

Public health considerations for the use of a first generation HIV vaccine

Report from a WHO-UNAIDS-CDC Consultation, Geneva, 20–21 November 2002

To accelerate the development and future availability of safe, effective and affordable HIV vaccines it is essential to address not only the associated biomedical obstacles, but also the logistic aspects that would guide the introduction and use of those vaccines. It is likely that initial vaccines may only be partially effective, and their public health use will have to be carefully considered. This report summarizes the discussions from a consultation held in Geneva (20–21 November 2002) organized by the World Health Organization (WHO), the joint United Nations Programme on HIV/AIDS (UNAIDS) and the US Centers for Disease Control and Prevention (CDC). The group identified a number of logistic issues that need to be addressed to accelerate the development and future availability of HIV vaccines, and made broad recommendations in four different areas: (a) Vaccine manufacturing and licensing; (b) vaccination acceptability and social marketing; (c) immunisation strategies and delivery; and (d) access and economic issues. The implementation of these recommendations will require the participation of multiple stakeholders in the public and private sector, in industrialized and developing countries. These actions will be essential to ensure widespread and rapid access to HIV vaccines globally, soon after their efficacy is demonstrated in clinical trials.

© 2003 Lippincott Williams & Wilkins

AIDS 2003, 17:W1–W10

Keywords: HIV vaccines, vaccine access, vaccine delivery, vaccine trials

Introduction

Just twenty years after its recognition, HIV/AIDS has become the most important infectious disease, the leading cause of death in sub-Saharan Africa and the fourth most common worldwide. From approximately 60 million who have been infected with HIV since the beginning of the epidemic, 20 million have already died of AIDS, and estimated 3.1 million in 2002 alone. Today, an estimated 42 million people are living with HIV/AIDS, 95% of them in developing countries, especially in sub-Saharan Africa, which is home to more than 29 million of those infected.

Despite the intense national and international efforts to control the AIDS epidemic, HIV continues to spread at a rate of nearly 15 000 new HIV infections every day, 95% of them in developing countries. These sustained

rates of transmission emphasize the need to develop additional biomedical preventive tools that are simple, effective and affordable, such as microbicides and preventive vaccines.

The search for an HIV vaccine started soon after HIV was identified as the etiological agent of AIDS. Since 1987 more than 30 different candidate vaccines have been tested in over 70 phase I/II trials in both developed and developing countries, to assess their safety and immunogenicity [1]. In all these years only one vaccine concept, based on monomeric gp120, has entered phase III efficacy evaluation in two trials conducted in North America and in Thailand. The preliminary results from the North American trial indicated that the vaccine had no overall efficacy, although an initial sub-population analysis seemed to indicate potential efficacy among black volunteers and,

Correspondence to: Dr. José Esparza, WHO-UNAIDS HIV Vaccine Initiative, World Health Organization, 1211 Geneva 27, Switzerland.

E-mail: esparzaj@who.int.

DOI: 10.1097/01.aids.0000076356.20434.a0

perhaps, also in women [2]. Although the overall results have been discouraging, the conduct of these initial phase III trials have already proved that these complex trials can be conducted [3] and, if the preliminary results are confirmed, could also provide important biological clues for the design of new trials. What is evident is that numerous clinical trials, including several efficacy trials, will be needed to develop a broadly effective HIV vaccine, and this effort will require intense international co-operation and collaboration.

To accelerate the development of a much needed HIV vaccine, it is important to address not only the numerous scientific challenges that have been identified, but also the logistic challenges that will emerge when a vaccine is finally developed and ready to be delivered to all populations in need. Clarity on how future HIV vaccines with different levels of protection will be used and delivered should serve as an incentive to accelerate their development.

To address these logistic issues the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the US Centers for Disease Control and Prevention (CDC), organized a consultation which was held in Geneva, 20–21 November 2002. This consultation provided a follow-up to a previous WHO-UNAIDS consultation held in October 2000 to discuss future access to HIV vaccines [4], and to a more recent CDC consultation held in Atlanta in January 2002, to advise CDC on critical issues that need to be addressed in anticipation of the eventual licensure and availability of an HIV vaccine in the United States [5].

The consultation was attended by 30 experts from 15 countries, including representatives from different national and international organisations, the pharmaceutical industry and staff from WHO, UNAIDS and CDC (participants listed in the Appendix; following WHO policy, representatives from the pharmaceutical industry were not present at the closing session where the recommendations were finally discussed and adopted). The meeting was chaired by Dr Judith Wasserheit, from the HIV Vaccine Trials Network, and Dale Hu, Quarraisha Abdool-Karim, Marie-Louise Chang, Luis Fernando Macedo Brigido, Jane Rowley and Viroj Tangcharoensathien served as Rapporteurs. The meeting was opened by Dr Catherine Hankins, Senior Scientific Adviser to UNAIDS, Dr José Esparza, Coordinator of the WHO-UNAIDS HIV Vaccine Initiative, and Dr Charles Vitek, from the HIV Vaccines Section of CDC.

