A safe, effective, and affordable vaccine remains the best long-term hope for bringing the global human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic under control. Recent scientific developments have suggested that the first generation of HIV vaccines available for public health care use will likely be of low to moderate efficacy, compared with currently licensed vaccines for other diseases. Nevertheless, such “partially effective” HIV vaccines could provide considerable individual and public health benefits. A consultation was held in January 2002 to advise the Centers for Disease Control and Prevention (Atlanta, Georgia) about critical issues that need to be addressed in anticipation of the eventual licensure and availability of an HIV vaccine in the United States. The present article summarizes the major issues discussed at the consultation with regard to the potential use of a partially effective vaccine in HIV prevention programs in the United States and the activities that are needed to prepare for vaccine availability.

More than 20 years after AIDS was first reported, the HIV pandemic continues to spread, with an estimated 14,000 new cases of HIV infection occurring daily. A safe, effective, and affordable vaccine remains the best long-term hope for bringing the global epidemic under control [1]. Recent scientific developments have suggested that the first generation of available HIV vaccines will likely be of low to moderate efficacy, compared with currently licensed vaccines for other diseases. Nevertheless, such “partially effective” HIV vaccines could provide considerable individual and public health benefits [2, 3].

In the United States, the Centers for Disease Control and Prevention (CDC; Atlanta, GA) plays an important role in the prevention of HIV infection and in HIV prevention research, and it will be responsible for guiding the implementation of HIV vaccination programs. During 16–17 January 2002, the HIV Vaccine Section of the CDC’s Division of HIV/AIDS Prevention held a consultation to advise the CDC regarding critical issues that need to be addressed in anticipation of the eventual licensure and availability of an HIV vaccine in the United States. A diverse group of consultants (see the Consultation Participants section at the end of the text) participated in presentations on salient topic areas complemented by discussions and working groups. The primary objectives of the consultation were (1) to identify and review major issues critical to the potential use of a partially effective HIV vaccine in a comprehensive HIV prevention program in the United States, and (2) to identify additional activities related to such a vaccine that the CDC should address.

**BACKGROUND**

Major challenges to HIV vaccine research and development include the lack of clearly identified immune correlates of protection from HIV infection or disease in humans, the incompletely understood significance of HIV genetic diversity, the absence of an ideal animal model, and the complexities of developing new vaccines. However, recent favorable developments in HIV vaccine research include the increasing number of vaccine candidates entering the development “pipeline” and the initiation of the world’s first phase III efficacy trials involving an HIV vaccine [4]. Some recent vaccine candidates that have been evaluated in preclinical, phase I, or phase II trials have produced promising immune responses [5–10]. The
first 2 phase III efficacy trials of an HIV vaccine are currently evaluating first-generation recombinant gp120 subunit vaccines. AIDSVAX B/B (VaxGen) is a bivalent formulation of 2 strains of HIV-1 subtype B and is being tested in North America and Europe; results of this trial will be available in early 2003. AIDSVAX B/E (VaxGen) is a bivalent formulation of the 2 primary HIV-1 subtypes B and E (also known as “circulating recombinant form CRF0_1AE”); the vaccine is currently being evaluated in Thailand, with end-of-trial results anticipated in late 2003. These trials have demonstrated that the scientific, logistic, and ethical challenges of conducting HIV vaccine efficacy (VE) trials can be met, given a high level of commitment [11, 12].

VE can be considered to have 3 components [13]. The first component, VEₚ, is the traditional measure of VE in reducing susceptibility to establishment of infection at the time of exposure. Compared with vaccines for other infectious agents (e.g., hepatitis B, measles, and tetanus), which have a VE of >90%, the first HIV vaccines potentially available for clinical use are likely to have a low to moderate VE, because of the scientific challenges inherent in developing HIV vaccines that prevent established infection [2]. The other 2 components of VE apply to vaccinated individuals who become infected: VEᵣ denotes the efficacy of a vaccine in mitigating the progression of disease, and VE represents the efficacy of a vaccine in reducing infectiousness. VEᵣ and VEᵦ may be very important measures of VE for early generations of HIV vaccines [14].

