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HIV VACCINES - ACCELERATING THE DEVELOPMENT OF PREVENTIVE HIV VACCINES FOR THE WORLD

SUMMARY REPORT AND RECOMMENDATIONS OF AN INTERNATIONAL MEETING

MARCH 7 - 11, 1994

BELLAGIO, ITALY

Sponsored by

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Preface

This report provides a brief summary of an international meeting convened by the Health Sciences Division of the Rockefeller Foundation in Bellagio, Italy, March 7 - 11, 1994. The purpose of the meeting was to investigate the state of progress towards the development of preventive HIV vaccines appropriate for use in developed and developing countries, and to explore possible routes for accelerating the development of HIV vaccines. Twenty-four individuals attended the meeting in their personal capacities, not as representatives of particular institutions. Participants came from 12 countries and had backgrounds in vaccine development, AIDS research and care, international health, international finance, pharmaceutical and non-pharmaceutical industries, and public-private collaborations. This report reflects the consensus of the meeting, but does not attempt to represent the views of each of the participants. A draft was circulated to all participants for comments, however, final responsibility for its contents rests with the writers of the report, Jane Rowley and Seth Berkley.

The Rockefeller Foundation
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Executive Summary

The epidemic of HIV-1 continues to spread throughout the world despite current prevention efforts. Between 1993 and 2000 the World Health Organization projects that at least 26 million people will become infected with HIV-1 – an average of 10,000 people a day over the 7-year period. While a substantial increase in the financial and human resources available for prevention activities would reduce the number of new infections, there is a growing realization that the current range of prevention activities will not be able to halt the epidemic. Other measures are urgently required. The development of safe and effective preventive HIV-1 vaccines would dramatically improve the prospects for controlling the HIV epidemic provided they be made accessible to those at greatest risk of infection.

Meeting participants acknowledged the unprecedented effort that has been made by the scientific community to understand the biology and pathogenesis of HIV since its discovery as the etiologic agent of AIDS in 1984. In addition, there has been considerable interest shown by national and international public and private sector institutions in the development of HIV vaccines. These ongoing efforts, while constrained by budgetary and human resource limitations, have lead to major advances in scientific knowledge, and there are now encouraging signs that the development of a preventive HIV vaccine may be possible. A number of obstacles, however, hinder product development, and make it unlikely that a vaccine appropriate for use throughout the world will be developed and made available in a timely fashion unless remedial actions are taken. In 1993 over US$ 1.5 billion was spent worldwide on HIV prevention and over US$ 5 billion on HIV-related health care. Yet, in the same year less than US$ 160 million was invested worldwide by the public and private sectors in HIV vaccine research and development. This was considered insufficient given the current and rising health, humanitarian, social, and economic costs of the HIV epidemic. The investment of additional resources was viewed as potentially making a significant difference, especially if targeted at the critical gaps in current development efforts.

The national research agencies of the developed countries have been playing a key role in vaccine research. Product development activities, however, have been left almost exclusively to the pharmaceutical and biotechnology companies. In the current environment the incentives for industry to invest substantially in the development of a preventive HIV vaccine are limited – there are a number of other products with more attractive investment prospects. To overcome this market failure and ensure more active industry participation, positive steps will need to be taken.

The dominance of the national research agencies of the developed countries and the pharmaceutical and biotechnology companies in HIV vaccine research and development has meant that current efforts are directed almost exclusively towards vaccine products catering to the needs of the developed world. This emphasis raises cause for concern about the ultimate provision of an HIV vaccine to those in greatest need - over 90% of new infections are occurring in the developing world. For example, the industry investment in product development has, in general, been targeted at those vaccine approaches that are perceived as the safest, and has been based upon the sub-types of HIV-1 found in developed countries. Approaches that have technical characteristics that may make them better suited for use in developing countries are not being pursued aggressively. The rationale is that proving efficacy of a vaccine is the priority, following which other products will be developed in a sequential fashion. Given the many scientific uncertainties remaining, participants at the Bellagio meeting concluded that the development and testing of multiple empirical approaches in a parallel fashion, rather than

sequentially, will be a faster route to the development of safe, effective, and inexpensive vaccines appropriate for widespread use. The primary focus of current efforts on the sub-types of HIV-1 found in developed countries may also delay the evaluation of candidate vaccines by restricting the sites where clinical trials can be performed.

The unique nature of the HIV epidemic and its devastating potential consequences led the participants at the Bellagio meeting to conclude that a new global initiative with the primary mandate of accelerating the development of preventive HIV vaccines appropriate for worldwide use should be established. A new global HIV vaccine initiative was viewed as the most effective method to accelerate the development of safe and effective preventive HIV vaccines in the shortest time possible. The initiative should focus on reducing the obstacles to vaccine development and filling the gaps in the current effort. By focusing on the obstacles and gaps, the initiative was seen as complementing, not competing with, existing national and international activities. Success in developing an HIV vaccine will require the involvement of both the public and private sectors. Collaborative ventures between the private and public sectors have been fruitful in a number of other sectors in galvanizing product research and development, while still respecting corporate profit motives and independence. A range of potential models and sources of funding for the new initiative was suggested. A small funding secretariat, or task force, with an international scientific steering committee was viewed as the most appropriate structure.

Introduction

The continued spread of HIV-1[1] presents a serious threat to public health and economic development throughout the world. The World Health Organization (WHO) estimates that 14 million people had been infected with HIV by 1993, and projects that at least another 26 million will become infected by the year 2000. The available evidence suggests that all infected individuals will ultimately suffer from AIDS, and that all individuals with AIDS will die within a few years, unless much better means are found to slow disease progression. Already HIV is a leading cause of adult and infant mortality in a number of urban centers in both developed and developing countries, and by 1990, according to World Bank estimates, HIV was the leading cause of disability-adjusted life years lost among young adult males living in developing countries.

The recognition of the potential impact of the epidemic led to the mobilization of financial and human resources to slow the spread of the virus. Information and education campaigns designed to modify practices placing individuals at risk of acquiring and transmitting infection along with the provision of condoms and the screening of blood, have played an important role in reducing the rate of spread of the virus. Despite these global efforts, currently estimated to cost over US$ 1.5 billion a year (US$ 200 million [13%] of which was spent in developing countries), the virus continues to spread – even in populations exposed to extensive prevention programs. New prevention measures are urgently required.