Plenary presentations and discussions took place before participants were divided into subgroups to develop recommendations in the following four areas: (a)

Manufacturing and licensing; (b) acceptability and social marketing; (c) immunisation strategies and delivery; and (d) access and economics issues.

Framing the issues

Defining vaccine efficacy

Defining vaccine efficacy (VE) is a crucial initial step in discussions on the public health use of first generation HIV vaccines. In the case of HIV/AIDS vaccines, the total effect of a vaccination strategy would depend not only on the protection of vaccinated individuals, but also on other effects or components [6–8].

The first component sometimes designated VE_S , is the traditional measure of vaccine efficacy in reducing susceptibility to the establishment of infection upon exposure; this effect has been considered as the primary endpoint of current HIV vaccine efficacy trials. The other two components, which have also been called secondary endpoints, apply to effects that may be seen among vaccinated people who become infected: VE_P , vaccine efficacy in mitigating disease progression, and VE_I , vaccine efficacy in reducing infectiousness. Measuring VE_I and VE_P will require complex study designs. For example, estimation of VE_I will require augmented partner study designs; these studies collect data on the infectiousness of vaccinated individuals who become infected.

Since viral load has a well-established relationship with both disease progression and infectiousness, viral load may be a suitable surrogate measure for VE_P and VE_I . As some candidate vaccines have lowered the viral load set point and delayed disease progression in animal models, these components of vaccine efficacy, VE_P and VE_I , will likely be very important for early generations of HIV vaccines. These early vaccines are likely to be of low to moderate VE_S but they may provide slowing of disease progression (VE_P) or lowering of infectiousness (VE_I) in vaccine recipients who become HIV infected. In addition, it is likely that initial HIV vaccines may be “leaky” in that vaccinated persons may have partial protection from infection upon different frequencies of exposure. For all components of vaccine efficacy, there are factors that may affect efficacy such as viral strain or subtype, mode of transmission, and the effect of host genetics. In addition, the duration of vaccine efficacy for current and future HIV vaccine candidates is unknown [9,10].

Adding to the increased complexity of vaccine trial design and longer follow-up, the use of additional measures of vaccine efficacy such as VE_P and VE_I requires careful consideration of a number of factors. One factor is the potential bias when comparisons are

made between infected vaccine recipients compared to infected placebo recipients. Furthermore, the analysis of surrogate endpoints such as viral load may be complicated by the use of antiretroviral therapy which is becoming increasingly available globally. It might be useful to build the provision of HAART into vaccine trial designs while continuing to study the optimal use of viral load surrogate markers [11]. This may necessitate the use of surrogate markers obtained early in the trial, such as viral load before antiretroviral therapy initiation. However, the use of other potential surrogate markers will require following subjects for a number of years. Study designs that are capable of measuring infectiousness are logistically and statistically complex and may be feasible only in certain populations.

Recent scientific developments have suggested that the first generation of HIV vaccines available for public health use will likely be of low to moderate efficacy, compared to currently licensed vaccines for other diseases. Such “partially effective” HIV vaccines, however, could provide considerable individual and public health benefit. Control of the HIV epidemic could be achieved, if the reproductive number (R_0), (the average number of secondary infections produced by an infected individual) can be reduced to below 1 by the effects of vaccination, especially if augmented by other control measures. Preliminary modelling studies have indicated that HIV vaccines of even relatively low (30%) efficacy, administered at high coverage levels, could significantly reduce HIV epidemics in high incidence countries and could be valuable clinical and public health interventions [12–14]. Even if people become infected after vaccination, the individual and public health benefits from an HIV vaccine that decreases disease progression and infectiousness could be substantial.

However, these effects could be blunted or lost for vaccines of low to moderate efficacy if risk behaviour increases as a result of an unwarranted sense of protection among the vaccinated individuals. Although participants in the recent phase III trials in North America and Thailand have not shown increases in risk behaviour, it is impossible to accurately predict what will be the trends in risk behaviour once a vaccine is licensed and implemented.

Efficacy of the first generation vaccine may only be low to moderate, but the overall public health efficacy may actually turn out to be much higher when combined with other forms of prevention, such as voluntary counselling and testing (VCT), and if “herd immunity” is taken into account. “Herd immunity” is not studied in an efficacy trial, but it is an important factor from a public health perspective. Herd immunity can be considered as an indirect protection of unvacci-

nated susceptibles by high levels of vaccination amongst the remaining section of the population.

Manufacturing and licensing issues

Before a vaccine can be adopted for public health use, it must be licensed by the National Regulatory Authorities (NRA) in the countries in which it is to be used. NRAs will need sufficient and reliable data to evaluate the safety, purity, potency, quality, consistency of manufacture, and suitability for the intended population and clinical indication of an efficacious candidate vaccine. Obtaining the data required to support licensure should be planned even prior to the conduct of phase III efficacy trials, if there is to be a rapid deployment of an efficacious vaccine, although this is rarely the case [15].

