individual governments, in collaboration with the concerned nation and international partners.

APPENDIX 6  
AIDS VACCINE  
CANDIDATES IN  
DEVELOPMENT

**AIDS VACCINE CANDIDATES IN DEVELOPMENT**  
JULY 2000

AIDS Vaccine Candidate Category	Production	Comments
Recombinant proteins	Various rDNA expression systems	Many other products from various expression systems have been licensed; hence, most safety issues known
Virus vectors	Avian or mammalian fibroblasts, or continuous cell lines	Regulatory issues need to be identified and resolved
Bacterial vectors	Bacterial culture systems	Regulatory issues need to be identified and resolved; however, most will be similar to those of live bacterial vaccines
DNA vaccines	Various synthetic methods, expression and delivery systems	Regulatory issues have been generally identified; work is in progress to resolve for other products and for AIDS vaccines

Sources: - AIDS vaccine candidates in development, pp. 149-170 in *The Jordan Report 2000: The Accelerated Development of Vaccines*, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA  
- Dr. E. Griffiths, WHO Department of Vaccines and Biologicals (personal communication)