In nonhuman primate models, no candidate vaccines have provided high-level protection against establishment of infection after challenge with simian immunodeficiency virus (SIV) or with hybrids of SIV and HIV. However, some candidate vaccines did lower the virus load set point and delay disease progression [5, 7, 9]. The term “partially effective” vaccines has been used to refer to future HIV vaccines with a low to moderate VE, [2, 3]. Although not formally defined previously, “partially effective” vaccines have been provisionally defined, for the present discussion, to include vaccines with a VE of 30%-80%; these vaccines also may slow disease progression (VEᵦ) or lower infectiousness (VEᵣ) among vaccine recipients who do become infected with HIV. Partially effective vaccines could be licensed in the United States. Discussions between VaxGen, the US Food and Drug Administration (FDA; Rockville, MD), and an FDA advisory committee suggest that AIDSVAX B/B would be considered for licensure if the lower boundary of the 95% CI of VEᵦ exceeds 30% [15].

Preliminary modeling studies have indicated that HIV vaccines of even relatively low efficacy (e.g., 30% efficacy), if administered at high coverage levels, could significantly reduce the severity of HIV epidemics in countries in which the incidence of HIV infection is high, and that they could be valuable clinical and public health interventions [2, 3, 14, 16]. Even if people become infected after vaccination, the public health benefit provided by an HIV vaccine that decreases infectiousness and disease progression could be substantial. In fact, the widespread use of other vaccines, of which none have been 100% effective in preventing infection, has been among the most cost-effective public health interventions in history [17].

However, partially effective HIV vaccines pose a unique challenge because the dominant modes of HIV transmission are unprotected sexual intercourse and injection of drugs with the use of contaminated equipment. The potential exists for individuals to increase their HIV risk behavior as a result of being vaccinated and, therefore, to believe themselves to be protected against HIV infection. Since the availability of HAART, an analogous increase in HIV risk behavior has been reported among some men who have sex with men (MSM) [18, 19]. Thus, HIV vaccine–associated increases in risk behavior could paradoxically contribute to increased HIV transmission in a community [20].

**CURRENT AND PROPOSED CDC ACTIVITIES RELATED TO PARTIALLY EFFECTIVE HIV VACCINES**

In addition to developing, implementing, and evaluating other HIV prevention measures, the CDC is currently engaged in several areas of HIV vaccine development and evaluation. The consultation participants reviewed and made recommendations for both current and proposed efforts of the CDC in the following areas: (1) preparation for the implementation and integration of the use of HIV vaccines with other prevention programs, (2) development of mathematical and decision-analysis models for HIV vaccine use, (3) behavioral and community assessment, and (4) collaborative epidemiological and laboratory-applied research.

**Preparation for HIV vaccine implementation and integration with other prevention programs.** In view of the CDC’s role in the implementation of currently licensed vaccines, consultation participants proposed that the CDC, in conjunction with other agencies and institutions, play a lead role in planning and guiding the implementation of licensed HIV vaccines in the United States and, also, integrate the use of licensed HIV vaccines with other prevention efforts. The Advisory Committee on Immunization Practices (ACIP) has played a leading role in developing recommendations for the use of licensed vaccines in the United States and will play a similar role in the development of recommendations for the use of HIV vaccines. However, consultation participants recommended that the community provide enhanced input into the process of developing recommendations. These efforts should be coordinated jointly with those of the National Institutes of Health (NIH; Bethesda, MD), the FDA, and the National Vaccine Ad-
visory Committee. Participants at the consultation believed that the ACIP should establish a working group on HIV vaccines and that the CDC should task HIV prevention experts (1) to work closely with HIV vaccine experts in informing the ACIP working group, (2) to identify other stakeholders in the implementation of an HIV immunization program, and (3) to facilitate increased community input into the development of recommendations for HIV vaccines.

Given the current epidemiology of HIV in the United States, the strategy for an immunization program that uses an HIV vaccine of low to moderate efficacy may likely be directed toward persons at higher risk for HIV infection (e.g., MSM, injection drug users [IDUs], and heterosexuals at high risk for infection) and would need to be integrated into a comprehensive HIV prevention program. Adolescents, especially high-risk adolescents, are a key group toward whom HIV prevention efforts, including planning for implementation of HIV vaccines, should be directed. An HIV vaccine may be especially important for this group, some subgroups of which have reported high rates of risk behaviors and HIV incidence [21, 22]. Implementation of HIV vaccine programs that target adolescents will require (1) involvement of adolescents in vaccine research, including their participation in efficacy trials or in “bridging” studies once a vaccine is demonstrated to be effective in adults, and (2) development of successful programs to reach at-risk adolescents and offer them vaccination. The CDC and the NIH have active projects in HIV prevention research among adolescents, and the consultation participants emphasized the importance of expanding these projects to address issues related to vaccine research and implementation.