For a highly efficacious vaccine, as is the case for many licensed vaccines, a single efficacy trial might be sufficiently compelling to support licensure. However, for a modest or low efficacy vaccine, it may be necessary to conduct at least two complementary efficacy studies to provide compelling evidence of efficacy, as is required for most drugs and biologicals.

In addition, the manufacturer must plan ahead to have the data on the entire manufacturing process that will be required by the NRA. This includes finalization of all manufacturing process refinements and validation of the manufacturing processes, including scale-up to commercial scale production. If these steps are not completed prior to the conduct of phase III trial(s), it will be necessary to finalize these prior to licensure and to conduct studies that enable comparability of the new process to the process used to manufacture the phase III clinical lots (bridging studies). Consistency of manufacture will need to be demonstrated through a clinical consistency study. If licensure is to be sought for a better vaccine formulation, or for a population other than that (or those) studied in the phase III trial(s), bridging studies for that population will be needed. Likewise, bridging studies are needed if different dosing schedule, formulation, route of delivery, or different target population is chosen for licensure or public health implementation. Unfortunately, in the absence of a clear correlate of protection, such bridging studies are made much more difficult; surrogate markers, such as selected immune response parameters, can be used to support licensure but must be clearly justified. Fortunately, a number of studies have demonstrated a strong relationship between viral load and both disease progression and infectiousness.

The NRA of some countries may require bridging studies to provide data on vaccine effect pertinent to their own populations, with their own unique ethnic mix, if the efficacy trials or other prior studies were not performed in their country. Sufficient safety data to

support licensure, generally requiring the study of thousands of vaccine recipients, must also be obtained, preferably from randomized, controlled trial(s) conducted according to Good Clinical Practices (GCP). If the efficacy trial(s) and earlier randomized controlled trials are not of sufficient size to provide such safety data, an additional large safety study may need to be undertaken, preferably while the efficacy trial is ongoing, so that the safety study may be conducted as a randomized, placebo-controlled trial. If resources by the manufacturer were not devoted to obtaining these data prior to the conduct and outcome of the efficacy trial(s), then they must be performed after the efficacy trial is concluded and prior to seeking licensure.

Although many decisions will need to be made under situations of uncertainty, observed risks and benefits from clinical trials will inevitably influence whether a manufacturer will seek licensure and if licensure is sought, the data will be necessary for review by regulatory and advisory bodies to recommend public health vaccine use for different populations. Uncertainty and unknowns must, however, not delay vaccine development.

Several issues remain open to further discussion: If the manufacturer of a low efficacious vaccine applies for licensure with the U.S. Food and Drug Administration (FDA), and the FDA does not approve such a vaccine, will it be licensable by another NRA? What would be the minimal level of efficacy that should be recommended to agencies for implementation? What surrogate markers of efficacy, if any, could be accepted by the NRA for licensure? Since reduced virus load has been accepted as an end-point for therapeutic vaccines, would it be equally acceptable for preventive vaccines? Even if viral load is reduced, for how long will that be maintained? Could that be a provision for "conditional licensing"? Will an HIV vaccine application come under the U.S. policy for "accelerated approval" which is a form of "conditional licensing"? How "licensable" will a vaccine be which shows only a degree of short-term protection?

Acceptability and social marketing

Whether a future HIV vaccine will be accepted by the population targeted for vaccination will depend on a number of factors, amongst them, the vaccine efficacy [16–17]. The communications material needed should convey all the facts known, the risks and the benefits of vaccination, and the level of efficacy. Should the vaccine show only low efficacy, this material will need to be backed-up scientifically and partial efficacy outlined clearly. Precaution must be taken not to create expectations beyond those that are reasonable and the information given should be factual and transparent.

The communication material could initially be targeted

at the national government level as this will be the level where decisions and priorities are made. Material should also be widely made available to different groups and stakeholders. Analyses to assist governments to make decisions of the acceptability of a low efficacious vaccine must be conducted [18].

Independently of the governments' decisions, there might be a social demand for the vaccine, i.e. individual people might request to have the vaccine. Or the vaccine might merely be passively accepted, denoting compliance by the public and yields from the recommendations and/or social pressure of health workers and community leaders. The potential acceptance of an HIV vaccine may depend on background risk. If the background risk is high, the target groups will be more likely to accept the vaccine and vice-versa.

History with other vaccines have shown that there is a risk that anti-vaccine movements can arise on the basis of rumours or conspiracy-type theories. When the refusal to be vaccinated is based upon scientific concern, there might be room for dialogue leading to informed consent. When refusal is based on religious or other non-scientific beliefs, it may be much more difficult to use scientific data to convince the objectors that they, or their children, or members of their community might someday engage in HIV risk behaviours. The question of resistance or opposition against vaccination, is relevant in the context of parental consent, as well as when determining the type of information to be developed to inform the community and target group about HIV vaccination.

There is also another scenario which is that of demand exceeding supply, likewise for this scenario, clear messages has to be developed as to priorities and chosen strategies.

