

Future access to HIV vaccines

Report from a WHO-UNAIDS Consultation, Geneva, 2–3 October 2000*

Summary Results from the first phase III efficacy trial of an HIV vaccine will be available within the next 2-3 years. Thus, it is imperative to start planning now to address how any effective vaccines should be used. In the absence of definitive information on the characteristics of the first generation of HIV vaccines, the following assumptions were made: the vaccine will (i) have only low to moderate efficacy (on the order of 50%); (ii) not be inexpensive (on the order of 10 to 30 US \$ per dose); (iii) require multiple doses; and, (iv) at least initially, be available in limited quantities.

A vaccine with that profile would not be suitable for general use in all countries, and it might have to be initially targeted to populations at higher risk of HIV infection. These populations will differ from region to region, according to the epidemiological situation. In most high and middle income countries potential target groups for an initial HIV immunization programme would include intravenous drug users, gay men, commercial sex workers, and high-risk heterosexuals, as well as healthcare workers exposed to blood. In sub-Saharan Africa, future HIV immunization programmes might include larger segments of the population.

In order to plan future vaccination programmes it is important to estimate the need (size of target population) and the demand (uptake in target populations) for future HIV vaccines. In addition to the public sector demand for an HIV vaccine (to be used in public health programmes), there will also be a private sector demand driven by the willingness and ability of individuals and employers to pay for the vaccine.

HIV vaccines would need to be delivered as part of comprehensive HIV prevention packages, including behavioral and health promotion interventions. This would be especially important with vaccines of moderate efficacy, in order to prevent increased risk behavior among vaccine recipients. To avoid false expectations, the vaccine message would need to be recast as part of the total prevention strategy, rather than the “magic bullet” that people have come to expect.

Initial deployment of HIV vaccines could proceed through targeted vaccination campaigns, drawing from experience with other vaccines. These campaigns would be complex and expensive, and would require full participation and collaboration from all levels of the community, as well as considerable strengthening of the infrastructures required for vaccine delivery.

Current candidate vaccines in phase III trials may not be appropriate for much of Africa and South Asia, two areas most in need of an HIV vaccine. Credible international efforts (“push and pull” mechanisms) are needed to create incentives for the industry to develop vaccines for these regions. Feasible financing mechanisms may have to be established to cover the cost of production and delivery of vaccines, in order to ensure equitable access to HIV vaccines around the world.

*This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization (WHO) or of the Joint United Nations Programme on HIV/AIDS (UNAIDS). Participants are listed in the Appendix.

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In parallel to the deployment of the initial vaccine, additional bridging studies and effectiveness trials may be needed to expand vaccine use. Research should also continue at an increased pace to develop new generations of more effective vaccines, especially vaccines appropriate to Africa.

Achieving these goals will require real political commitment from government and international organizations, to be materialized in specific actions and budget allocations. The daunting challenge of making future effective vaccines accessible to all populations in need will require a sustained collaborative effort on the part of all parties involved.

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Introduction

A consultation organized by the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) was held in Geneva, 2–3 October 2000, to discuss issues related to access to future vaccines against HIV/AIDS. The consultation was attended by 29 experts from 10 countries, including representatives from different national and international organizations, as well as 14 members of the WHO and UNAIDS Secretariat (List of participants in the Annex). The meeting was opened by Dr. Yasuhiro Suzuki, Executive Director for Health Technology and Pharmaceuticals, WHO. The objectives of the meeting were described by Dr. José Esparza, Coordinator of the WHO-UNAIDS HIV Vaccine Initiative and Dr. Julie Milstien, Coordinator of the Team on Access to Technologies, of the WHO Department of Vaccines and Biologicals, both of Health Technology and Pharmaceuticals.

The objectives of the consultation were:

- To review ongoing HIV vaccine trials, with special emphasis on timelines for decisions;
- To identify issues to be considered to ensure that HIV vaccines become available and affordable soon after their efficacy is demonstrated in clinical trials;
- To discuss potential immunization strategies, including potential target populations and preliminary demand estimates;
- To discuss needs for bridging studies and effectiveness trials to be conducted after initial efficacy is demonstrated; and
- To identify issues related to acceptability, delivery, production, procurement, affordability, purchasing, and financing of future HIV vaccines.

Participants in the consultation reviewed the main issues before the group was divided into two working groups: Demand and Delivery. Each working group

summarized the situation and made recommendations for future activities.

Framing the issues

This session, chaired by Dr. Bhamarpravati Natth, provided a review of the major issues to be considered in planning use of future HIV vaccines.

HIV vaccines in the pipeline and timelines for decisions (Esparza) [1]

The first phase I trial of an HIV candidate vaccine was conducted in the United States in 1987. Since then, more than 60 phase I/II trials have been conducted, with a total of approximately 30 different HIV candidate vaccines. Most of these trials have been conducted in the US and Europe, but since 1993 trials have also been conducted in developing countries (Brazil, China, Cuba, Thailand and Uganda). At the present time 19 preventive HIV candidate vaccines are at different levels of clinical evaluation in the US, including recombinant proteins, synthetic peptides, nucleic acid vaccines and different recombinant live vectors.

The only HIV candidate vaccine that has entered phase III efficacy evaluation is a gp120 product. Two different versions of that product are being tested in the United States and in Thailand. A bivalent candidate vaccine (based on two subtype B strains) entered a phase III trial in the US in June 1998, involving 5,500 volunteers, mostly men-who-have-sex-with-men (MSM). A bivalent BE gp120 candidate vaccine entered phase III evaluation in Thailand in March 1999, involving 2,500 recovering intravenous drug users (IDU) in Bangkok. The interim efficacy analysis of the US and Thai trials will take place in November 2001 and August 2002, respectively, with final results becoming available one year thereafter.

There are plans to initiate a second phase III trial in the

United States and in several countries in the Caribbean and South America, using a prime-boost strategy including two different subtype B products: a canarypox-HIV recombinant vector followed by gp120. This phase III trial could start sometime in 2002, with efficacy results becoming available 3–4 years later. Another prime-boost phase III trial is being discussed for implementation in Thailand, using a subtype E canarypox-HIV recombinant vector followed by a gp120 BE boost.

In summary, the earliest that an HIV vaccine could become available would be late 2002, or in 2003, depending on the results of the ongoing phase III trials.

Defining HIV vaccine efficacy from phase III trials (Longini) [2–4]

HIV vaccines could have at least three important protective effects:

- They could reduce the susceptibility to infection in vaccinated people, *i.e.*, *vaccine efficacy for susceptibility* (VE_S);
- They could reduce the rate of infection and/or disease progression in vaccinated people who get infected, *i.e.*, *vaccine efficacy for infection and/or disease progression* (VE_P); and
- They could reduce the level of infectiousness of infected vaccinated people, *i.e.*, *vaccine efficacy for infectiousness* (VE_I).

Vaccine trials can be designed to measure all or some of these effects through a number of primary and secondary endpoints. The primary endpoint is usually how well the vaccine protects against HIV infection, comparing the infection rate in the vaccinated versus the unvaccinated.

A number of secondary endpoints are of interest. A good measure of progression of the infection could be the level of HIV-RNA in plasma. In this case, measures such as virus loads in the vaccinated and unvaccinated infected participants are compared after the set point has been established, four to six months following infection. Differences in virus loads between the two groups could suggest a protective effect of the vaccine. Another measure of the VE_P could be to compare the percentage of infected unvaccinated and vaccinated participants with a predefined low virus load level after the set point.

The VE_I measures another important secondary endpoint. For sexual transmission this can be measured through the augmented sexual partners design. Additionally, virus load measurements can indirectly indicate decreased transmission potential, with levels below 1500 RNA copies per ml associated with very low transmissibility.

All of the above mentioned VE measurements could be stratified by the circulating HIV subtypes, although it is recognized that the significance of HIV genetic subtypes in terms of potential vaccine efficacy is not known, and it could be different with candidate vaccines based on different vaccine concepts.

Further secondary endpoints could involve finding potential immune correlates of protection, such as antibody levels and CTL function following vaccination.