Key to the successful prevention of many other infectious diseases has been the development and distribution of safe, effective, and inexpensive vaccines. Vaccines have played a pivotal role in eradicating smallpox worldwide, in eliminating polio from the Americas, and in controlling measles in a number of countries. The development and distribution of a safe, effective, and inexpensive vaccine to prevent HIV infection probably represents the best hope of controlling the global HIV/AIDS pandemic.

There are many scientific challenges that will need to be overcome before a preventive HIV vaccine is developed. The development of a vaccine, however, is only the first step. Experience with drugs and vaccines for other diseases suggests that measures will need to be taken to ensure that once a vaccine is developed that it is accessible to those at risk of infection throughout the world with the least possible delay.

This report broadly summarizes the deliberations of an international meeting convened by the Rockefeller Foundation in March 1994. The meeting, held in Bellagio Italy, was attended by 24 scientists, public health specialists, industry and private sector representatives serving in their personal capacities. The document is divided into five sections: the need for and ideal characteristics of a preventive HIV vaccine; current efforts to develop HIV vaccines; obstacles to developing and making HIV vaccines available; accelerating the development of HIV vaccines; and future activities.

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[1] Throughout this document the term HIV refers to HIV-1. The focus of the meeting was on HIV-1, rather than HIV-2, as HIV-1 accounts for over 90^{+} % of all HIV infections, is spreading faster, and is more easily transmitted than HIV-2.

1 The need for and ideal characteristics of a preventive HIV vaccine

1.1 The need for a preventive HIV vaccine

The last decade has witnessed the rapid spread of HIV throughout the world. By mid-1993 the WHO estimated that worldwide over 14 million people have been infected with HIV since the beginning of the epidemic. The vast majority of these infections, over 11 million, were in the developing world, and in some urban centers in sub-Saharan Africa it is estimated that already 1 in 3 adults is infected. Serological data record a rapid rise in the prevalence of HIV in many developing countries. For example, estimates of the number of infected individuals in Thailand increased 10-fold between 1990 and 1993 – from 50,000 to 500,000.

Over the last decade financial and human resources have been mobilized to slow the spread of the virus by modifying those practices that place an individual at risk of infection. Despite these global efforts, currently estimated to cost US$ 1.5 billion, the WHO projects that between 1993 and 2000 at least another 26 million people will become infected, over 90% of them in the developing world. In other words, over the 7-year period between 1993 and 2000, an average of 10,000 people each day will be infected with HIV. Even with an immediate 10- to 15-fold increase in the amount spent each year on AIDS and STD services in the developing world (an estimated annual expenditure of between US$ 1.5 billion and US$ 2.9 billion), the WHO projects that the number of new infections by the year 2000 would be reduced by at most 50%. In other words, substantially increasing the financial and human resources available will not be sufficient to halt the spread of the epidemic.

The development of safe and effective preventive HIV vaccines appropriate for use in developed and developing countries would dramatically improve the prospects for controlling the epidemic. The development of a vaccine would also be of enormous help in reaching those populations that might not otherwise be accessible to behavioral prevention efforts. Often those at highest risk of infection are alienated from society, are of low social status, have little education, or are illiterate, making them difficult to target with behavioral prevention efforts. Furthermore, it is possible that more virulent sub-types of HIV may evolve over time – another factor highlighting the importance of developing and ensuring that preventive HIV vaccines are made available as soon as possible.

Meeting participants regarded the development of preventive HIV vaccines appropriate for worldwide use as of the utmost urgency for a variety of reasons.

- Public health: HIV is one of the most deadly human viruses known – the available data suggest that it is 100% fatal – and at present there is no cure. While the current range of prevention activities are slowing the rate of spread of the epidemic they will not be able to halt its spread even with a substantial increase in investment. In countries where the epidemic is already established, all sexually active individuals who are not monogamous, or those who have partners who are not monogamous, are at risk of infection. The demand for health care from infected individuals is placing a substantial burden on health care systems that are already over-extended. For example, in a number of urban hospitals in sub-Saharan Africa over 70% of hospital beds are occupied by HIV-positive individuals. The negative consequences of the epidemic for public health are further compounded by the impact the epidemic is having on the rate of spread of other infectious diseases, such as tuberculosis.

- Humanitarian and social: Much of the burden of HIV is placed upon those least able to cope with it: the poor, the marginalized, and the young. Africa, the region with the weakest economy in the world, has over 60% of the current HIV burden. In many areas individuals who are not in a position to adopt risk-reduction measures, such as young women, are placed at a high risk of infection, not because of their own activities, but rather by the activities of their partner. Premature mortality and AIDS-related morbidity among adults are also having a serious impact on child welfare. For instance, the WHO estimates that in the 1990s there will be over 10 million AIDS orphans in Africa.

- Economic: AIDS primarily affects young adults in the most productive age groups and as a result the indirect costs associated with the epidemic are significant. The reduction in the supply and productivity of labor from HIV-related mortality and morbidity, and the financial burden of paying for HIV-related treatment and other needs have serious economic consequences for households, productive enterprises, and countries. In the case of affected households the illness or death of a productive member can tip vulnerable households into poverty. The direct costs of the epidemic are also substantial. By 1993, HIV-related medical care costs in the developed countries had already reached US$ 4.8 billion a year and US$ 340 million in developing countries – figures that will continue to rise in the foreseeable future.

The participants at the Bellagio meeting also expressed concern about the long-term financial sustainability of the current range of prevention activities. Behaviour modification activities are both costly and labor intensive and will almost certainly need to be continued indefinitely to ensure that newly sexually active individuals are educated and to reinforce the knowledge of those already sexually active. The limited impact that prevention activities appear to be having on the rate of spread of HIV, and the decreasing prominence of HIV and AIDS as a health and development issue in developed countries, however, may lead donors to reassess their financial commitment to prevention, with serious consequences for prevention activities in the future.