Immunisation strategies and delivery

Soon after the efficacy of an HIV vaccine is demonstrated in phase III trials, there will be limited quantities of the vaccine available. It will therefore be necessary to determine the short and medium term immunisation strategies assuming that, over time, more vaccine will become available for administration as manufacturing facilities are scaled up.

Before addressing potential immunisation strategies the following questions need to be answered: (a) What will be the most effective strategy in stemming the tide of the disease in a country (an overarching public health goal)? (b) What is the most fair or just strategy to the population that will be immunized (an ethical goal)? And (c) what will be the most efficient strategy (a practical or feasible goal)?

In the short-term, several immunisation strategies can

be considered. Phase IV effectiveness trials could be conducted to address the uncertainties about the practical generalizability of vaccine performance, community effects and behavioural disinhibition (i.e. removal of inhibitory constraining behaviour). Depending on the availability of the vaccine, an alternative to a phase IV trial could be a formal phased introduction, since setting up phase IV trials might be very time consuming. A targeted approach to groups at higher risks (e.g. migrants, truck drivers, commercial sex workers, military personnel) might also be a likely method, either through a trial based setting (phase IV) or not, depending on availability of the vaccine. However, there are difficulties in accessing high-risk populations and such a vaccination strategy could result in stigmatization and discrimination of the populations selected for vaccination.

In the medium term, there are other potential vaccination strategies, including: (a) Integration within current programmes (existing HIV/AIDS prevention and care facilities, or immunisation services); (b) targeting specific populations; and (c) mass campaigns.

Under these circumstances, vaccinating the general population, or large segments of the general population (i.e. “universal vaccination”), might be the only possible immunisation strategy, assuming that there is no limitation on the supply of the product and that there are no budget constraints. Choosing to vaccinate universally would imply singling out age groups of the population and accessing them. Since increased risk behaviour is a significant concern with use of a low efficacious vaccine, the vaccine could be given only as a part of a bigger package of interventions, for instance in tandem with condoms.

In certain populations in developing countries it might not be appropriate to discuss the choice between targeted and universal vaccination, as there are no well defined high risk groups since the epidemic has spread to the general population. This is evident from the high prevalence of HIV/AIDS in pregnant women. It might be more feasible to vaccinate certain age groups such as adolescents, i.e. teenagers and pre-teenagers. If the vaccine is of low/moderate efficacy, the adolescents vaccinated would contribute to herd immunity. Accepting the vaccine must therefore be of a certain degree of altruistic nature if it has little individual protection. The social marketing strategies must be adapted as appropriate. Vaccination of adolescents requires the development of innovative strategies that are ethically, legally and logistically feasible [19–21]. Adolescents are more likely to be uninfected, yet they are at risk. However, the question remains, which age group to target, and epidemiological data is necessary to back up any decision taken. Young people require interventions which recognize the unique psychosocial

situation of adolescence. In addition to reaching this group with HIV vaccines, increased emphasis must be placed on interventions such as condom promotion and delayed-sexual debut as risk-reduction strategies.

If parents are reluctant to contemplate that their child might someday be at risk of contracting HIV, their tolerance for vaccine-related risks could be low. Thus, despite the preventive nature of vaccination, the parental instinct to shelter children from perceived unnecessary risks may translate into a reluctance to support adolescent vaccination campaigns against HIV. On the other hand, in countries with high HIV prevalence, parents may be very supportive of any intervention which could spare their children from an otherwise likely HIV infection in the future. Indeed vaccination of school-aged children, would be undertaken with an eye to preventing vulnerability in the future.

From a public health standpoint, adolescents may not be the highest priority for vaccination as there are trade-offs between prioritising adolescent immunisation strategies and strategies for the other groups whom it may be important to vaccinate from a public health perspective. The relative importance of the different groups will depend on the country specific epidemiology of HIV. However, a strong argument for adolescent vaccination is that if it is possible to initially reach a large proportion of pre-sexual teenagers and continue to vaccinate cohorts the following years, it will be possible to stem the tide of the epidemic, because there will be no one to fuel the epidemic in high-risk groups as they will already be vaccinated.

If initial HIV vaccines are only able to offer a temporary protection which decreases over time, or if they require multiple booster dosages scheduled many years apart, then vaccination of young adults outside of the setting of educational institutions will require a determined effort and might not be feasible.

The paradigm of how vaccines have been delivered until now has been through liquid vaccines delivered through needles. This might be changed to include powder vaccines (e.g. jet gun injection of microparticles) as it will be crucial to maximize the conduct of safe immunisation practices and any real or perceived risk must be reduced to the absolute minimum.

A sufficient infrastructure will be required to support vaccination, and some of the countries that need an HIV vaccine the most, are lacking the necessary structure and will need significant resources to build the necessary capacity. At least four factors will influence delivery: (a) The existing service level, (b) existing logistics; (c) vaccine supply; and (d) vaccine quality.