Regulatory considerations in relation to Phase III HIV vaccine trials (Goldenthal) [5–7]

Prior to the initiation of a phase III efficacy trial, the US Food and Drug Administration (FDA) would expect to review information pertaining to the following areas: i) recent epidemiological data (*e.g.*, recent seroincidence, endemic subtypes) from the intended trial population; ii) data supporting the safety and immunogenicity of the product (including the basis for selecting the proposed formulation, dose and schedule), and; iii) the “scientific rationale” for conducting the trial. The “scientific rationale” for a phase III trial includes human immunogenicity data from phase I/II trials. Animal challenge/protection data may also play a prominent role. Issues related to the vaccine product including stability are also important. Because of the potential differences in safety, immunogenicity (and potential efficacy) between populations, safety and immunogenicity data should also be obtained using the candidate vaccine in the specific population in which the efficacy trial will be performed.

Appropriate laboratory assays should be available to detect vaccine-elicited immune responses, and to identify and characterize HIV strains from infections occurring in the trial population. The validation of these laboratory assays should include relevant data, *e.g.*, on specificity, sensitivity, ruggedness, and reproducibility.

The efficacy trial protocol should describe the inclusion/exclusion criteria for the study population, the control group, the randomization schema and study masking, and the parameters (safety, immunogenicity, efficacy) to be monitored with the time schedule. The vaccine efficacy trial protocol must include information regarding surveillance plans and length of follow-up. Surveillance for efficacy should be performed from the time of randomization. Prototype case report forms, subject diaries and consent forms should be submitted along with the protocol. Information should also be provided regarding logistics (such as specimen collection and shipping).

Possible outcomes that might be observed in an HIV vaccine phase III efficacy trial can be summarized as follows: i) prevention of infection; ii) prevention of

chronic infection (transient infection); iii) occurrence of infection, but AIDS is prevented or delayed (assessed by candidate surrogate markers such as virus loads, or by clinical findings such as AIDS or mortality); iv) occurrence of infection but vaccinee is less infectious; and v) combinations of above. The primary endpoint for both ongoing VaxGen efficacy trials (with gp120) is prevention of infection.

The statistical section of the protocol should include prospective and detailed information, especially for the primary endpoint, and 95% confidence limits of efficacy estimates. Both intent-to-treat and “per protocol” estimates of vaccine efficacy using the primary endpoint are of interest. Plans for any interim analysis must be described.

At least for the initial HIV vaccine efficacy trials, FDA would convene an advisory committee meeting to review and comment on protocol design and relevant data. Both FDA staff and sponsors would present information and issues at such meetings.

An important outcome of efficacy trials is the possibility of identifying immune correlates of protection, defined as particular type and quantity of immune response(s) associated with protection from infection or disease. Immune correlate(s) of protection could be useful for interpreting future trials with immune response endpoints, such as bridging studies. However, identification of correlates is *not* a requirement for US licensure. Examples of vaccines licensed without an identified immune correlate of protection include acellular pertussis, typhoid, and tuberculosis (BCG).

Future clinical bridging studies could be needed to i) address concerns that manufacturing changes might have resulted in a “different” vaccine no longer clinically equivalent to the previous version used in the efficacy trial; ii) provide evidence that efficacy data can be extrapolated to different populations; and iii) support new dosing schedules.

Foreign efficacy trials have been used to support licensure in the United States, including vaccines against typhoid fever, Japanese encephalitis, pertussis, and hepatitis A. However, in this situation, bridging studies for safety and immunogenicity could be needed, at a minimum, for licensure in the United States.

In conclusion, HIV vaccines present unique considerations for product and clinical development. Overall careful planning is needed to permit timely development. In this regard, important areas include: i) product characterization and manufacturing; ii) anticipating needs of future trials (e.g., developing and validating critical assays); iii) accumulating sufficient safety, immunogenicity and efficacy data during clinical develop-

ment. The latter includes planning and conducting clinical bridging studies (for example, in relation to use in different populations and product scale-up) needed for approval. Sponsors are encouraged to utilize FDA resources and documents to facilitate these activities.

Potential bridging and effectiveness trials with HIV vaccines (Clemens) [8]

Bridging studies are conducted to address uncertainties about *biological* generalizability of vaccine performance. Effectiveness (phase IV) trials are conducted to address uncertainties about *practical* generalizability of vaccine performance.

After a candidate vaccine has shown efficacy in well-controlled phase III trials, additional clinical evaluation would be needed to address the biological vagaries and novelties that could challenge the generalizability of a vaccine’s performance, including: i) changes in manufacture, formulation, dosage and administration of vaccine; and ii) changes in the target population for the vaccine, including changes in the epidemiology of the target infection (route of transmission, intensity of transmission, and antigenic variation).

Vaccine bridging studies may need to be conducted to support approvals for marketing. Examples of bridging studies that could be needed for the first generation of effective HIV vaccines include: different schedules of administration, different routes of transmission, and protection against different strains.

Additional questions that may remain after vaccine licensure include: i) how well will the vaccine work under realistic conditions (expanded spectrum of vaccine recipients, administration of the vaccine under routine conditions, co-administration of other vaccines or drugs, and against outcomes of pragmatic interest to decision-makers)? ii) how well will the vaccine be accepted? iii) how logistically feasible will it be to use the vaccine? iv) how cost-effective will the vaccine be? v) what will be the total impact of the vaccine (direct and indirect effects)?

Effectiveness trials are conducted to answer some of the above questions, especially the impact of the vaccine on practical health outcomes, assessed under ordinary conditions of a public health programme. The research question posed by effectiveness trials is: “What are the practical health outcomes, both beneficial and not beneficial, when the vaccine is administered under the ordinary conditions of a public health programme?”. Phase IV observational studies of vaccine effectiveness are performed after licensure and rely upon the comparative occurrence of outcomes in persons who are or are not vaccinated in routine practice, using cohort or case-control study designs.

The conduct of effectiveness trials with future HIV vaccines will be justified only when there is a “decisional equipoise”, which will be influenced by numerous factors including political considerations.

Potential HIV immunization strategies (Longini) [9–11]

It is expected that soon after the efficacy of an HIV vaccine is demonstrated in phase III trials, there will be limited quantities of vaccine available for administration. When a limited supply of vaccine is available, its distribution may involve determining the proportion of the various population groups that should be vaccinated in order to minimise the impact of HIV. The solution to this problem depends on a number of factors including the following:

- i) vaccine efficacy;
- ii) HIV subtypes circulating;
- iii) important “risk groups”, including “core” transmitters;
- iv) mixing behaviour of “risk groups”;
- v) quantity of vaccine available;
- vi) vaccine acceptance and possible distribution levels;
- vii) objectives of HIV control.

For a particular population, the vaccine deployed should be effective against the major immunotypes of HIV circulating in that population. The prime candidates for receiving vaccine would be the important “risk” groups, and “core” transmitters within those risk groups. If the quantity of vaccine is not sufficient to slow transmission substantially in the important risk groups, then it may be best to use these limited quantities of vaccine in the most vulnerable people in the population.

Once the above seven factors have been determined for a particular population, the optimal distribution of a limited quantity of vaccine can be determined that achieves the objective specified in item (vii) above (HIV control). The optimal distribution can be studied by constructing a mathematical model of HIV transmission for the population in question and then minimising the objective function subject to the constraints on vaccine availability and distribution possibilities. This modelling solution provides qualitative guidelines for potential vaccine distribution.

The seven factors listed above will vary for each population under study, and mathematical models will be used to analyse different scenarios.

Operational issues for HIV immunization delivery systems (Nkowane)

In relation to operational issues for future HIV immunization delivery systems, much can be learned from the experience with other vaccines being delivered

through the Expanded Programme on Immunization (EPI).

Any immunization delivery system should take into consideration: i) the characteristics of the vaccine; ii) the target or at risk group or population, and; iii) the programme objectives (individual protection, disease prevention, disease control or disease elimination or eradication).

The EPI is a delivery system primarily targeting infants, and heavily dependent on a functional health system. Routine programmes include primary immunization of infants, children and adolescent, and booster immunization. In addition, regular “catch-up” or targeted mass campaigns are also implemented for routine vaccine delivery, to improve coverage, or for disease prevention and control (in case of epidemics). Existing immunization schemes for different vaccines target infants, pre-school children, school children, adolescents or adults, which are accessed in different places (hospitals, health centres, pre-school organizations, schools, and/or workplaces).