1.2 Ideal technical characteristics of a preventive HIV vaccine

A preventive HIV vaccine intended for use throughout the world ideally would have the following technical characteristics:

- Protection: Able to stimulate the production of durable, functional protective immune responses against most, it not all, sub-types of HIV[2] to which an individual is likely to be exposed, and from all potential routes of exposure. The mobility of people (and therefore viruses) highlights the need to protect individuals not just from the sub-types currently circulating where they live but also from those they may encounter in the future.

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[2] Isolates of HIV from different geographic regions, from different individuals in the same region, and even from a single infected individual often carry distinctly different genetic sequences. Isolates can be grouped by genetic relatedness; nine groups or sub-types of HIV-1 have been identified so far. In North America one sub-type (B) is prevalent in the infected population. In a number of regions, however, several different sub-types can be found.

- Safety: Safe in both the short and long term. Safety concerns include reversion to infectious HIV, oncogenic potential, and immunosuppression in those vaccinated. The vaccine should also be safe to deliver without prior screening for HIV infection (i.e., the vaccine should not induce any adverse reactions when given to HIV positive individuals). Although complete safety is the ideal, the risk to benefit ratio in populations at high risk of infection may justify the use of a vaccine that has some risks or before every aspect of safety has been exhaustively evaluated.

- Delivery: Provide long-lasting protection with a minimum number of doses (preferably one), have a long shelf-life, be heat stable, and be simple to administer (preferably oral).

- Unambiguous marker for seroconversion: Provide health care professionals with a marker which enables seroconversion due to vaccination and seroconversion due to infection to be distinguished rapidly, easily, and inexpensively.

- Cost: The final price of the vaccine should be such that it will be affordable for wide-scale distribution to all at risk of infection throughout the world.

2 Current efforts to develop HIV vaccines

2.1 Progress in HIV vaccine research

Since the discovery of the etiologic agent of AIDS there has been an unprecedented scientific effort to understand its structure, function, pathogenic mechanisms, and routes of transmission. More advances have been made over the last decade on this virus than on any other organism in history, and new advances are being announced each week. The information from the ongoing research efforts has provided the essential underpinning for efforts to develop preventive vaccines and treatments for those infected. This worldwide effort has led to the design of a number of different candidate vaccines which are currently being explored in the laboratory and in animal models (see Table 1). These include:

- Peptides based on key portions of HIV structural proteins;
- Protein subunits based on HIV structural genes;
- Virus-like particles and other particles including pseudovirions;
- DNA that encodes one or more HIV proteins;
- Live recombinant viral and bacterial vectors that express one or more HIV proteins;
- Whole killed virus;
- Live attenuated virus.

In addition, a number of new adjuvants and delivery methods are under evaluation.

A number of key scientific challenges, however, remain. These include:

- The nature of the immune response required to prevent HIV infection: Infection may occur by both cell-associated and free-virus particles, and either through mucosal or systemic routes of exposure. Whether specific mucosal immune responses will be required to prevent infection and how best to stimulate them remains unknown.

- The nature of the immune response required to prevent HIV diseases: At present, the methods of HIV clearance following natural exposure have not been demonstrated. By analogy with other viral diseases, neutralizing antibodies and cytotoxic lymphocytes responses are thought to be important, but neither has been shown definitively to confer protection against HIV disease progression in infected individuals.

- The immunological importance of the different sub-types of HIV: The genetic diversity of the viral sub-types found worldwide is large. At present the immunological importance of the different sub-types is not known. The WHO Network for HIV Isolation and Characterization is collecting and analyzing samples from around the world to improve current understanding of this issue.

- Animal models: There is no readily available reliable animal model of HIV disease. SIV in monkeys has some potentially important differences from HIV, and HIV infected chimpanzees do not develop disease.

- Endpoints for vaccine efficacy trials: There is doubt about what endpoints to use for vaccine efficacy trials owing to the uncertain relationship between surrogate markers of disease progression (CD4 count, viral burden) and subsequent disease progression, and the long latency period between infection and development of disease.

Meeting these challenges will provide a major impetus to the development of preventive HIV vaccines. The meeting participants, however, felt that it was important that product development work and the clinical trials of candidate vaccines should not be overly delayed by the unsolved scientific challenges. Vaccine development and the clinical testing of other viral vaccines have occurred despite the existence of profound scientific challenges and much has been learned from this work. In the case of HIV, where no good correlates of protection have been identified and there is no readily available reliable animal model, there is no substitute for scientifically and ethically sound human trials. While there are certain characteristics of HIV that warrant caution, the consensus was that new information will rapidly be generated from trials in humans regardless of whether or not the candidate vaccine was successful in protecting a large percentage of volunteers.

2.2 Progress in HIV vaccine development

Product development efforts have focused predominantly on three vaccine strategies – peptides based on key portions of HIV structural proteins, protein subunits based on HIV structural genes, and live recombinant viral or bacterial vectors that express one or more HIV proteins. In the last few years over a dozen products have entered Phase I clinical trials (small-scale safety and immunogenicity trials) (see Table 1) and two products have entered phase II (large scale safety and immunogenicity trials). The majority of the products currently being tested are based upon key portions of the HIV envelope protein (gp160 or gp120). Products based on a highly immunogenic portion of the HIV envelope, the V3 loop, as well as products based on recombinant viral vectors using pox viruses to express the HIV envelope, are also undergoing Phase I clinical investigations. None of the Phase I trials have demonstrated any problems with safety and in several trials, virtually all of the volunteers who received a series of injections produced antibodies capable of neutralizing laboratory strains of HIV. The trials, however, involve small numbers of volunteers and have a limited time period of observation. The long term side-effects and duration of immunity remain to be determined.

Phase III studies (large-scale efficacy trials) have not yet been initiated but are expected to begin in 1995. To prepare for these trials national governments and the WHO are developing the necessary infrastructure in various countries. These efforts include: the characterization of HIV sub-types found in possible trial populations, the training of investigators, the determination of the seroincidence of HIV, general strengthening of the infrastructure and field management capacity to undertake vaccine trials, and the development of the political support necessary for the conduct of such trials.