Immunization of adults often has not received as much attention from some members of the public and health care communities as has immunization of children. In addition, among high-risk minority populations, distrust of federal public health programs remains high because of the effects of the Tuskegee syphilis study and other previous programs [23]. Current funding and support for immunization of adults and adolescents in the United States are limited and are primarily available to elderly individuals (through Medicare) and to individuals covered by some private insurance plans or by occupational safety programs (e.g., hepatitis B vaccination for health care workers) [24]. Immunization programs for adults and adolescents in populations at high risk for HIV infection are even less well developed [25]. Limited pilot programs for immunization of high-risk populations (e.g., MSM, IDUs, and prisoners) with hepatitis B vaccines have achieved modest success [26–28]. Successful and sustainable implementation of an HIV immunization program will require (1) preparation of medical providers, the general community, and high-risk populations to create an environment favorable to immunization; (2) development of a medical infrastructure that can access and follow these varied high-risk populations; (3) expansion of comprehensive, ongoing prevention programs, for which vaccination would be one component of the prevention effort; and (4) establishment of funding mechanisms for vaccination of adults in populations of nonelderly individuals.

Consultation participants proposed that the CDC should do the following:

1. Begin to actively engage communities regarding HIV vaccine issues through community planning groups and other venues, by use of the CDC’s program infrastructure and prevention partners, such as nongovernmental organizations, state and territorial AIDS directors, and state and local health departments
2. Improve the environment for immunization of adults and adolescents by using the media to target medical providers and the public regarding adult immunization in general and HIV immunization in particular; this communication effort should be coordinated with other agencies
3. Accelerate the integration of biomedical HIV infection preventive and treatment interventions (such as antiretroviral therapy and, eventually, vaccines and microbicides) into prevention programming
4. Identify access points for high-risk populations, clarify barriers to successful immunization, and identify mechanisms to overcome these barriers, including appropriate incentives for providers and patients
5. Develop model programs for delivering vaccine to high-risk populations, building on the example and infrastructure of current pilot programs for hepatitis B immunization
6. Engage the private medical sector, through professional societies, to educate providers and develop partnerships for delivering immunization to adults and adolescents, including those at high risk for HIV infection
7. Support efforts to increase payment for delivery of immunization to adults and for related clinical testing
8. Support a national program to finance immunization of adults and adolescents
9. Conduct these activities with ethical vigilance, addressing such issues as distributive justice, beneficence, and respect for persons

The CDC has the responsibility for monitoring the programmatic implementation and effectiveness of vaccination and, in collaboration with the FDA, the safety of vaccines. For other vaccines, monitoring effectiveness depends on surveillance supplemented by surveys, investigations, and other special studies. Vaccine safety is monitored by national surveillance of adverse events through the Vaccine Adverse Event Reporting System, which is administered by the FDA and the CDC [29]. Vaccine safety is also monitored by enhanced surveillance stud-
ies that actively follow specific populations, such as the CDC’s Vaccine Safety Datalink project [30].

Immunization programs that deliver partially effective HIV vaccines to individuals in high-risk populations will pose challenges for traditional approaches to monitoring effectiveness and safety. Monitoring effectiveness will require innovative methods because current surveillance for HIV infections is limited, and because some HIV vaccines may have a limited effect on transmission. Although some HIV vaccines may effectively reduce disease progression, the number of AIDS cases will be an imperfect indicator because of the extended period from infection to disease and because of the effects of antiretroviral therapy. New approaches to measuring immunization coverage will be needed, given the targeting of the vaccine to high-risk adult populations. Challenges to monitoring safety include the limited representation of high-risk populations in current enhanced surveillance studies for adverse events.

Novel challenges for an HIV immunization program include monitoring increases in risk behavior and its impact on vaccine effectiveness, as well as monitoring potential social harms, such as those resulting from vaccine-induced HIV seropositivity. Participants believed that the CDC, in collaboration with the FDA, should play a prominent role in designing and implementing postlicensure studies to monitor vaccine effectiveness and safety and to monitor vaccine coverage in high-risk populations.

**Development of mathematical and decision-analysis models for HIV vaccine use.** Mathematical modeling of infectious disease epidemiology is especially useful for exploring the effects of parameters for which existing data may be incomplete or unavailable. A variety of approaches have been developed to model the potential impact of HIV vaccines by use of existing data from epidemiological studies [3, 14, 20].