There is currently no generally accepted way of delivering vaccines to adolescents. The Expanded Programme on Immunisation (EPI) is traditionally targeted to childhood vaccines only, and experience in the area of childhood vaccination programmes has consistently demonstrated how difficult it can be to achieve the level of coverage needed [22]. Other vaccines such as meningococcal vaccine are given to adults but primarily through mass immunisation campaigns. New strategies for reaching adolescents will have to be developed by drawing on lessons from other vaccines. School-based programmes could potentially cover school attendees; globally this represents 75% of the primary school-aged population and 35% of the high school-aged population. Such programmes could be cost-effective, facilitate documentation and may allow for the vaccination to be enforced. EPI tetanus and rubella immunisation programmes have attempted to reach adolescents through school-based programmes, but very little information is available as to the coverage levels. However, there is a danger of missing the 25% of children not enrolled in schools, and these might be the children at highest risk (e.g. marginalized street children). An effort to reach un-enrolled school children are crucial and experience has shown that this is possible [23]. Alternatively, other service structures through which an HIV vaccine could be given to adolescents and adults include existing health services, sexually transmitted infections clinics, commercial sex work places, and family planning clinics.

There is an overall strong consensus against compulsory HIV immunisation program. Mandatory immunisation may require parental consent and law modifications; historically, there has been strong opposition against mandatory vaccination and such programmes might create tension, rumours and adverse publicity.

HIV screening is a controversial issue and needs to be dealt with well in advance of vaccine licensure. Should there be a system in place for HIV screening in advance of vaccination, and if so should screening be mandatory and a prerequisite to immunisation? If screening should be done, should voluntary testing and counselling (VTC) also be done? Screening tests will be costly, and will slow things down tremendously.

If the vaccine is safe in HIV-infected individuals, the vaccine could be made available for all without screening, to simplify the strategy. A possible drawback is revaccination of individuals. However, if there are no adverse immunological effects to revaccination, then the financial cost of revaccination would need to be evaluated against the costs of screening.

In order to help countries decide on optimal vaccination strategies, it would be useful to develop a basic set of data parameters and to ensure that there is a well

functioning data collection systems in countries to obtain and validate this data. Critical data elements would include clinical and epidemiologic data on HIV infections, behavioural data, and social parameters. The focus should be on the collection on simple data (e.g.; age of sexual debut, frequency of partner change). Population dynamics and viral population dynamics should be modelled and followed as these elements may change swiftly.

For phase IV trials, a concerted effort should be made to collect data on: (a) VE_S, VE_P, VE_I ; (b) behavioural response of vaccinees; (c) baseline data and vaccinees response to the vaccine; (c) stage of the epidemic; and (d) baseline behavioural indicators, including percentage of young persons reporting use of condom with non-usual sex partners.

Access and Economic Issues

Specifically, a strategy is needed to ensure the timely and global availability of future HIV vaccines, soon after they are developed. Manufacturing, purchasing and distribution issues should all be essential components of such a strategy. All stakeholders, including governments, private sector industry, research community, consumers and community at large should be involved as soon as possible on an international debate. It is also important that national discussions take place, because it is precisely at the national level where many of the key decisions about vaccine adoption, use and financing will be made [24,25].

Vaccine financing is clearly an issue that should be addressed well in advance of licensing. Finding the necessary resources for financing vaccine purchase and delivery in developing countries (or in low and middle income countries) will require the active engagement of the international community (including the World Bank, the Global Fund, etc), developed and developing country governments, the private sector, private foundations, and individuals [26].

The national health budgets in countries most in need of an HIV vaccine are already over-stretched, and as a result it will be necessary to develop funding sources to purchase and deliver HIV vaccines from outside of the traditional health budget. This might include new loans or other financing mechanisms at the international level, and/or the mobilisation of additional domestic funds through general tax revenue, social health insurance, private insurance. Multilateral organisations, NGOs, and community groups have an important role to play in catalysing the mobilisation of these funds internationally and domestically. They also need, in parallel, to enter into a dialogue with the vaccine industry to look at options for ensuring that developing countries will be able to afford to vaccinate

their populations (e.g., tiered pricing, technology transfer).

In addition to mobilising resources to purchase HIV vaccines and to fund their delivery, there is still a need to increase the level of investment in HIV vaccine research and development. There has been a history of market failure in the field of HIV vaccine research. However, the chronic lack of private sector investment is general in the vaccine area, as vaccines have a limited market and low return on investments compared to drugs. World-wide, vaccine potential sales are estimated to be approximately US\$ 6.5 billion, which represents only about 2% of the global pharmaceutical market, an amount roughly equivalent to the sales of one successful ulcer drug. The public sector will therefore need to provide incentives on R&D for development of new vaccines and manufacturing capacity.

Encouraging early investment in vaccine manufacturing capacity is another challenge that will need to be met if we are to ensure early access. Constructing and testing vaccine manufacturing facilities is expensive and takes time. This is another area where the public and private sectors may be able to work together in a constructive fashion.

Lastly, community involvement in every aspect of HIV vaccine development, policy adoption, access, financing and delivery, is necessary to successful use of HIV vaccines.