Product development efforts have focused on a small number of the potential vaccine approaches. The participants at the Bellagio meeting expressed concern about the lack of attention being given to other approaches. A number of approaches are not currently being "championed", including the two classical strategies, whole killed virus and live attenuated virus (Table 1). These strategies, and in particular, the live attenuated virus approach, are perceived as potentially less safe. However, a WHO expert committee that reviewed this issue in June 1993 concluded that the live attenuated approach "should be intensively explored". While ethical principles must not be compromised, the participants noted that the high risk of infection in some populations may justify the use of vaccine approaches that could potentially be less safe. For example, a vaccine with a risk of a serious adverse reaction of 1 in 100,000 may be considered better than no vaccine by a population with a high risk of infection, or better than an alternative vaccine that has a lower risk of adverse reactions but is less efficacious. Live attenuated or whole killed vaccines, if found to be efficacious, could represent viable cost-effective approaches under some circumstances.

The meeting participants also noted that product development efforts have focused on the sub-type of HIV found almost exclusively in North America and Europe – sub-type B (see Table 1). Candidate vaccines representing sub-types prevalent in the developing world, and candidates based on multiple sub-types are not being widely developed. While the immunological importance of the different sub-types has not yet been determined, the current focus of development activities on sub-type B could present problems when it comes to carrying out efficacy trials and may result in substantial delays in the evaluation of candidate vaccines. In the absence of more information on the immunological importance of the different sub-types of HIV, it is important that vaccine trials are carried out with prototype vaccines based on the viral sub-types found in the trial site; otherwise, it will be difficult to evaluate the significance of a negative result. There are, however, only a small number of population groups (primarily intravenous drug users and individuals living in some resource-poor inner city areas) with high enough rates of infection with sub-type B to carry out efficacy trials using realistic sample sizes. Some clinical trials can almost certainly be done more effectively and expeditiously in developing country populations with a high incidence of infection.

2.3 Financial resources

A review of recent activities in both the private and public sectors suggests that in 1993, less than US$ 160 million was spent worldwide on HIV vaccine research and development (see Table 2). This represents less than 10% of the total amount spent on HIV/AIDS-related research and development. It is a fraction of the amount spent in 1992 on HIV prevention (US$ 1.3 billion in developed and US$ 0.2 billion in developing countries) and on HIV-related health care (US$ 4.7 billion in developed and US$ 0.34 billion in developing countries), and a very small fraction of the

amount spent on health research. The most recent survey of expenditures on health research conducted by the Commission on Health Research for Development estimated that in 1986 US$ 30 billion was spent worldwide on health research, of which less than 5% (US$ 1.6 billion) was spent on developing country-oriented research. Between 1986 and 1993 the total amount spent each year on health research increased markedly. This means that in 1993 expenditures on HIV vaccine research and development represented substantially less than 0.5% of the total global health research budget.

Public sector

The public sectors of the major developed countries are the main source of funding for HIV vaccine research and development. In 1993 it is estimated that they provided over 80% of the total global expenditure in this area, or between US$ 125 million and US$ 130 million (see Table 2). Their efforts to fund research on HIV and AIDS are constrained, however, by overall budgetary and human resource limitations, and the competing demands of other important diseases affecting human health. There is also competition for funds earmarked for HIV/AIDS research between basic research activities directed at increasing current understanding of the virus, activities directed at developing therapeutics to treat those currently infected, and activities directed at developing a preventive HIV vaccine. Of the three, preventive vaccine development has received the smallest proportion of the available funding. For example, in 1993 less than 10% of the US government's budget for HIV/AIDS related research and development activities was spent on preventive vaccines (see Table 2).

Within the public sector, the national health research agencies control the majority of the funds, and hence expenditures are also influenced by their general mission - to promote the health of persons living in their own country. The development assistance agencies, whose mandate is directed towards those living in developing countries, have not been active funders of HIV vaccine research and development to date.

Private sector

The private sector is an important source of funds for health research. The Commission on Health Research for Development estimated that in 1986, the private sector accounted for over 40% of the total amount spent on health research (US$ 13 billion out of US$ 30 billion). Estimates of the amount invested by the private sector in research and development activities related to preventive HIV vaccines are difficult to make. Results from an informal survey of the key players, however, suggest that in 1993 pharmaceutical and biotechnology companies invested less than US$ 25 million in preventive HIV vaccines, or under 15% of the total expenditure.

Both large pharmaceutical companies and the small biotechnology companies have been active players to date in HIV vaccine development. Funds for investment by the large companies come, in general, from within the company. The small biotechnology companies, however, rely primarily on venture capital for funding which, in general, has a limited time horizon for investment without quantifiable success. The prospect of price controls on health care in the United States is also making preventive vaccines a less attractive investment prospect.

The resources that have been invested by industry in the development of preventive HIV vaccines have been targeted predominantly at those approaches perceived as being safest (i.e., least likely to have untoward side effects and, consequently, with less potential for litigation should such

effects emerge), and have been based on the sub-type of HIV found in the US and Europe (i.e., greater likelihood of receiving a return on investment).

The meeting participants concluded that the current level of investment in research and development on preventive HIV vaccines was insufficient given the future health, humanitarian, social, and economic costs of the HIV/AIDS pandemic. The investment of additional resources was viewed as potentially making a significant difference, especially if targeted at the critical gaps in current development efforts.

3 Obstacles to developing and making HIV vaccines available

3.1 Obstacles to vaccine development

In the industrialized countries, vaccine development is almost exclusively a commercial enterprise. The resources, expertise and experience for product development, preparation for licensure application, and manufacturing lie predominantly in the private sector. As a result, whatever research priorities are set by the public sector, the ultimate decision to develop and manufacture a vaccine for general use rests in the hands of the private sector and, in particular, the large vaccine companies, most of which are also large pharmaceutical companies.

The decision to invest in the development of a new product reflects a careful assessment of a variety of external and internal factors that determine the opportunity costs of investing in the product, the risks involved in developing and marketing the product, and its potential profitability. Three key external factors are the state of science, the size of the market, and the public policy environment. Internal factors include the skills base of the company, and the fit with the current research and development portfolio.