Mass immunization campaigns are time-limited activities done once or twice a year, and they are most effective if targeted, and when objectives are achieved after a limited number of doses of vaccines are deployed. Campaign fatigue is a major problem. Mass campaigns require mobilization of communities and partners, and the most successful campaigns use volunteers. The role of health care workers is often limited to supervision of activities.

Factors which are critical for potential immunization delivery of future HIV vaccines are service level, logistics, and vaccine supply and quality. The level of service will depend on the coverage obtained in the target group, the drop out rate (if more than one dose is required), and the quality of the service (*i.e.*, injection safety issues). Logistics will depend on the proportion of days in which service can be realistically offered, the systems for disposal of wastes and used equipment, and the communication between the various levels of the system. Finally, factors related to vaccine supply and quality are related to the regularity of supplies and equipment, wastage of vaccine, and systems for monitoring adverse events.

Different options can be considered for potential immunization delivery of future HIV vaccines: i) integration into routine EPI programmes; ii) targeting groups outside routine EPI; iii) immunization campaigns, and; iv) combinations of the above. Integration of future HIV vaccines into routine/existing EPI programmes has a number of limitations. They would only reach infants or women and more importantly, would depend on the duration of immunity and the

ability to provide booster injections during childhood and early adulthood. The immediate option to deliver an HIV vaccine would be to target immunization programmes to individuals at higher risk. This could be an expensive option, but it should be viewed in the context of health systems development. Private service delivery could be a critical factor for success. Finally, targeting groups through mass immunization campaigns may be necessary when an HIV vaccine becomes available. Targeting will be required for the initial years of the campaign to achieve the immediate objectives (especially if insufficient vaccine is available for general use). Additional resources for operations will be needed for the many years that the campaign may last.

In summary, the nature of future HIV vaccines will determine the critical operational issues for delivery. Currently available immunization delivery systems in many priority countries may not meet the immediate objectives of a new HIV immunization strategy. Targeted approaches outside of the existing delivery systems will be needed in the initial phases of HIV vaccine delivery. There is, however, adequate experience in immunization programmes to develop appropriate delivery systems for HIV vaccines, even in the most difficult settings. Advocacy, political support and long term funding will be critical for delivery of future HIV vaccines to those who need it the most. A sustainable delivery system should be based on infrastructure strengthening rather than in the development of a parallel delivery system.

Targeting populations for HIV vaccination (Mastro) [12,13]

Possible strategies for the use of future HIV vaccines could include vaccination of everyone at risk of HIV infection, of those at highest risk, of targeted groups, or some combination of the above. The selection and implementation of any strategy will be highly dependent on existing national systems, availability of funds, and a possibility of phased introduction of the vaccine in different populations.

The information needed to set an HIV immunization strategy is: the status of the epidemic and the identification of people at risk. Data sources for such information are AIDS case reports (where the epidemic *was*), HIV surveillance (where the epidemic *is*), HIV inci-

dence (where the epidemic *is going*), behavioral surveillance (where the epidemic *might go*), sexually transmitted diseases (STD) reports and surveys, and *ad hoc* research studies. The quality of those data sources, however, varies greatly from country to country.

In the United States in the mid 1990s, the estimated HIV prevalence was about 600,000 persons living with HIV/AIDS, and the estimated incidence was about 41,000 new HIV infections per year. The most affected populations are injecting drug users (IDU), men who have sex with men (MSM), and at risk heterosexuals (ARH) (Table 1).

It must be noted, however, that there are other epidemiological and demographic aspects that will need to be considered when identifying potential target populations for a possible HIV immunization strategy in the United States. In recent years, the number of cases of AIDS has been steadily decreasing among white non-Hispanic individuals, and increasing among black non-Hispanic persons. In addition, the distribution of cases is not uniform among the different states.

In Thailand, the best source of epidemiological data is the HIV sentinel surveillance programme, which is conducted annually in all 76 provinces, including blood donors, pregnant women, female sex workers, drug users, and male STD patients. In addition, biannual random surveys are conducted among 21-year-old military conscripts. HIV prevalence among IDU has been increasing in the country, with median provincial seroprevalence in 1999 of more than 50%. Prevalence among brothel female commercial sex workers (CSW) has declined slightly, with a median provincial seroprevalence in 1999 close to 20%. Median seroprevalence among other female CSW and male STD patients is in the order of 10%, and the prevalence among women attending antenatal clinics is close to 2%. Among the military conscripts, the highest HIV prevalences were recorded from 1990 to 1993 in the northern provinces (6-8%); these rates decreased to less than 2% in 1999, to a level similar to that in other regions.

Epidemiological data from most African countries are often less comprehensive. AIDS case reports are very incomplete and HIV surveillance data vary greatly in quality. However, available data do allow for general

Table 1. Estimated HIV prevalence and incidence in the United States (96 metropolitan areas, mid 1990s).

Population at risk	Size of population	Estimated HIV prevalence	Estimated HIV incidence per year
IDU	1.5 million	204,000 (14%)	19,000 (1.5/100PY)
MSM	1.7 million	314,000 (18%)	9,800 (0.7%/100PY)
ARH	2.1 million	47,000 (2.3%)	9,300 (0.5/100PY)
Total	5.2 million	565,000 (11%)	38,000 (0.8/100PY)

characterization of the severity of the epidemic. In one hypothetical “representative” sub-Saharan African country, HIV seroprevalences in different populations are represented as follows: pregnant women (20% urban, 14% rural), STD patients (22% urban), blood donors (18%), factory workers (23% urban), military recruits (15%), female CSW (56%), tuberculosis patients (60%).

Modeling the benefits of an AIDS vaccine (Bishai)

Two models of the economic benefits that could be gained through the provision of HIV vaccines to various populations could be considered. One model, called the *health sector model*, considers only the benefits achieved from preventing the need for medical spending on behalf of vaccine recipients and the people they may secondarily infect. The other model, called the *societal model*, considers prevented medical spending as well as prevented losses of productive capacity for vaccine recipients and the people they may secondarily infect.

Different assumptions can be made in both models, including different levels of vaccine efficacy. In these models, the non-budgetary (intangible) benefits of HIV vaccines, such as avoided pain, suffering, and grief are likely to be large, but are ignored, not because they are insignificant, but because the current way that typical financial decisions are made ignores intangible costs.

The structure of the models is such that the economic benefits are not necessarily highest where incidence is highest, but where *incidence and medical spending and GDP* are high. Data on HIV incidence, medical spending, and GDP are used to calculate the benefits of AIDS vaccines in different age groups. Table 2 shows some examples of the *health sector* benefits in adult men and women in selected developed and less-developed regions of the world. The essential result is that the economic benefits of prevented medical spending per

Table 2. Health sector perspective estimates among adults in selected regions: Net expected benefit of vaccination by group and region (US\$).

Regions	Women	Men
Western Europe	87.13	342.87
Australia and New Zealand	0.51	72.00
North America	209.51	850.66
Japan	0.83	388.07
North Africa and Middle East	0.15	0.89
Sub-Saharan Africa	2.61	2.67
South and South East Asia	1.32	4.59
East Europe and Central Asia	8.14	31.80
China	0.17	3.95
Caribbean	36.63	76.03
Latin America	2.86	14.35

patient vaccinated are highest in developed countries and lowest in less developed countries. This is in opposition to where the greatest epidemiological benefit should be.

From the health sector perspective, the global demand for HIV vaccines would be greatly influenced by price, with a significant potential increase in vaccine use if the price drops below US\$ 50 per course.

Low production capacity will not be the only factor that could keep the supply low following vaccine discovery. Patents and licenses provide monopolistic incentives that can also keep the supply of vaccine low.

Anticipating possible obstacles to expanding the vaccine supply, policy leaders are proposing tax credits for a supplier who builds capacity in order to offer vaccines to impoverished countries. Policy makers may also need to contemplate the genuine possibility of several years of high spending with an HIV vaccine whose production costs are high. Even at a price of US\$ 10 per course of vaccine, health minister in poor countries could still be reluctant to purchase vaccine, because US\$10 per person would exhaust their average health budget. The models discussed predict that at this price it would require a roughly US\$ 9 purchase subsidy per person to make the most optimal vaccine purchase affordable for health ministries in sub-Saharan Africa. That would require a vaccine purchase fund on the order of US\$ 10 billion. An additional source of financing for the subsidies could be realised under a tiered pricing regime. Co-operative bargaining between the manufacturers and international agencies could maintain tiered pricing and potentially offer the manufacturer a guaranteed share of the consumers’s surplus in exchange for subsidising below marginal cost prices for nations whose ability to pay is less than marginal costs.