Recommendations

Participants at the consultation developed a number of broad recommendations which need to be implemented, not only by WHO and UNAIDS, but by all institutions and organisations working on HIV vaccines.

Manufacturing and licensing

- a) Strengthen the regulatory framework for HIV vaccine activities in existing and emerging NRA by: Encouraging global harmonization, expanding training activities, and identifying mechanisms for, and alternatives to HIV vaccine licensure for countries that do not have NRA.
- b) Facilitate the collection and evaluation of potential endpoints for vaccine efficacy (susceptibility, infectiousness, disease progression, and waning of vaccine efficacy) around the world to support licensure.
- c) Expand the assessment of HIV vaccine demand by regions and over time, to assist vaccine manufacturers to plan supply.
- d) Catalyse discussions aimed at increasing global HIV

vaccine manufacturing capacity, through defining incentives, and the removal of disincentives.

- e) Develop a position on HIV vaccine-related patents, to balance the need to respect these patents as important incentives, with the need to see that these are not used in detriment of global distribution of effective vaccines.

Acceptability and social marketing

- a) Develop a broadly-based global platform to start planning for the future introduction of HIV preventive vaccine programmes in different countries, as part of a vaccine preparedness programme. This process should include representatives of governmental funding agencies, members of national health ministries, leaders of health advocacy groups and other non-governmental organisations, industry representatives, communications experts, communities, and other relevant parties. Issues to be considered should include accurate information about the vaccine, including degree of efficacy, potential side effects, and other risks and benefits. These plans should emphasize that preventive HIV vaccines should be part of a total prevention package. Once plans are accepted by the core group, they should be presented to stakeholders at the national level.
- b) Adapt the global platform for future vaccine introduction to the needs of individual countries, taking into account cultural, epidemiological, and economic differences. Each country should consider forming an operational action group including, amongst others, experts from WHO/UNAIDS, national and local health advocacy groups, public health specialists, and a comprehensive list of stakeholders to be identified. National groups would then be responsible for making strategy and allocating actions for introduction and implementation of vaccines in the country.
- c) Establish an international partnership comprising of representatives from the public and private sector and international agencies to offer guidance and assistance on how to establish and implement the vaccine programme as part of the total prevention package.

Immunisation strategies and delivery

- a) Develop national policies supporting HIV vaccination programmes, in collaboration with communities and media, assisting national authorities with defining the critical data needed to guide this development, including: Development of models for its collection and analysis (these activities should include the development of a degree of consensus among modellers); planning for phase IV studies, to answer issues about optimal implementation tactics; obtaining and interpreting data on safety in HIV positive individuals, to help guide decisions on

screening; obtaining and interpreting data on potential cross-clade protection, to guide the use or testing of vaccines in populations where the circulating HIV clades do not match the vaccine; and planning studies on vaccine effect on secondary transmission.

- b) Ensure that future HIV vaccines are delivered along with other HIV prevention counselling/measures to maximise vaccine effectiveness and to minimize increases in risk behaviour after introduction of HIV vaccination programmes.
- c) The initial strategy for implementation of HIV vaccines under conditions of limited vaccine availability may focus on immunisation of epidemiologically relevant groups and areas, with expansion of immunisation to the general population in high incidence countries as the vaccine becomes more available. Advocate for a strategy that leads to mass immunisation in countries where epidemiologically appropriate. Develop and promote methods to evaluate and validate this strategy.
- d) The evaluation of HIV immunisation strategies and programmes will be critical and will require methods unlike those used for childhood immunisation programmes. Develop pilot methods for evaluation of HIV immunisation programmes, including coverage, effectiveness, and safety.
- e) The introduction of HIV vaccines will create the need and opportunity to reconceptualise immunisation and prevention programmes, to optimally address the prevention needs of adolescents and young adults. Support pilot studies of new delivery structures that can reach and deliver prevention services to adolescents and young adults. Encourage programs that bundle HIV vaccines with hepatitis B vaccines and other vaccines that may be available in the near future (such as HPV and HSV-2).

Access and economic issues

- a) The goal is to ensure that future HIV vaccines are globally available and utilised to maximize public health benefits. To achieve this goal, a two prong approach is needed, namely evidence generation (research) and advocacy. Government, industry, research community, consumers and community should be involved in all aspects of vaccine development, vaccine adoption, financing and delivery.
- b) Conduct research to obtain information for policy-makers/government on the following: Cost and benefits of HIV vaccination programmes; demand for HIV vaccines; total resource implications of vaccine introduction; development of user friendly tools to assist policy makers for introduction vaccine under different scenarios; and strengths and weaknesses of different financing options, and modalities of delivery systems.
- c) Explore different financing options, including: Voluntary tiered pricing mechanism by the vac-

cine producers; HIV vaccine as a public global good, with the World Bank, donor communities, public and private sector and other players being responsible to ensure purchasing and delivery capacity; government responsibility to ensure that HIV vaccines are used to maximise public health benefits, with adequate funding; and multilateral organisations catalysing national governments and private sectors to dedicate adequate resources to purchase and deliver HIV vaccines for the world.