In the case of HIV, the current level of investment by the private sector suggests that, at present, industry does not regard the development of a preventive HIV vaccine as a very attractive commercial enterprise. The opportunity costs of investing in the vaccine are not insignificant - the development of an HIV vaccine will almost certainly require a substantial investment of financial and human resources over an extended period of time. The risks are also great. There is no guarantee that a preventive HIV vaccine can be developed, and even if a company did develop a vaccine the size of the market and the price the market will bear are both uncertain, as are the potential liability costs.

State of the science

The rapid scientific advances made in the last decade provide the essential underpinning for efforts to develop preventive HIV vaccines. There is, however, no guarantee that it will be possible to develop a preventive vaccine, and in the interim there are a number of important scientific challenges that need to be met (see Section 2.1). These uncertainites make investing in an HIV vaccine a risky prospect.

Market considerations

Estimates of the size of the market for a preventive HIV vaccine are difficult to make as there are many uncertainties, including the acceptability of the vaccine to the population; the perceived risks of acquiring HIV; the amount people or institutions will pay for a vaccination course; the willingness of different institutions to cover the costs of a vaccination course for those who cannot afford to pay; and national government vaccine policies.

In the developed countries, in the absence of broad recommendations for vaccination the greatest demand for a preventive vaccine will come from those individuals who regard themselves as at high risk of infection. Estimates of the percentage of the population who regard themselves as at high risk of infection are small. The experience with the use of hepatitis B vaccine in health care providers and homosexuals also confirms the difficulty of expecting a broad voluntary uptake. Among population groups identified as at high risk of infection, such as sexually active homosexuals and intravenous drug users, it is likely that only a proportion of individuals will come forward to be vaccinated even if the vaccine is free or highly subsidized. Individuals may not identify themselves as at risk of infection, and in areas where intravenous drug use is illegal or homosexuality is stigmatized, they may not be willing to step forward to be vaccinated. Even if all homosexuals and intravenous drug users were vaccinated, the number of vaccination courses required is not large. Assuming 2% of adult males are sexually active homosexuals, and 0.1% of the adult population uses intravenous drugs, then less than 5 million full courses would be required to vaccinate all members of these two groups in the developed world, and probably less than 150,000 courses a year to vaccinate all individuals entering the two groups. Heterosexuals with multiple sexual partners and certain cadres of medical professionals (e.g. surgeons) have also been identified epidemiologically as being at high risk of infection. The prevailing view is that only a very small proportion of heterosexuals consider themselves at risk of infection. It is difficult to predict, however, how the general heterosexual population will respond to the availability of a preventive HIV vaccine.

The developed countries account for only 15% of the worlds population and 7% of new births. In other words, the potential demand for an HIV vaccine is substantially greater in the developing world than in the developed world. The resources to purchase a preventive HIV vaccine, however, lie disproportionately within the developed countries and will continue to do so for the foreseeable future in the absence of international subsidies. In general, the countries with the highest incidence of HIV and hence with the greatest need for a preventive vaccine are also among the poorest. For example, the total per capita expenditure on health care in sub-Saharan Africa (including both public and private funding but excluding South Africa) in 1990 was US$ 13.5 and in India US$ 21, a fraction of the amount spent in Europe or North America. Comparable figures for France and the United States were US$ 1,945 and US$ 2,763 respectively.

Public policy environment

The meeting did not focus on the public policy environment in detail. The general view, however, was that the current public policy environment for vaccine development was not favorable. Positive steps will have to be taken if pharmaceutical and biotechnology companies are to be encouraged to commit more fully their expertise, experience and resources to the development of a preventative HIV vaccine. This is especially true if industry is to be encouraged to invest in vaccines that will meet the technical requirements of the developing world.

Interventions to encourage industry participation are basically of two types – those that reduce the prelicensure costs and risk of developing a vaccine candidate, and those that make the environment for vaccine manufacturing more hospitable. Incentives could include improving the legal and regulatory environment, reducing the potential costs of liability exposure, or ensuring the availability of patent protection for those working on preventive HIV vaccines. Other incentives include:

- financial assistance with research and development in the form of grants, cooperative research and development agreements, tax credits, or other fiscal incentives;
- access to pilot production facilities;
- assistance with access to clinical and field trial sites;
- financial assistance with clinical trials and field testing;
- harmonization of international regulatory procedures for vaccine approval;
- assistance in the assembling intellectual property rights;
- guaranteed procurement of vaccine;
- establishment of an HIV vaccine injury compensation program.

3.2 Obstacles to vaccine availability

Ensuring that once a safe and efficacious preventive HIV vaccine is developed that it is made available promptly to those individuals at high risk of infection is of utmost importance. Experience with drugs and vaccines for other diseases (e.g. hepatitis B), however, suggests that worldwide availability will not occur without specific attention being given to the needs and requirements of developing countries. Issues relating to the manufacture, purchase and distribution of HIV vaccines will need to be addressed and steps taken in advance to ensure that extended delays do not occur. WHO, UNICEF (United Nations Children's Fund), and a number of other international agencies have extensive experience with these issues from working on the worldwide Expanded Programme on Immunization.

4 Accelerating the development of HIV vaccines

4.1 The need for a new initiative

The participants at the meeting expressed concern about the direction and pace of current efforts to develop a preventive HIV vaccine that would be appropriate for use in developed and developing countries. This concern reflected an assessment of a number of issues:

- There is no coordinated international strategy backed with adequate resources for the development of preventive HIV vaccines appropriate for use throughout the world. This has meant that there are important gaps in the overall picture of vaccine development.
- The financial resources for preventive HIV vaccine research and development are limited (presently estimated at under US$ 160 million a year) and come primarily from the public sector of the major developed countries. These resources are invested almost exclusively in vaccine candidates and approaches that are directed at meeting the needs of the developed countries, and stress research rather than vaccine development. The vast

majority of infected individuals, however, live in the developing world, and it is here that the epidemic is spreading most rapidly.

- Most of the research funding from the public sector is done through researcher originated mechanisms. Although this is an excellent way to make new scientific breakthroughs, it is not necessarily the most effective way to develop a particular product.