To the extent that world markets are used to distribute vaccines, they will allocate vaccines to populations and regions based on ability to pay just like any other commodity. Achieving equity with less reliance on political support for taxation would suggest the alternative of tiered pricing.

Behavioral issues related to future HIV vaccine use (Stanton)

Future use of an HIV vaccine will need to seriously consider a number of behavioural issues, for the following reasons: i) initial vaccines might not be fully effective; ii) existing interventions can already reduce HIV infection on a public health scale; and iii) at-risk populations often tend to be those with least access to health care.

The two main questions to be addressed are related to vaccine acceptance and vaccine effect on behaviour.

There is little available information in relation to the acceptability of future HIV vaccines. On the other hand, there are several studies in relation to willingness to participate in HIV vaccine trials. For example, a study conducted in Uganda showed that 88% of the military would participate in trials. Studies conducted in three cities in the United States among MSM revealed that willingness to participate in trials declined from 37% at baseline to 21% at 12 and 18 months, underscoring the importance of the informed consent process. Willingness to participate in trials change depending on the educational level, perception of risk, and age. Altruism and a desire for protection are common motivators for participation, and vaccine safety is usually the major concern. Interest in participating in trials also declines as the hypothetical regime becomes more demanding.

Studies of acceptability of a hypothetical HIV vaccine conducted among college students in the United States have suggested that universal vaccine acceptance can not be assumed, and that certain health beliefs and previous experiences will influence acceptability. Safety and high vaccine efficacy will have strong influence on acceptability, followed by vaccine type and cost. Low efficacy vaccines (50%) were largely unacceptable.

There is conflicting data in relation to changes in risk behaviour during participation in HIV vaccine trials. Some studies have documented an increase in risk behaviour, whereas others have suggested that intensive counselling can prevent such changes. In any case, this is an important concern in the planning of HIV vaccine trials, and will be a key element of any future HIV immunization strategy.

Relevant behavioural data applicable to future HIV vaccine use could be obtained from the present experience with post-exposure prophylaxis (PEP) and the expanding access to highly active antiretroviral therapy (HAART).

Also relevant to future HIV immunization strategies is data indicating that *intensive* (but not brief) counselling and HIV testing alone can change behaviours. This suggests that the behavioural interventions accompanying future HIV vaccination programmes may have to be intensive to be effective.

Different scenarios for future vaccine use

This session, chaired by Inge Van den Bussche,

reviewed potential scenarios for future use of HIV vaccines in industrialized and developing countries..

Introduction to scenarios (Rowley) [14]

It is essential to start thinking now about access to future HIV vaccines, to avoid what has happened with other vaccines in the past (*i.e.*, twenty years after hepatitis B was licensed, only 30-50% of the world's infant cohort are vaccinated against hepatitis B).

An ideal HIV vaccine would be one that is completely safe, easy to administer, requires only one dose, provides life-long protection, is easy to transport, stable under field conditions, inexpensive to manufacture, protects against all HIV subtypes, and can be given to infants as part of the EPI.

What is becoming clear is that the first generation of HIV vaccines, at least, will not meet those ideal requirements. We must be prepared to consider the use of HIV vaccines with low to moderate efficacy (40 to 60%). The duration of protection of those initial vaccines could be short (even only one year) and immunity could wane with time, necessitating the administration of several doses and repeated boosting injections.

The initial vaccines may not be available in large quantities, thus requiring careful considerations on how to use these vaccines for public health purposes. An initial HIV vaccination programme could target high-risk populations, adolescents and sexually active adults. This strategy will confront the problem that the population pool to be vaccinated would be many times the size of the cohort that is added to the risk pool every year. It is also understood that there will be a continuous need to counsel vaccinees and to maintain prevention programmes for the whole population.

The other major challenge in an HIV immunization programme will be the cost of the vaccines, which will not be inexpensive. Production costs could be on the order of US\$ 10 or more per dose, with distribution costs adding additional expenses. In this regard it could be illuminating to remember that the average cost of the EPI immunization programme (for 6 vaccines) is US\$ 20-25 per child (US\$ 1.50 for vaccine cost, plus US\$ 20 for delivery).

Country reports

Thailand (Chutima, Chaiyos) [15,16]

Several factors related to the public health implications of future adoption of an HIV vaccine include:

- Vaccine costs (direct costs; administrative costs; number of doses and delivery costs);
- Vaccine effectiveness (vaccine efficacy; vaccine cov-

erage; potential groups of population for vaccination; affordability; willingness to pay);

- Policy and public concerns (financing of phase III and phase IV trials; cost and effectiveness of alternative measures; impact of additional role of vaccines on the HIV epidemic; public concerns, pressure, and awareness; perception of vaccine as private or public goods to be financed by public funds).

The potential use of an HIV vaccine in Thailand was estimated based on a cost of US\$ 100 per full immunization course (four doses at US\$ 20 each, plus related costs). Efficacy was modeled at four levels: 30, 40, 50 and 60 %. Potential target population included IDU, CSW, male STD patients, MSM, military conscripts, and others. For simplicity, it was assumed that the government is the sole purchaser and distributor of vaccines. In Thailand, the direct and indirect cost for HIV/AIDS was calculated in US\$ 3,390 per year, and that amount was used to calculate the averted costs by vaccination.

A comprehensive HIV immunization programme in Thailand could include vaccination of the above mentioned risk groups, with a total catch-up size of more than 4 million people, and a total cost of more than US\$ 700 million. If the vaccine has a 50% efficacy, that vaccination campaign could avert almost 300,000 new HIV infections after the first year launch of the vaccination program.

The estimated cost per averted HIV infection varied in the different populations, mostly depending on HIV incidence. The potential target group with the highest rate of HIV infection is IDU (with an estimated HIV prevalence of 48%). In this population, a vaccine with 50% efficacy would avert about 100,000 new infections, at a cost of US\$ 76 per averted infection. The same 50% effective vaccine used among direct CSW (HIV prevalence of 21%) would avert 12,673 new infections, at a cost of US\$ 455 per averted infection. The use of the same vaccine in military conscripts (with a HIV prevalence of 2%) would avert 1,000 new infections, at a cost of US\$ 3,900 per averted infection.

Additional studies are needed to address the following issues:

- How to bring vaccine costs down to more affordable levels?;
- Financing mechanisms (including the conduct of phase III and IV trials);
- Role of government on financing vaccine purchase;
- Studies to assess government demand for vaccine;
- Studies to identify the potential use of vaccines as complement to other existing HIV preventive interventions;
- Similar studies in other countries.

Brazil (Texeira)

The total number of HIV infected people in Brazil has been estimated to be over 500,000, although the AIDS incidence has shown a decline since 1996. On the other hand, a trend towards an increased incidence among women and into smaller communities has been observed. Brazil has been involved in preparatory vaccine research, including HIV isolation and characterization, establishment of cohorts of MSM, and the conduct of a phase I/II trial in 1994. Available data suggest a major HIV-1 B epidemic, with two predominant V3 loop variants (GWGR and GPGR). Two minor subtypes have been isolated in different areas of the country (F and C), and subtypes D and A have also been described. The extensive use of antiretroviral drugs in Brazil, provided by the government, has resulted in the development of experience and infrastructure that could be used for the eventual distribution of an HIV vaccine. In general, vaccine acceptability in Brazil is very good, albeit very limited information is available on HIV vaccine issues. A recent study with 815 participants of an HIV incidence cohort showed 70% willingness to participate on HIV vaccine trials, mostly for altruistic reasons. The interest in an HIV vaccine should increase as the national program intensifies its actions in this area, and safety information from ongoing trials is made available to the general public.

Mexico (Whittington)

A contingent valuation conducted in 1999 among 234 randomly selected adults in Guadalajara, Mexico, suggested that a conservative estimate of the willingness to pay for a 100% effective HIV vaccine that would provide lifetime protection was US\$ 669, with 25% of the respondents willing to pay over US\$ 1,000. Willingness to pay was higher among younger respondents and among people with higher incomes.