- d) Collaborate with the vaccine industry by: Providing incentives on R&D for development of new vaccines and to accelerate manufacturing capacity to match demand; identifying and implementing mechanisms for ensuring that adequate manufacturing capacity is in place for global access (this manufacturing capacity, if possible, must be in place before the end of phase III trials); and encouraging technology transfers for manufacturing of vaccine to developing countries.
- e) Facilitate the evaluation and development of infrastructures for future vaccine delivery, including: Investments by multilateral organisations, governments, and the private sector on health care delivery infrastructure globally, to ensure there is the capacity to deliver HIV vaccines. Regular evaluation of service provision is a key component with regular feedback to communities and stakeholder organisations; establishing systems to provide regular assessment and evaluation of the use, cost and outcome of HIV vaccines; and review the systems that are currently available to determine if they are adequate for assessment.
- f) Ensure community involvement in the whole process of vaccine policy adoption, access, financing and delivery systems.

Acknowledgements

The first part of this report was prepared by M-L Chang, C. Vitek and J Esparza, based on the presentations made during the consultation and the notes provided by the Rapporteurs (Dale Hu, Quarraisha Abdool-Karim, Marie-Louise Chang, Luis Fernando Macedo Brigido, Jane Rowley, Viroj Tangcharoen-sathien). The recommendations were developed by working group participants and approved by consensus at the end of the meeting, without the participation of representatives from the vaccine industry.

References

1. Esparza J, Osmanov S. **HIV vaccines: a global perspective.** *Curr Mol Medicine* 2003, **3**:183-94.

2. Berman P. **Preliminary results of the phase III efficacy trial of AIDSVAX B/B.** Presented at: *Keystone Symposium on HIV Vaccine Development*; 2003; Banff, Canada.
3. Francis DP, Heyward WL, Popovic V, et al. **Candidate HIV/AIDS vaccines: lessons learned from the World's first phase III efficacy trials.** *AIDS* 2003, **17**:147–156.
4. WHO-UNAIDS. **Future access to HIV vaccines. Report from a WHO-UNAIDS Consultation, Geneva, 2–3 October 2000.** *AIDS* 2001, **15**:W27–W44.
5. Hu DJ, Vitek CR, Bartholow B, et al. **Key issues for a potential human immunodeficiency virus vaccine.** *Clin Infect Dis* 2003, **36**:638–644.
6. Halloran ME, Struchiner CJ, Longini IM Jr. **Study designs for evaluating different efficacy and effectiveness aspects of vaccines.** *Am J Epidemiol* 1997, **146**:789–803.
7. Longini IM Jr, Datta S, Halloran ME. **Measuring vaccine efficacy for both susceptibility to infection and reduction in infectiousness for prophylactic HIV-1 vaccines.** *J Acquir Immune Defic Syndr Human Retrovirol* 1996, **13**:440–447.
8. Longini IM Jr, Hudgens MG, Halloran ME, et al. **A Markov model for measuring vaccine efficacy for both susceptibility to infection and reduction in infectiousness for prophylactic HIV vaccines.** *Stat Med* 1999, **18**:53–68.
9. Boily MC, Masse BR, Desai K, et al. **Some important issues in the planning of phase III HIV vaccine efficacy trials.** *Vaccine* 1999, **17**:989–1004.
10. Desai KN, Boily MC, Masse BR, et al. **Simulation studies of phase III clinical trials to test the efficacy of a candidate HIV-1 vaccine.** *Epidemiol Infect* 1999, **123**:65–88.
11. Gilbert P, DeGruttola V, Hudgens M, et al. **What constitutes effectiveness for an HIV vaccine that ameliorates viremia: issues involving surrogate endpoints in efficacy trials [84].** Presented at: *10th Conference on Retroviruses and Opportunistic Infections*; 2002; Boston.
12. Anderson RM, Swinton J, Garnett GP. **Potential impact of low efficacy HIV-1 vaccines in populations with high rates of infection.** *Proc R Soc Lond B Biol Sci* 1995, **261**:147–151.
13. Anderson RM, Garnett GP. **Low-efficacy HIV vaccines: potential for community-based intervention programmes.** *Lancet* 1996, **348**:1010–1013.
14. Barth-Jones DC, Longini IM, Ackers ML, et al. **Evaluating HIV vaccination strategies: vaccination policy is a critical determinant in achieving optimal control of HIV transmission [TuC4833].** Presented at: *XIV International AIDS Conference*; 2002; Barcelona.
15. WHO-UNAIDS. **Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines: report from a WHO-UNAIDS consultation, 13–15 March 2001, Geneva, Switzerland.** *AIDS* 2002, **16**:W15–W25.
16. Streefland PH. **Introduction of a HIV vaccine in developing countries: social and cultural dimensions.** *Vaccine* 2003, **21**:1304–1309.
17. Mugenyi PN. **HIV vaccines: the Uganda experience.** *Vaccine* 2002, **20**:1905–1908.
18. Esparza J, Chang M-L, Widdus R, et al. **Estimation of “needs” and “probable uptake” for HIV/AIDS preventive vaccines based on possible policies and likely acceptance (a WHO/UNAIDS/IAVI study).** *Vaccine* 2003, **21**:2041–2050.
19. Zimet GD, Blythe MJ, Fortenberry JD. **Vaccine characteristics and acceptability of HIV immunization among adolescents.** *Int J STD AIDS* 2000, **11**:143–149.
20. Liao A, Zimet GD. **The acceptability of HIV immunization: examining vaccine characteristics as determining factors.** *AIDS Care* 2001, **13**:643–650.
21. Gagnon MP, Godin G. **Young adults and HIV vaccine: determinants of the intention of getting immunized.** *Can J Public Health* 2000, **91**:432–434.
22. Bland J, Clements J. **Protecting the world's children: the story of the WHO's immunization programme.** *World Health Forum* 1998, **19**:162–173.
23. Talaat M, Omar M, Evans D. **Developing strategies to control schistosomiasis morbidity in non-enrolled school children: experience from Egypt.** *Trop Med Int Health* 1999, **4**:551–556.
24. Tangcharoensathien V, Phoolcharoen W, Pitayarangsarit S, et al. **The potential demand for an AIDS vaccine in Thailand.** *Health Policy* 2001, **57**:111–139.
25. Whittington D, Matsui-Santana O, Freiburger JJ, et al. **Private demand for a HIV/AIDS vaccine: evidence from Guadalajara, Mexico.** *Vaccine* 2002, **20**:2585–2591.
26. Batson A, Ainsworth M. **Private investment in AIDS vaccine development: obstacles and solutions.** *Bull World Health Organ* 2001, **79**:721–727.