- The expertise and resources for vaccine product development reside overwhelmingly in the larger commercial vaccine companies. The opportunity costs of investing in HIV vaccines, the perceived returns to investment and the potential costs (including liability) have meant that only a few companies are investing substantially in preventive HIV vaccines.

- Small biotechnology companies have been active players in vaccine development to date. They are, however, constrained by their reliance on venture capital for funding which, in general, has a limited time horizon for investment without quantifiable success.

- The limited resources being invested in HIV vaccine research and development has meant that HIV vaccine development is following a sequential, not a parallel approach. Given the many scientific uncertainties remaining, the development and testing of multiple empirical approaches in a parallel fashion, rather than sequentially, will be a faster route to the development of safe, effective, and inexpensive vaccines appropriate for widespread use.

- Vaccine approaches perceived as more speculative are not being actively pursued by commercial vaccine companies, even though they may offer other desirable attributes, such as the potential for higher efficacy or use with fewer doses.

- Candidates developed from sub-types of HIV found in areas where most new infections are occurring are not being aggressively developed in parallel to the developed country prototypes, even though many scientists are of the opinion that efficacy testing can be done much more effectively and expeditiously in high HIV-incidence developing country sites.

- Scientists and public health officials from developing countries have little involvement in, or influence on, the decision-making process for the development of preventive HIV vaccines.

The participants concluded that a new global HIV vaccine initiative should be established with the primary mandate of accelerating the development of preventive HIV vaccines. The main role of the initiative should be to redress system or market failures with respect to product development and its activities should focus on reducing the obstacles to vaccine development and filling the gaps in the current effort. By focusing on the obstacles and gaps, the initiative would complement, not compete with, the existing efforts in HIV/AIDS vaccine development, such as national programs and private sector vaccine development. The initiative was seen as providing support to a number of parallel development efforts prior to the time when a definite choice between alternative strategies can be made. A secondary goal of the initiative would be to work with organizations such as WHO, UNICEF, and other national and international agencies, to ensure that once a vaccine is developed that it is made available for use throughout the world with the least possible delay.

4.2 Characteristics of a new initiative

The participants felt that the new initiative must have a well defined mandate, and must work closely with and be responsive to the needs of industry, national research agencies, national governments, and international agencies.

Other characteristics identified were:

- The ability to mobilize the collective efforts of a number of different sectors of the world economy – national governments, private companies, non-governmental organizations, and international organizations.
- The ability to act decisively, rapidly and to be flexible.
- The ability to undertake innovative development projects entailing calculated scientific and financial risks.
- A commitment to the highest scientific standards and full respect for ethical considerations and human rights.
- A finite lifespan.

The final form of the initiative and its sources of funding will need to be developed in consultation with the anticipated major collaborators. The advantages and disadvantages of various models for the new initiative were discussed at the Bellagio meeting. Models discussed include (see Table 3):

- Task force;
- Donor collaboration;
- Private consortia;
- Public/private consortia;
- Not-for-profit institute.

Experiences with specific programs were also discussed. Particular attention was given to the Children's Vaccine Initiative (CVI), as in many ways the role of the proposed initiative is analogous to the role CVI is playing in the development of childhood vaccines.

The view of the meeting was that a small secretariat, or task force, with an international scientific steering committee would be an appropriate structure. The secretariat would strive to accelerate the development of preventive HIV vaccines both by working with other organizations to reduce the disincentives and by targeting research funds at the critical gaps in product development as identified by the scientific steering committee. The secretariat would carry out no research of its own but rather would contract research out to companies, universities and government laboratories throughout the world.

The meeting participants felt that it was essential that the initiative have its own mandate and governing structure. It was recognized, however, that given the time delay and resources required to establish a new organization, it might be appropriate for the initiative to be housed, at least initially, in an existing organization. Potential homes for the initiative include the World Bank,

another multilateral agency, the new UN AIDS program (once established), or an international foundation.

Possible sources of funding for the secretariat and its associated activities were discussed. Sources mentioned included multilateral agencies, national agencies with interests in health or international development, philanthropic organizations, pharmaceutical and biotechnology companies, and the general public. An innovative model of a stock corporation owned by a number of pharmaceutical companies, multilateral agencies, private funders and developing country governments, and receiving developed country co-funding or loan guarantees for bonds sold on commercial markets, was offered as one possible funding approach. This approach has the advantage of not requiring substantial public sector funding unless the effort is ultimately unsuccessful. Another approach discussed was obtaining new public funding through a special appropriation by national governments.

The importance of both the private and public sectors playing an active role in the new initiative was stressed. The success of any new initiative will depend upon the willingness of both sectors to be involved. Collaborative ventures between the private and public sectors have been fruitful (eg. Sematech, Airbus) in a number of other sectors in galvanizing product research and development, while still respecting corporate profit motives and independence.

The value of both developed and developing country governments being actively involved was also emphasized. The need for a preventive HIV vaccine is greatest in parts of the developing world and, as a result, it is important that the requirements of these countries are taken into account. As well, the testing of candidate vaccines may be conducted more efficiently in high-incidence settings in developing countries than in developed countries. Those countries that participate in clinical trials should receive full credit for their part of the partnership in the development of an HIV vaccine. Involvement in the new global initiative may also assist countries by stimulating their own capacity to conduct vaccine research and clinical trials, and produce and deploy vaccines – an important additional benefit.

4.3 Activities of a new initiative

To achieve the initiative's goals, it was envisaged that a number of different activities would need to be carried out in close collaboration with the appropriate national and international agencies. The exact activities will need to be decided following discussions with potential collaborators. Among the activities identified during discussions at the Bellagio meeting were:

- Developing and disseminating a scientific strategic plan for vaccine development and candidate assessment; monitoring progress towards accomplishing the plan and closing the remaining gaps.

- Mobilizing additional financial resources that can be used to accelerate the development of preventive HIV vaccines.

- Encouraging the development of vaccine approaches that are not actively being pursued and new approaches that could be appropriate for eventual use in developing countries by providing financial resources and other types of incentives (see section 3.1). This might include directly funding vaccine companies to undertake particular steps in developing promising vaccine candidates.