Kenya (Forsythe) [17–21]

A random household sample of 890 Kenyans (from Nairobi and rural Thika) was conducted to assess the willingness to be vaccinated, willingness to pay for an HIV vaccine, and willingness to pay subsidies for others to be vaccinated.

Acceptance to be vaccinated was slightly associated to its potential efficacy, with 68% positive responses if the vaccine was 100% effective and 64% if it was only 50% effective. The mean willingness to pay for a 100% effective vaccine was US\$ 10, and US\$ 6.86 for a 50% effective vaccine.

Willingness to be vaccinated increased with number of sexual partners and level of education. The most common reasons for refusing vaccination were the perception of not being at risk of HIV infection (47%),

concerns about the safety of the vaccine (4%), and probability of already been infected (3%).

Although an HIV vaccine was considered a high priority, the main interest of the community was on voluntary testing and counseling (VTC). Another important consideration is price. A vaccine costing US\$1 would consume 8% of the Kenya health budget.

In conclusion, the acceptability of an HIV vaccine would be lower within the general population than within risk groups. About 35% of Kenyans would decline vaccination if a completely safe HIV vaccine were available today (although only 10% of the highest risk groups would decline vaccination). Those most at risk of getting HIV infection are also the most likely to pay for a vaccine. Because of the high costs involved, there is a need to conduct additional studies in terms of the medical and financial feasibility of future vaccine use. The affordability of an HIV vaccine will depend greatly on: amount the government is willing and able to pay or borrow; amount that citizens are willing and able to pay; level of donor subsidies; frequency of boosters; who will be vaccinated; and what existing infrastructure can be used to vaccinate.

Tanzania (Pallangyo)

In Tanzania (as in several other African countries) HIV transmission is no longer confined to special groups, but it has spread to the general population in most communities. Consequentially, all sexually active adults and adolescents are at substantial risk of HIV infection. Nevertheless, CSW, military personnel, police, and migrant workers may be at higher risk than the general population.

Though the potential demand for an HIV vaccine is likely to be great, a number of factors are likely to be significant obstacles to accessibility or use by the majority of those at greatest risk:

- Financial capability to pay for a vaccine;
- Stigma;
- Misconceptions about vaccines;
- Negative/hostile campaign from groups opposing HIV vaccines;
- Other situations, such as fear that vaccines may spread the disease (or make people infertile).

Consequently, strategies to address these concerns need to be in place to ensure acceptability and accessibility of the vaccine to all those in need. Both potential demand and acceptability will be significantly influenced by the safety and efficacy of the vaccine in question.

Consideration must be given to the potential risks for social discrimination and harm that could be associated

with the use of HIV vaccines. Extensive public education regarding all aspects of the intended vaccine should be provided, including the options not to be vaccinated and the consequences of the different scenarios, efficacy of the vaccine, deleterious effects of the vaccine, and false security among vaccinees. In addition, education/discussions should be held with the government and with political and community leaders at all levels, to ensure understanding and cooperation.

Spain and South-European countries (Casabona) [22,23]

The characteristics of the HIV/AIDS pandemic in Europe are not homogeneous, not even taking into account only western European countries. In south-Europe, the epidemic grew exponentially to very high incidence and prevalence rates during the second half of the 80s, and IDU accounted for the majority of cases. In this regard, Italy, France, Spain and Portugal accounted for 58.5% of all AIDS cases diagnosed in Europe during 1998. After 1999, however, Portugal is the country with the highest AIDS incidence rate (88 per million in 1999). Although all these countries have access to highly active antiretroviral therapies (HAART), and therefore they have experienced an important decrease in the number of new AIDS cases after 1996, they still have high HIV prevalence among specific subgroups, and the HIV heterosexual transmission is steadily increasing.

Spain is a very good paradigm of the HIV/AIDS situation in south-Europe. In Catalonia (a north-east autonomous region with a population of six million), where second generation HIV surveillance is in place since 1994, the number of new AIDS cases diagnosed has decreased in 18.5% from 1998 to 1999, and AIDS is no longer the leading cause of death among youth, as it was during 1993-1996. Heterosexually acquired cases, however, have increased from 4% in 1988 to 33% in 2000, and the overall number of women with AIDS has increased from 14.2% in 1986 to 22.1% in 1999. According to data from the anonymous unlinked study of newborns, and from women who undertake voluntary abortions, the HIV prevalence among sexually active women has remained constant since 1994, around 0.2%. Data from behavioral monitoring of IDU indicate that, while drug use risk behavior has decreased over time (34% of needle sharing in 1993, to 12.1% in 1998), sexual risk behavior has increased in this population, particularly among female IDU. In this regard, 64% of male IDU have sex with non-injecting women, and the proportion of those who never use condoms with occasional and steady sexual partners is 24% and 64%, respectively. The HIV unlinked voluntary screening of IDU in 1998 revealed an overall HIV prevalence of 39.7%, and the prevalence of other sexually transmitted diseases is increasing.

From this data it is clear that IDU are playing a crucial role in bridging the HIV epidemic to the heterosexual population and that, in south-European countries, heterosexual transmission will be important. Therefore, it is possible to identify core groups –such as IDU- and vulnerable ones –such as young females-, which should be a clear priority target for future HIV vaccines.

An HIV vaccine acceptability study performed in Catalonia in 1994–1995 showed that, while both IDU and health professionals were interested in HIV vaccine studies, the willingness to participate in a project with a product which will make the person seropositive to HIV was below 20% in all groups. Nevertheless, if a safe and effective preventive HIV vaccine is developed, it is very probable that its acceptability will be good, not only among the above mentioned risk groups, but also –following the hepatitis B model- among all adolescents.

It is difficult to estimate the number of full courses of HIV vaccines which will be required in Catalonia. Nevertheless, some surrogate indicators could be used, as follows: the number of adolescents (13–19 years) and young adults (20–29 years) in 2000 (457,029 and 992,236, respectively); the number of IDU, estimated in 1993 by capture-recapture methods (13,000 to 14,000); the average number of HIV tests performed annually in the public sector (79,000); and the number of hepatitis vaccine units used in 1999 among groups with high-risk behaviors (21,000) or adolescents (mandatory since 1991, 56,000).

Finally, some possible “side effects” of introducing a preventive HIV vaccine in these scenarios could be envisaged. Some of the parents may be reluctant to vaccinate children or adolescents, because of an associated perception of stigma; risk behavior could increase because of the existence of the vaccine; interference with the interpretation of sero-epidemiological due to vaccine-induced seropositivity; and probable difficulties in implementing effectiveness trials due to the lack of political support.

Other logistical issues

The session, which was chaired by Dr. Richard Mahoney, discussed a number of logistical issues related to the future use of HIV vaccines.

Future use of HIV vaccines as part of the overall prevention effort (de Zoysa)

For people working on HIV/AIDS prevention, the future use of HIV vaccines raises several concerns. An HIV vaccine might lead to increased risk behaviour in vulnerable communities, to reduce emphasis on other

preventive interventions, to increased division between the “haves” and the “have nots”, and to dampening other research and development efforts (*e.g.*, microbicides).

Thus, the challenge is to avert those potential “perverse” effects by positioning HIV vaccines and vaccine research appropriately, by modelling opportunities and synergies with other preventive interventions, by developing alliances and partnerships with other groups working on HIV prevention and control, and by conducting the necessary operational research.

The hope, of course, is that a vaccine will provide an additional preventive tool in a comprehensive package, which will increase the impact of other interventions, reaching populations with low access to other interventions, increasing hope and decreasing denial, and ultimately, boosting the overall prevention effort.

Community roles in HIV vaccine delivery and access (Collins)

The current perception is that vaccines are now being sold as “*our only hope*”, as a magic bullet to control the HIV epidemic. But if a future vaccine is not accessible to the populations in need, it could also become the ultimate international symbol of privilege and disenfranchisement.

“Communities” are different for HIV vaccines and for other vaccines. Stigma would be a major consideration for its “consumers”, which will be largely sexually active adolescents and adults, many of whom are marginalised in health care and society (*e.g.*, women, gay men, minorities, poor, young, IDU).