On the basis of detailed studies of HIV-1 load and transmission probabilities in Africa, Gray et al. [31] presented models to assess the impact of preventive and therapeutic vaccines on transmission, given different assumptions of efficacy and coverage. Reductions in transmission resulted from the use of vaccines of even low to moderate efficacy. However, for vaccines of low to moderate efficacy, these effects could be blunted or lost if the risk behavior increased as a result of an unwarranted sense of protection among immunized individuals.

Consultation participants recommended that the CDC expand modeling activities related to HIV vaccines and that they coordinate with other agencies and academic institutions to share modeling approaches and definitions. Additional modeling needs include evaluation of measurements of end points and surrogate markers; identification of critical data needs to guide implementation; determination of optimal vaccine-use strategies, given ranges of anticipated efficacies in various populations; and estimation of cost-effectiveness and other resource measures of benefit.

**Social, behavioral, and community assessment.** The CDC became involved in HIV vaccine preparedness cohort development in the United States in 1992, after having conducted trials of hepatitis B vaccine and studies of HIV natural history and risk behaviors among MSM. The goals of the vaccine preparedness studies were to conduct prospective cohort studies that would assess incidence; identify predictors of HIV seroconversion; develop efficient methods of screening, enrolling, and following at-risk MSM; identify knowledge, attitudes, and beliefs regarding vaccines and research among potential target populations; and assess willingness to participate in HIV vaccine trials [32–37]. A qualitative study was conducted to inform strategies for enhancing community collaboration in HIV vaccine efficacy trials [23, 38]. Internationally, the CDC has been involved in HIV vaccine trial site planning and cohort development since the early 1990s, when the CDC, in collaboration with Thai public health officials, assessed the HIV-1 incidence rates and the willingness of IDUs in Bangkok, Thailand, to participate in vaccine trials [39, 40].

These activities led the CDC to collaborate in the North American phase III efficacy trial of AIDSVAX B/B and the Thai phase III efficacy trial of AIDSVAX B/E, as well as to conduct supplemental studies supporting these trials. These studies will identify the biomedical, ethical, and sociobehavioral factors that may be important for the design and conduct of future trials, including the potential for increases in risk behavior after participation in a vaccine trial [41].

Consultation participants advised that the CDC build on the knowledge gained from vaccine preparedness studies and efficacy trials and then design studies to assess the relevance of the results to actual vaccine programs. The CDC should also increase its efforts to engage at-risk communities, to ensure the ethical conduct of vaccine programs by maximizing beneficence across communities and by minimizing potential stigmatization associated with HIV vaccination. These efforts would complement the work of the NIH.

Consultation participants recognized the importance of ensuring that HIV vaccination programs include mandatory comprehensive risk reduction counseling while expanding access to the highest possible proportion of individuals at greatest risk for HIV infection. Participants recommended additional research to address this issue as well as appropriate communication related to HIV vaccines and the perceptions of the intended recipients of such messages.

**Collaborative epidemiological and applied laboratory research.** The availability of partially effective HIV vaccines will create public health issues requiring collaborative epidemiological and laboratory research. The need for improved HIV surveillance led to the development of serologic testing algorithms for detecting recent HIV seroconversion (STARHS); these methods have generated widespread interest for use in...
estimating incidence from both cross-sectional surveys and HIV surveillance [42, 43]. Participants recommended that the CDC continue its lead role in the evaluation and improvement of STARHS to help estimate incidence for trial design as well as for surveillance and vaccine implementation planning.

Other public health laboratory research needs include developing the capacities to distinguish true HIV infection from HIV vaccine–induced seropositivity and to characterize other immune responses among vaccine recipients. Many candidate HIV vaccines elicit antibodies that may be detected by standard serologic tests. A study conducted among gp120 subunit and live vector HIV vaccine construct recipients reported that 20% of recipients had reactions to ≥1 serologic screening test, and that vaccine-induced seropositivity increased with vaccine complexity [44]. Consultation participants recommended that the CDC continue to develop capacity in characterizing vaccine-induced immune responses and to lead in developing recommendations and capacity for differentiating immune responses elicited by HIV vaccination from true HIV infection. Consultation participants also recommended that the CDC should play a key role (in collaboration with vaccine trial site investigators) in the long-term follow-up of HIV vaccine trial participants to evaluate safety and the duration of immune responses and efficacy, as well as to measure different surrogate markers of HIV immune responses over time. The use of surrogate makers may be particularly important for bridging studies that use markers of immunogenicity in populations not included in efficacy trials and future trials of combination vaccines.