In addition the initiative will need to work with other national and international agencies to:

- Ensure the active participation of individuals from all areas of the world in the planning, conduct, and evaluation of research and development for HIV vaccines. Provide additional financial and human resources to strengthen local capacities where necessary.

- Encourage and facilitate collaboration between the public sector and the private sector.

- Monitor the worldwide progress of promising vaccine approaches and candidates, and the global capacity to conduct safety and efficacy testing of vaccine candidates.

- Encourage national and international authorities to consider and resolve issues identified by the private sector as disincentives to vaccine development in general, and to HIV vaccines in particular, such as:
  - The commercial unpredictability arising from the lack of efficient mechanisms for dealing with liability and compensation for vaccine injury not associated with manufacturer negligence;
  - The lack of consistent international guidelines on issues relating to safety and efficacy testing, and licensure of vaccine candidates against HIV;
  - The lack of harmony among international regulatory agencies;
  - The commercial unpredictability arising from the lack of recommendations for vaccine use.

- Ensure HIV vaccines will be accessible and affordable for those at risk of infection. Activities that the initiative may need to consider undertaking include:
  - Identification of potential markets for vaccines in developed and developing countries and the creation of markets where they do not exist by ensuring that funds will be available for vaccine procurement (options include exploring the possibility of using the World Bank's International Development Association loans as a way of guaranteeing a hard currency market for HIV vaccines that meet certain specifications).
  - Development of plans for ensuring the financing of adequate supplies of vaccine for use in developed and developing countries once licensed for use.
  - Strengthening the capability for self-reliance in vaccine quality assurance, vaccine "finishing" and in manufacturing where appropriate and necessary.
  - Development of strategies for technology transfer if and when it becomes feasible.

5. Future Activities

The pace of scientific progress and recent research findings are encouraging that an HIV vaccine can be developed. While this is not certain, the rapid rate of spread of the HIV epidemic, the gravity of its potential consequences, and the limited impact of current prevention efforts, highlight the importance of mobilizing additional resources for HIV vaccine research and development. The HIV epidemic is truly a global epidemic, and as a result the development of preventive HIV vaccines will benefit the human race.

The organizations currently engaged in HIV vaccine research and development all have mandates that limit the scope of their vaccine research and development agendas. To date, the major source of funding for vaccine research has come from the public sectors of the developed countries and the vast majority of these funds have been administered by agencies with a domestic focus. The development assistance agencies, whose mandate is directed towards those living in developing countries, have not been major funders. Product development has been left almost exclusively in the hands of the private sector where the expertise and resources lie. In the current environment, however, the risks and potential returns from investing in the development of HIV vaccines are not sufficient for the private sector to make a substantial commitment to vaccine development. Without the expectation of adequate returns it is unrealistic to expect commercial vaccine companies to divert resources in favor of the development of a vaccine merely for the good of the public. Commercial manufacturers cannot be expected to bear the sole responsibility of developing high-risk, low-priced products. As a result, the public sector will need to reduce the disincentives for industry to invest if a vaccine is to be developed with the least possible delay.

The successful development of a preventive HIV vaccine will almost certainly depend upon the involvement of both the private and public sectors from around the world. In the current environment, no one government or company has the resources and incentive to take on the challenge of developing an HIV vaccine alone. The potential resources, however, that could be mobilized if the public and private sector of different countries were encouraged to work together would be substantial. Within the public sector, the development of an HIV vaccine is of importance for a number of different agencies, including those with concerns in health, economic development, and international development.

The participants at the meeting concluded that the establishment a new global HIV vaccine initiative with the primary mandate of accelerating the development of preventive HIV vaccines would be the most effective method of ensuring that a safe and effective preventive HIV vaccine appropriate for worldwide use is developed and made available in the shortest time possible. The establishment of a new global initiative backed with sufficient resources could potentially alter the future course of the HIV epidemic, save the lives of large numbers of people, and reduce the economic consequences of the epidemic. Such a global partnership would be a winning situation for all involved.

Due to the important implications of starting a new initiative and the resources that will be required, participants considered that the plan needed further discussion to define more accurately the steps that will need to be taken. In particular, additional guidance will need to be sought from the private sector. For the short term the meeting recommended that:

- The concept of the establishment of a new initiative should be discussed with potential collaborators;

- A preliminary scientific research agenda should be developed;

- A proposal detailing the scientific and business plan of the initiative, organizational structure, and funding mechanism should be developed.

The participants at the Bellagio meeting considered that the development of preventive HIV vaccines appropriate for worldwide use was of great urgency and deserving of extensive support. The World Bank's 1993 World Development Report concludes that "Historians will look back on the latter half of this century as having had one great medical triumph, the eradication of smallpox, and one great medical tragedy, AIDS." Perhaps it is not too late for the world to rise to the challenge of averting this tragedy.

Table 1. Investment in preventive vaccine product development by approach and virus sub-type. Vaccine approaches are ordered from left to right according to perceived safety.

Sub-type	Peptides	Protein subunits	Virus-like particles and other particles	DNA	Live recombinant vectors	Whole killed	Live Attenuated
B*	+	+	+	+/-	+	0	0
A	+/-	0	0	0	0	0	0
C	+/-	0	0	0	0	0	0
D	+/-	0	0	0	0	0	0
E	+/-	0	0	0	0	0	0
F	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0

* Virus sub-type B predominates in North America and Europe.

0 No product in development
+/- Product in development but not yet in human trials
+ Product currently in Phase I/II trials in humans

Table 2. Estimates of the global annual expenditure in 1993 on HIV/AIDS research and development in US$ million.

	Total expenditure on HIV/AIDS	Expenditure on preventive HIV vaccines
Intergovernmental		
WHO	10.0	2.7
European Union	8.2	1.3
Other	*	< 1.0
Governmental		
France	36.0	6.9
Germany	11.7	2.1
Japan	4.8	0.7
Sweden	6.5	1.0
United Kingdom	23.0	2.5
United States	1362.0	111.0
Other	*	< 5.0
Commercial	*	< 25.0
Philanthropic	*	< 2.0
TOTAL		< 160.0

* Data not available.