Controversy and confusion are likely to arise, including issues related to a perceived need for protection; concerns about safety; opposition by the anti-vaccine movement; complexity of immunization regimes; level of efficacy and its relation to protection against different HIV subtypes; lack of belief, or of patience, for “future” products; contradictory messages from advocates and press; and distrust of authorities.

In considering the issue of demand for HIV vaccines it is important to understand that the word “demand” could mean many things:

- Willingness of individuals and insurance companies to pay;
- Willingness of countries and international organizations to pay;
- Current delivery capacity;
- People who say they want a vaccine.

The definition of “demand” could also be different for communities and for advocates. Communities will

support access to vaccines for *those who need it*. Advocates will support access to *those who want it*. Demand can be unpredictable, but it can be shaped by policy and marketing, and it can be influenced from external factors.

For communities, future use of HIV vaccines will be “an exercise in trust”. They will be asked to accept “judgement calls” by public officials on when to stop a trial, on what level of efficacy is acceptable, on who gets the vaccine, on how it is distributed, and on waiting for a second generation of “better” vaccines.

There is a need to plan now a process to involve and build trust with communities, to educate them about the limits of HIV vaccines, to be transparent in decision making, to explain access plans for vaccines in phase III trials, to plan access to all populations, and to maintain a strong commitment for prevention.

Community involvement will help, provided that they accept the vaccine and its dissemination plan; that political and public health leaders are motivated; that the effective vaccine began to be disseminated; and that there is a perception of equity and respect for human rights.

Community involvement also means inclusion of the general population, of marginalised groups and of service providers; participation in decision making; and assistance with dissemination of the plan, social marketing, and preventive education. Integrating vaccines and behavioural prevention would be essential.

Partnering on the policy agenda is needed to:

- Address stigma;
- Maintain ongoing prevention;
- Explore possibilities for the establishment of a purchase fund or loans;
- Discuss tiered pricing;
- Estimate in-country demand for vaccine by citizens and leaders.

Assuring financing for HIV/AIDS vaccines (Batson)

The major reasons to address at once the issue of financing HIV vaccines are:

- To set expectations of governments and donors (HIV vaccines will be more expensive than existing vaccines);
- To provide a credible guarantee for future markets (which could act as an incentive for private investment in the development, production scale-up, and eventual affordable pricing);
- To establish a system for rapid purchase (in order to

accelerate introduction of the vaccine once it is available).

The HIV Vaccine Task Force of the World Bank (WB) was established to identify why private investment on HIV vaccines is so low; to identify ways to address the market failure for HIV vaccines; and to work with industry, industrial country partners and developing countries partners to develop feasible approaches/financial instruments.

The Task Force is working in several areas:

- *Industry study*, to explore perception and motivations of industry and their reaction to possible interventions from the World Bank;
- *Demand studies*, to estimate developing country potential demand and willingness to pay for an HIV vaccine;
- *Consultation with donor and developing country partners*, to explore findings and discuss partners perspectives on most feasible way forward; and
- *Instrument development*, to develop a financial mechanism based on the work with the industry and developing and industrial country partners.

Potential financing options should be acceptable to donors, with minimal opportunity costs, credible to industry (including realistic demand estimates and pricing strategies), capable of managing risks (including addressing possible “changes of mind of the public sector going for the cheapest price, and the need to also consider financing subsequent generations of HIV vaccines).

Potential “pull” strategies to support HIV vaccine research and development include: expand lending for existing vaccines; establishing market guarantees (vaccine purchase fund, contingent lending, high profile signing of intent); low-cost borrowing by countries from the WB; provision of better information on developing country markets; and granting of patent extensions.

Potential “push” strategies include investment in trials and process development, technology transfer, and production and scale-up.

The way for financing an HIV vaccine could be paved by:

- Governments taking responsibility through national budgets;
- Global Alliance for Vaccines and Immunization (GAVI) Global Fund financing procurement and distribution of existing vaccines, demonstrating the potential for funding future vaccines;
- WB increasing support for existing vaccines;

- Possibility of WB-donor funding mechanisms to reduce cost of borrowing and to provide assurance of future funding;
- GAVI Financing Task Force work in preparing work plans to implement strategies (pull and late stage push) for 2–3 near term candidate vaccines.

Potential approaches to assist the private sector (Shin) [24–27]

The specific example of VaxGen was presented. The company has two related gp120 candidate vaccines in phase III trials, a BB vaccine in the United States and the Netherlands and a BE vaccine in Thailand. If the trials demonstrate vaccine efficacy, the BB vaccine could receive approval in 2003. The approval for the BE vaccine could follow in 2004. Earlier approval could occur if the interim analysis of the trials demonstrate efficacy.

There are major challenges in making the vaccine widely available at affordable prices. The vaccine is composed of recombinant HIV envelope glycoproteins (rgp 120) produced in Chinese hamster ovary (CHO) cells. Because of the need for mammalian cell fermentation and because of the very complex structure of gp120, this vaccine is inherently more costly to produce compared to, for instance, recombinant hepatitis B vaccine produced in yeast. Furthermore, there is a global shortage in large-scale CHO fermentation capacity required to manufacture the gp120 vaccines. In order to supply the vaccine without unacceptable delays quickly after its efficacy is proven, VaxGen would have to establish new manufacturing capacity well in advance of the final analysis. But construction of a CHO manufacturing facility requires a long lead time and a very large capital investment. According to a recent study, at least four years are required to build such a plant, including architectural and engineering design, construction, test operation and validation, and FDA inspection and licensure. The capital investment needed would be in the order of US\$ 150 to US\$ 300 million, plus land cost, depending on the location of the plant and the size of the initial installed capacity.

It is important to recognize, however, that the two candidate vaccines being tested in phase III trials are based on the major subtypes (B and E) present in the Americas, Europe and the Western Pacific Rim countries, where an adequate potential market is perceived to exist to justify the significant investment needed to develop, test and manufacture the vaccines. It was stated that for that reason, VaxGen has been able to support the development of these candidate vaccines entirely by private funding.

Unfortunately, the BB and BE vaccines may not be appropriate to Africa and South Asia, where most of new HIV infections are due to the A,D and C

subtypes. If subtype-specific gp120 proves to be essential for vaccine efficacy, as many expect, new candidate vaccines containing the relevant gp120 must be developed for these regions. In fact, from the global health perspective, Africa and South Asia are the two areas most in need of an HIV vaccine. But it is unlikely that the private industry will find sufficient financial incentives to develop vaccines that will be useful primarily in the poorest countries, unless the public sector provides appropriate mechanisms to create an adequate vaccine “market”.

The public sector could facilitate the process of HIV vaccine development for developing countries, particularly for Africa and South Asia, by “push/pull” mechanisms. Push mechanisms could include public funding to develop and manufacture candidate vaccines against HIV subtypes prevalent in developing countries, public assistance for clinical trials at appropriate study sites, and provision of uniform and accelerated regulatory reviews. Pull mechanisms should include credible and realistic demand and market estimates, an adequate and assured mechanisms for public sector purchase (e.g., advance purchase order for developing country markets), and development of delivery infrastructure, and co-financing for construction of manufacturing facilities.

HIV vaccines are now widely recognized as international public goods. We need to develop, with a sense of urgency, innovative new mechanisms to promote public-private collaborations to accelerate the development, production and equitable distribution of HIV vaccines.

Conclusions and recommendations from the Working Groups

The working Group on “Demand” was chaired by Dr. Martha Ainsworth. The Working Group on “Delivery” was co-chaired by Drs. Peter Ndumbe and Jean-Marc Olivé. Dr. Roy Widdus chaired the general discussion.

Estimating “demand” for future HIV vaccines

The size of the target population that could benefit from a future HIV vaccine defines the *needs* for such a vaccine. However, of more practical importance may be the quantification of the *demand* for future vaccines, as defined by a realistic estimate of vaccine uptake by the target population. In any case, estimates of both needs and demand would assist in planning future access to HIV vaccines.

A reasonably accurate estimate of the demand will require a refinement of the assumptions made regarding

the characteristics of the vaccine: different scenarios of vaccine efficacy (high, moderate, low), price (zero, low to moderate, high), number of doses required (one, multiple, boosters), and duration of protective immunity (short, intermediate, long).

Since no effective HIV vaccine has ever been developed, and the final result from the only ongoing phase III trials will be available only within the next 2-3 years, there is no alternative but to begin the planning process based on a number of uncertain assumptions.