Appendix. List of participants

Temporary Advisers

Quarraisha Abdool-Karim, University of Natal, Durban, South Africa.

Daniel Barth-Jones, Wayne State University School of Medicine, Detroit, MI, USA.

Eduard Beck, McGill University, Montreal, Canada.

Jorge Beloqui, Grupo de Incentivo á Vida, São Paulo, Brazil.

Luis Fernando Brígido, Ministry of Health, Brasilia, Brazil.

Manuel Carballo, International Center for Migration and Health, Geneva, Switzerland.

Chris Collins, AIDS Vaccine Advocacy Coalition, New York, NY, USA.

Cintia Folch, Centro de Estudios Epidemiológicos sobre el SIDA, Barcelona, Spain.

Henry Francis, National Institute on Drug Abuse, NIH, Bethesda, MD, USA.

Geoff Garnett, Imperial College School of Medicine, London, United Kingdom.

Ron H Gray, Johns Hopkins University School of Public Health, Baltimore, MD, USA.

Prayura Kunasol, Ministry of Public Health, Bangkok, Thailand.

Ruth Macklin, Albert Einstein School of Medicine, New York, NY, USA.

John G. McNeil, US Army Vaccine Development, Rockville, MD, USA.

Madeleine Sassan Morokro, Project Retro-CI, Abidjan, Cote d'Ivoire.

Douglas Owens, Stanford University, Stanford, CA, USA.

Supachai Rerks-Ngarm, *Ministry of Public Health, Bangkok, Thailand.*

Jane Rowley, *International AIDS Vaccine Initiative, London, United Kingdom.*

Rebecca Sheets, *Vaccine Research Center, NIH, Bethesda, MD, USA.*

Viroj Tongcharoensathien, *Mahidol University, Bangkok, Thailand.*

Nusara Thaitawat, *Ministry of Public Health, Bangkok, Thailand.*

Tim Tucker, *South African AIDS Vaccine Initiative, Cape Town, South Africa.*

Judith Wasserheit, *HIV Vaccine Trial Network, Seattle, WA, USA (Chair)*

Mercedes Weissenbacher, *Centro de Referencia para el SIDA, Buenos Aires, Argentina.*

Industry representatives

Paul Coplan, *Merck, West Point, PA, USA.*

Gerald Cunningham, *Merck, West Point, PA, USA.*

Charles de Taisne, *Aventis Pasteur, Lyon, France.*

Donald Francis, *VaxGen, Brisbane, CA, USA.*

William L Heyward, *VaxGen, Brisbane, CA, USA.*

Joachim Hombach, *GlaxoSmithKline Biologicals, Rixensart, Belgium.*

Guy Houillon, *Aventis Pasteur, Lyon, France.*

Maria Lattanzi, *Chiron Vaccines, Siena, Italy.*

Joachim Schwarzkopff, *Chiron Vaccines, Marburg, Germany.*

Beth Waters, *Cooney Waters Group, New York, NY, USA.*

CDC staff

Kate Buchacz, Dale Hu, Charles Vitek.

WHO and UNAIDS staff

Marie Louise Chang, John Clements, José Esparza, Ulla Griffiths, Catherine Hankins.