Source: Data from multilateral and national programs, and personal communications from commercial and philanthropic organizations.

Table 3. Potential models for a new global HIV vaccine initiative.

Model	Examples
Task Force	Task Force for Child Survival and Development – An international effort to enhance worldwide immunization of children and to reduce the burden of infection and malnutrition in children. Founded by the WHO, UNICEF, UNDP (United Nations Development Programme), World Bank, and Rockefeller Foundation, it has a free standing secretariat housed at the Carter Center in the United States. The International Task Force on Hepatitis B Immunization – An international effort to make hepatitis B vaccine affordable for wide-scale use and to integrate the vaccine into national immunization programs in areas where hepatitis B is hyperendemic. The task force is composed of independent professionals working in the areas of hepatitis B and international health. The operating agency for the task force is PATH (the Program for Appropriate Technology in Health) which is based in the United States.
Donor collaboration	The Children's Vaccine Initiative (CVI) – An international effort to harness new technologies to advance the immunization of children throughout the world. The CVI was founded by the WHO, UNICEF, UNDP, World Bank, and Rockefeller Foundation and has recently moved its headquarters to the WHO. The founders recognized that other entities needed to be involved which led to the formation of the CVI consultative group which is composed of representatives of national immunization programs, multilateral, governmental, and nongovernmental organizations, and commercial and public-sector vaccine manufacturers. The activities of the CVI are carried out by task forces and product development groups. Consultative Group for International Agricultural Research (CGIAR) – An informal association of 41 public and private sector donors that supports a network of 18 international agricultural research centers. Donors give to the center of choice. The association has two secretariats – technical (provided by the FAO) and management (provided by the World Bank). In 1992 the financial resources available to the 18 centers totaled US$ 335 million. Global Environmental Facility (GEF) – An umbrella administrative mechanism for a wide range of environmental financing operations housed at the World Bank. The GEF was launched in May 1991 as a three-year pilot project with commitments from participating governments totaling US$ 1.4 billion. The funds are to be used to make grants and concessional loans to finance projects in developing countries, generating global environmental benefits not possible under normal lending operations of the multilateral financial community. The GEF is managed by the three sponsoring agencies: the World Bank, UNDP, and UNEP (United Nations Environment Programme).

Private consortia	Inter-Company Collaboration for AIDS Drug Development – A collaboration of 15 pharmaceutical companies engaged in ongoing HIV antiviral research. The collaboration was formed to facilitate the conduct of early human effectiveness trials of antiviral drugs by better enabling companies to conduct independently early stage combination studies of their respective investigational antiviral AIDS compounds. Electric Power Research Institute (EPRI) – A consortia of 720 U.S. electric utilities founded in 1972 with the objective of applying science and technology to the benefit of consortia members and their customers. The consortia is funded by member contributions and in 1990 had a budget of US$ 360 million. EPRI functions primarily as a secretariat and contracts research out to other organizations. Microelectronics and Computer Technology Corp (MCC) – A consortia of 21 U.S. electronics, high-tech, and aerospace firms formed in 1977 to enhance competitiveness in information technology. The consortia acts as a central research laboratory for its members with over 90 % of its work completed in MCC laboratories. MCC is funded primarily by contributions from its member companies and had a budget of US$ 65 million in 1990.
Public/ Private consortia	Semiconductor Research Corporation (SRC) – A consortia founded by 7 U.S. device companies and 4 U.S. integrated computer-device companies in 1982. The SRC coordinates efforts that bring academics and industrial scientists together to work on problems in microstructure sciences, manufacturing sciences, and design science. The SRC maintains no laboratories or working scientists of its own. Instead it focuses on merging the efforts of industrial and academic scientists through its committees. After a program has been agreed upon, the SRC provides funds received from member companies to universities and also serves as the administrator of programs funded by government agencies. SRCs budget for 1990 was US$ 35 million. Sematech – A consortia of 17 U.S. semiconductor and computer companies and the U.S. government formed in 1987 to conduct research and development that would provide the U.S. semiconductor industry with the domestic capability for world leadership in manufacturing. The consortia receives funding from member companies and the U.S. government. In 1990 the total budget reached US$ 200 million, over 50 % of which was provided by member companies. Research in Advanced Communications for Europe (RACE) – A consortium formed in 1985 to develop the technology base for integrated broadband networks in Europe. Over 100 organizations and the European Commission are members and it has an annual budget of around US$ 650 million. The project was scheduled to last for 10 years.

	Optical Technology Research Corporation (OTRC) – A consortia of 18 Japanese companies formed in 1986 to develop and produce second-generation optoelectronic integrated circuits. OTRC carries out its own research and has an annual budget of US$ 6.7 million. The project was scheduled to last for 10 years. Airbus – A consortia of 4 European companies formed to create a partnership that could compete head-on in the world aircraft market. Funding is provided by the companies, government subsidies, and now from sales of aircraft.
Not-for-Profit Institute	The Population Council – An international not-for-profit organization applying science and technology to the solution of population problems in developing countries. The Council, based in the United States, solicits funds required for its work. More than half of the Council's funds come from governments and United Nations agencies. Program for Appropriate Technology in Health (PATH) – An international not-for-profit, non-governmental organization focusing on the effectiveness, availability, safety, and appropriateness of technologies for health and family planning in developing countries. Support comes from a wide variety of funding sources including international health and family planning agencies, national governments, private foundations, and corporations. PATH is based in the United States. The National Foundation for Infantile Paralysis – A foundation established in the 1930's in the U.S. to develop a vaccine against polio. Funds were raised through public appeals (e.g. the March of Dimes) and from wealthy donors. The funds were used to sponsor basic research and once clear leads were identified to fund vaccine development. As vaccine candidates became available for human trials, the foundation assisted in the development of guidelines for conducting trials and also provided financial support. The Concept Foundation – A foundation established by the WHO's Special Programme for Research and Training in Human Reproduction (WHO/HRP) to hold and manage intellectual property rights to new products emerging from WHO/HRP research. The Concept Foundation is based in Thailand.