The limited data available suggest the first generation of HIV vaccines will:

- Have low to moderate efficacy (perhaps around 50%);
- Reduce virus load in vaccinated individuals who become infected (although the possibility of “sterilizing” immunity can not be discarded);
- Have narrow efficacy against different HIV strains;
- Be expensive, at least initially (perhaps on the order of US\$ 10 to 30 per dose);
- Require multiple doses;
- Not confer lifelong protection, but require continuous boosting; and
- Be initially available in limited quantities.

This scenario makes imperative careful planning in order to decide whether and how such a vaccine could be used.

In relation to price, it must be indicated that it will be influenced by the size of the market. A small market will lead to higher prices than a larger market. It is likely that initially the price in developed countries and other rich markets could be quite high and comparable to, for instance, the price for the new conjugated pneumococcal vaccine (*i.e.*, around US\$ 60 per dose). On the other hand, given the sensitivity of vaccine production costs to volume, the marginal cost of production would be much lower than the average production cost providing the opportunity for tiered pricing wherein the public sector in developing countries might obtain the product for much less than US \$ 10 per dose.

Different constituencies will define demand based on different perspectives and concerns:

- *Public health officials* would like to target vaccine use to those individuals and populations at higher risk of HIV infection, with the goal of reducing the reproduction rate (R_0) of the epidemic (reducing transmission);
- *Non Governmental Organizations (NGOs) and civil society* would like to ensure equitable access to the

vaccine, and would be concerned with issues of stigmatization; and

- *Industry* would like to identify a public and private market for the vaccine to ensure profitability, and it would be concerned about marketing issues.

Potential needs and demand estimates could be stratified according to the economic and epidemiological characteristics of countries and regions:

- In *high income countries* (usually with low HIV prevalence) the public health use of the vaccine would target “risk groups” (at least in the short term), especially IDU, MSM, and perhaps CSW. NGOs would advocate for wide and equitable access. Industry may target private individuals, with potentially high profits. Special populations such as health care workers, police force and the military could also be considered;
- *Middle income countries* may have to be stratified according to HIV prevalence. In most Latin American and Asian countries, the identified target populations are those at higher risk of HIV infection, such as IDU, CSW and MSM. In at least some countries, NGOs are likely to also demand wide and equitable access to vaccines. A private market, with moderate profits may also exist;
- In *lower income countries*, especially those with high HIV prevalence (such as several sub-Saharan African countries), vaccines may need to be provided to large segments of the population. In Africa, vaccines will need to be relevant to the different HIV subtypes circulating in different regions of the continent. Because of the high HIV incidence in Africa, and the perception of general risk, there may be a profitable private market for HIV vaccines in Africa (with a lower price than in industrialized countries but a larger market);

There are a number of gaps in our knowledge that demand further attention and research. Additional studies and information are needed in the following areas:

- *Public health strategies* for the use of HIV vaccines with different levels of efficacy and complexity of implementation. Approaches will be needed to promote public health-based HIV vaccination strategies to decision-makers and communities;
- *Cost-effectiveness studies of vaccines of different characteristics* in different settings, from different perspectives (e.g., individuals, health insurance, employers, society, among others), and in comparison with other preventive interventions;
- *Country-by-country studies of plausible scenarios*, to estimate demand and to engage key actors in the policy dialogue;
- *Alternative methods for estimating demand*, based on feedback from key players, including national and

- international public health authorities, industry, donors and financing institutions, and communities;
- *Estimates of private demand for HIV vaccines*, including willingness to be vaccinated and to pay, consumer attitudes, perspectives of private health insurance and employers;
 - *Effectiveness of broad versus targeted HIV vaccine use* in different epidemiological situations and immunization scenarios;
 - *Behavioural issues associated to HIV immunization*, both among vaccinees and in the population at large. Studies are needed to understand what would be the behavioural response after vaccination, and to develop behavioural interventions that should be incorporated into an HIV vaccination programme;
 - *Alternative payment mechanisms* appropriate for different countries, including private health insurance, employer purchase and provision, private sector subsidies, etc.

In addition to the above issues, a major effort must be made to identify, and work for, the characteristics of a future HIV vaccine which would lead to a *paradigm shift in vaccine availability*, to ensure vaccine access in developing countries simultaneously or soon after licensure in industrialized countries.

Developing “delivery” systems for future HIV vaccines

Before considering the initial introduction of a future HIV vaccine, these important issues need to be addressed:

HIV vaccines as part of the overall prevention effort

A future HIV vaccine should contribute to the overall HIV prevention effort and it should not detract from, or delay, other prevention or treatment efforts. In fact, HIV vaccines would have to be provided as part of comprehensive prevention packages. The initial introduction of an HIV vaccine should: i) Strengthen other preventive interventions; ii) Integrate vaccine access with existing interventions; iii) Not interfere with access to other preventive interventions or future “improved” HIV vaccines.

Suitability of the vaccine for different populations

A low efficacy vaccine may be targeted only to populations with higher risk of HIV infection, especially if those populations are not easily reached with other preventive interventions. The HIV subtype specificity of the vaccine could also limit the general applicability of the vaccine.

An initial HIV immunization programme would be:

- i) *Initially target adults*, to obtain a more immediate public health benefit. Vaccination of adolescents and children could be phased in after completion of

- any necessary bridging studies conducted in those populations;
- ii) *Targeted demographically* rather than by “risk groups”, to avoid stigmatisation of vaccine recipients;
- iii) *Based on mass immunization campaigns*. The structure and nature of the campaigns will require innovative thinking and partnerships, and would necessitate considerable infrastructure strengthening;
- iv) *Country and region specific*, as they would need to take into account the local epidemiology, prevalent HIV strains, available infrastructure, and vaccine characteristics, and be appropriately tailored to each community’s needs.
- v) *Include a comprehensive social science component*. If the vaccine is of low or moderate efficacy, then interventions are needed to prevent undesirable behavioural changes that could offset the vaccine’s benefit. Thus, in parallel studies must be conducted to evaluate the impact of the vaccination campaign in the behaviour of vaccine recipients and in the population at large.

Communication strategies and community participation

It would be important not to create false expectations in relation to HIV vaccines. Keeping in mind that the first generation of HIV vaccines might be of limited efficacy, vaccines need to be recast as part of the total prevention strategy rather than the “magic bullet” that people have come to expect.

The success of any future vaccination effort would require that the communities be educated and mobilised at all levels, including the general population, opinion leaders, public health officials, governments, and all other agencies involved.

There is a need to explore new ways of reaching out to the public by partnering with communication experts to ensure that the right message is getting across.

Lessons learned from other immunization programmes

Based on the experience acquired with other vaccines, it is believed that once an HIV vaccine is available, *it will be possible to deliver it* –but the appropriate target populations need to be identified and mass campaigns designed accordingly. Those campaigns will most likely be expensive given the nature of the vaccine and the target population, and the preparation of the required delivery infrastructures must be initiated as soon as possible.

It will be important to learn from past immunization experiences, from successes with immunization of “non-captive” adult populations (such as measles in South Africa and Latin America, Td in the former Soviet Union, and meningococcal vaccines), as well as

failures in regions without appropriate community involvement (such as tetanus toxoid).

Access to the necessary resources

Appropriate financing would be required to implement appropriate HIV vaccination strategies. In addition to the price of the product, it would be important to include costs for infrastructure, including: i) Delivery; ii) Communication and social marketing; iii) Strengthening existing interventions; iv) Bringing the delivery system “up to speed”; and v) Developing national financing mechanism for sustainability.

In all of these areas it would be helpful to draw upon the experience of GAVI.

Appropriate financing mechanisms need to be considered to offset those costs, including: i) Tiered-pricing at the time of vaccine introduction; ii) National budget allocations for vaccine purchase and delivery infrastructure; iii) Reduced cost of borrowing from lending institutions; iv) Future purchase guarantees, with special consideration given to low and middle income countries; and v) Reduction in the cost of vaccine research and development (*e.g.*, through supplemental grants).

Policy dialogue

Policy dialogue is required to increase awareness and real political commitment of leadership at all levels. Political commitment from government and international agencies and organizations must be demonstrated with specific actions and budget allocations.