SUMMARY OF CONSULTATION PROPOSALS

I. The CDC should begin to develop the process by which recommendations for use of a partially effective HIV vaccine should be made
   A. The ACIP should establish a working group on HIV vaccines (established in July 2002)
   B. The CDC should do the following:
      1. Provide staff to work closely with the ACIP
      2. Identify other stakeholders
      3. Develop measures to increase community input into recommendations
      4. Expand modeling activities
         a. Share approaches and develop definitions with other institutions
         b. Evaluate cost-effectiveness and other resource measures of benefit for a range of contingencies
         c. Evaluate the use of various end points and surrogate markers of vaccine efficacy
   II. The CDC should prepare for the implementation and integration of HIV vaccines with other prevention programs and should then do the following:
      A. Engage communities through community planning groups and other venues by use of the CDC’s program infrastructure and prevention partners
      B. Develop and implement communications strategies that do the following:
         1. Promote hepatitis B vaccination and other adult immunization in preparation for future HIV immunization
         2. Inform medical providers, the general public, and high-risk groups
         3. Include an evaluation of effectiveness in intended target communities
         4. Coordinate with other federal and state agencies
      C. Address implementation of HIV vaccines with other biomedical HIV-preventive interventions into traditional prevention programming
      D. Study models for the delivery of risk reduction counseling to vaccine recipients
      E. Extend evaluation of vaccine-related behavioral issues to high-risk communities
      F. Ensure the ethical conduct of HIV vaccine programs by maximizing benefits, minimizing risks, and respecting the right of individuals to exercise autonomy
      G. Begin development of HIV immunization infrastructure and funding
         1. Identify access points for immunization of high-risk populations
            a. Clarify barriers
            b. Identify mechanisms to overcome these barriers
         2. Evaluate the potential impact of HIV and risk-reduction counseling requirements on immunization coverage among high-risk groups
         3. Develop model programs for delivering vaccine to high-risk populations
         4. Engage the medical societies to develop partnerships for delivering immunization to adults, including high-risk adults
         5. Support efforts to increase payment for immunization of adult and related services
         6. Support a national program to finance adult immunization
      H. Begin designing postlicensure studies and systems to monitor vaccine effectiveness, coverage, and safety in high-risk populations
      I. Develop and maintain high level laboratory support to address vaccine-related public health questions,
such as distinguishing vaccine-induced immune responses from true infection

CONSULTATION PARTICIPANTS

Invited participants included Guthrie S. Birkhead (New York State Department of Health, Albany, NY [represented the Council of State and Territorial Epidemiologists, or CSTE]), Donald Burke (Center for Immunization Research at the Johns Hopkins University, Baltimore, MD), Chris Collins (AIDS Vaccine Advocacy Coalition [AVAC], New York, NY), Don Des Jarlais (Edmond de Rothschild Chemical Dependency Institute, Beth Israel Medical Center, New York, NY), Maria Ekstrand (Center For AIDS Prevention Studies, AIDS Research Institute, University of California, San Francisco) Patricia Fast (International AIDS Vaccine Initiative, New York, NY), Bruce Gellin (Vanderbilt University School of Medicine, Nashville, TN [represented the National Network for Immunization Information]), Karen Goldenthal (FDA, Rockville, MD), Barney Graham (Vaccine Research Center, NIH, Bethesda, MD), Ronald H. Gray (Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD), Franklyn Judson (Denver Public Health Department, Denver, CO), Dale Lawrence (NIH), Myron Levin (University of Colorado School of Medicine, Denver [represented the ACIP]), Robert J. Levine (Yale University, New Haven, CT), Ira Longini (Emory University, Atlanta, GA), Mark Loveless (Oregon Health Division, Portland [represented the National Alliance of State and Territorial AIDS Directors, or NASTAD]), Carlos Molina (Body Positive, New York, NY), Douglas Owens (Stanford University, Stanford, CA), Philip Renzullo (Walter Reed Army Institute of Research, Rockville, MD), Liza Solomon (Maryland Department of Health and Mental Hygiene, Baltimore, MD [represented NASTAD]), Duncan Teague (Georgia State University, Atlanta), Sten Vermund (University of Alabama at Birmingham), Steve Wakefield (HIV Vaccine Trials Network, Seattle, WA), Judith Wasserheit (HIV Vaccine Trials Network), Joy Workman (Center for Community-Based Health Strategies, Academy for Educational Development, Washington, DC), and Joe Wright (community representative, Washington, DC).

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