Policy dialogue is also needed to advance incentives that are attractive to industrial vaccine manufacturers (*e.g.*, patent extensions, tax benefits, high profile signing of intent documents) and public health recommendations for HIV vaccination at country level.

The way forward

There are critical public health and economic reasons to begin now planning strategies to ensure access to future HIV vaccines.

There are also ethical imperatives of justice, requiring that after the efficacy of a candidate vaccine is demonstrated, the vaccine should be made available to the population where it was tested, and to other populations at high risk of HIV infection. The UNAIDS Guidance Document on “Ethical considerations in HIV preventive vaccine research” (May 2000) stipulates in its Guidance Point 2, that “plans should be developed at the initial stages of HIV vaccine development to ensure such availability” [28].

In addition, if communities, governments, and international agencies embark on a serious effort to make future HIV vaccines widely accessible, these actions will send a strong signal to the private sector, serving as an incentive for the pharmaceutical industry to invest more on HIV vaccine development.

Since the first generation of HIV vaccines may not have the ideal level or breadth of protective efficacy, it is essential that HIV vaccine research and development continues at an increased pace. That is especially true for vaccines appropriate for Africa, which would have to confer protection against multiple strains of HIV, and that for logistical reasons, would need to be easy to administer and available at the lowest possible price. A new African initiative, the African AIDS Vaccine Programme (AAVP), is being established to promote such development.

The initial development of an effective HIV vaccine, even if only partially protective, it is expected to serve as an incentive for additional work on HIV vaccines, by providing a “proof of concept” of the feasibility of developing preventive HIV vaccines.

Streamlining and harmonising the regulatory process would undoubtedly facilitate and accelerate HIV vaccine development. Regulatory agencies from developing countries should be brought into the discussion and decision-making process.

In addition to initial vaccine deployment and parallel development and evaluation of additional HIV vaccine concepts, there may also be a need to conduct selected bridging or effectiveness trials, to expand the potential use of the initial vaccine product in other populations.

The challenge of making a future HIV vaccine available to all populations in need is daunting and it will require the collaboration of multiple partners at the national, regional, and international levels, in the public and private sectors. Using their comparative advantage, international agencies and organizations (especially those that participated in the consultation: WHO-UNAIDS, the World Bank, the European Community (EC), the International AIDS Vaccine Initiative (IAVI), the International Vaccine Institute (IVI) and others), must establish immediate and effective collaboration to implement the strategies and recommendations identified during the consultation.

Selected References

1. Esparza J, Bhamarapravati N: **Accelerating the development and future availability of HIV-1 vaccines: why, when, where, and how?**. *Lancet* 2000, **355**:2061–2066.
2. Gilbert PB, Self SG, Ashby MA: **Statistical methods for assessing**

- differential vaccine protection against human immunodeficiency virus types.** *Biometrics* 1998, **54**:799–814.
3. Halloran ME, Longini IM, Struchiner CJ: **Design and interpretation of vaccine field studies.** *Epidemiol Rev* 1999, **21**:73–88.
 4. Longini IM, Datta S, Halloran ME: **Measuring vaccine efficacy for both susceptibility to infection and reduction in infectiousness for prophylactic vaccines.** 1996, *J Acquir Immune Defic Syndr Hum Retrovirology* **13**:440–447.
 5. Goldenthal KL, Vaillancourt JM, Geber A, Lucey DR: **Preventive HIV type 1 vaccine clinical trials: a regulatory perspective.** *AIDS Res Hum Retroviruses* 1998, **14**(Suppl 3):S333–S340.
 6. Horne AD, Lachenbruch PA, Goldenthal KL: **Intent-to-treat analysis and preventive vaccine efficacy.** *Vaccine* 2000, **19**: 319–326.
 7. Parkman SA, Hardegree MC: **Regulation and testing of Vaccines.** In *Vaccines*. Edited by Plotkin SA, Orenstein WA. 3rd Edition. Saunders, Philadelphia, 1999, 1131–1143.
 8. Clemens J, Brenner R, Rao M, Tafari N, Lowe C: **Evaluating new vaccines for developing countries. Efficacy or effectiveness?.** *J Am Med Ass* 1996, **275**:390–397.
 9. Jacques JA, Koopman JS, Simon CP, Longini IM: **Role of the primary infection in epidemics of HIV infection in gay cohorts.** *J Acquir Immune Defic Syndr* 1994, **7**:1169–1184.
 10. Longini IM, Ackerman E, Elveback LR: **An optimization model for influenza A epidemics.** *Math Biosci* 1978, **38**:141–157.
 11. Longini IM, Sagatelian K, Rida WN, Halloran ME: **Optimal vaccine trial design when estimating vaccine efficacy for susceptibility and infectiousness from multiple populations.** *Stat Med* 1998, **17**:1121–1136.
 12. Holmberg SD: **The estimated prevalence and incidence of HIV in 96 large US metropolitan areas.** *Am J Public Health* 1996, **86**:642–654.
 13. UNAIDS: **Report on the global HIV/AIDS epidemic.** UNAIDS, Geneva, June 2000.
 14. IAVI: **AIDS vaccines for the world, preparing now to assure access.** IAVI, New York, July 2000.
 15. Chanchaoren K, Kuananusont C, Yin D: **Resource utilization for HIV/AIDS in Thailand, a pilot study.** *XIII International AIDS Conference*, Durban, July 2000 [abstract WeOrD567].
 16. Tangcharoensathien V, Phoolcharoen W, Pitayarangarit S, et al: **The potential demand for an AIDS vaccine in Thailand.** *AIDS Economic Network Symposium*, Durban, July 2000.
 17. Jackson DJ, Martin HL Jr, Bwayo JJ, et al: **Acceptability of HIV vaccine trials in high risk heterosexual cohorts in Mombasa, Kenya.** *AIDS* 1995, **9**:1279–1283.
 18. Nichter M: **Vaccinations in the third world: a consideration of community demand.** *Soc Sci Med* 1995, **41**:617–632.
 19. Pennie RA, O'Connor AM, Garvock MJ, Drake ER: **Factors influencing the acceptance of hepatitis B vaccine by students in health disciplines in Ottawa.** *Can J Public Health* 1991, **82**: 12–15.
 20. Streefland P, Chowdury AM, Ramos-Jimenez P: **Patterns of vaccination acceptance.** *Soc Sci Med* 1999, **49**:1705–1716.
 21. Veenman J, Jansma LG: **The 1978 Dutch polio epidemic: a sociological study of the motives for accepting or refusing vaccination.** *Neth J Sociol* 1992, **16**:21–48.
 22. Brugal MT, Domingo-Salvany A, Maguire A, et al: **A small area analysis estimating the prevalence of addiction to opioids in Barcelona, 1993.** *J Epidemiol Comm Health* 1999, **53**:488–494.
 23. Centre d'estudis Epidemiològics sobre la Sida de Catalunya (CEESCAT): **Sistema integral de vigilància epidemiològica de l'HIV/sida a Catalunya (SIVES).** *Informe anual 1999.* Barcelona 2000.
 24. Berman, PW: **Development of bivalent rgp120 vaccines to prevent HIV type 1 infection.** *AIDS Res Hum Retroviruses* 1998, **14**(Suppl 3):S277–S289.
 25. Choopaya K, (BVEG) Bangkok Vaccine Evaluation Group: **Initiation of a phase III efficacy trial of bivalent B/E rgp 120 HIV vaccine (AIDSVAxTmB/E) in Bangkok, Thailand.** *XIII International AIDS Conference*, Durban, July 2000 [abstract WeOrC555].
 26. Harro C, Judson F, Brown SJ, et al: **Successful recruitment and conduct of the first HIV vaccine efficacy trial in North America and Europe.** *XIII International AIDS Conference*, Durban, July 2000 [abstract WeOrC556].
 27. Pitisuttithum P (BVEG) Bangkok Vaccine Evaluation Group: **Social harm monitoring among injecting drug users in a phase III HIV vaccine trial in Bangkok, Thailand – preliminary results.** *XIII International AIDS Conference*, Durban, July 2000 [abstract TuOrD448].
 28. UNAIDS guidance document: **Ethical considerations in HIV preventive vaccine research.** Joint United Nations Programme on HIV/AIDS, Geneva, 2000 (Document UNAIDS/00.070E).

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