

Cost effectiveness and delivery study for future HIV vaccines

WHO-UNAIDS collaborative group on cost-effectiveness, delivery and future access to HIV vaccines

Research teams from five countries, Brazil, China, Kenya, Peru and Thailand, have initiated a policy-maker survey on vaccine delivery, cost studies for future HIV vaccination programmes, and associated simulation modeling exercises analysing the relative cost-effectiveness of potential HIV vaccination strategies. The survey assesses challenges and opportunities for future country-level HIV vaccination strategies, providing data on the vaccine characteristics (e.g. vaccine efficacies for susceptibility, infectiousness and disease progression) and vaccination programme strategies to be considered in the cost-effectiveness modeling analyses. The study will provide decision-makers with modeling data on vaccination policy considerations that will assist in developing country-level capacities for future HIV vaccine policy adoption and effective delivery systems, and will help delineate the long-term financial requirements for sustainable HIV vaccination programmes. The WHO-UNAIDS HIV Vaccine Initiative and the collaborating researchers welcome comments or questions from policy makers, health professionals and other stakeholders in the public and private sectors about this effort to help advance policy and capacity related to future potential HIV vaccines.

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Introduction

The HIV/AIDS pandemic continues to spread at a soaring rate of 14 000 new infections per day, with 95% of these infections occurring in middle and low-income countries. The AIDS epidemic claimed more than 3 million lives in 2004, and an estimated 4.9 million people acquired HIV in 2004, bringing the number of people living with the virus up to 39.4 million globally [1].

Evidence from selected countries and communities shows that currently available HIV prevention programmes can control and even reduce the incidence of HIV infections [1,2]. Successes in population-wide HIV prevention often derive from major commitment and investment, sustained over time, for safer sexual and drug use

behaviors, access to condoms and safe injection equipment, and treatment for sexually transmitted infections, opportunistic infections, and HIV, including post-exposure prophylaxis to prevent mother-to-child transmission [3,4]. However, in most parts of the world to date, the commitment and investment in HIV prevention interventions has been insufficient to control the epidemic [5]. Country-level HIV prevention efforts will continue to be complicated by the factors often associated with HIV infection, including poverty, drug use and addiction, sexual behavior, gender, age and other factors contributing to a higher risk and vulnerability with regard to HIV infection.

The widespread delivery and accessibility of combination highly active antiretroviral therapies (HAART) against

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HIV have experienced a significant delay since efficacy was first demonstrated in the mid-1990s [6]. Many countries are only now initiating national HAART programmes, more than 8 years after HAART became a standard of care in high-income countries. The effective use of HAART has been shown to be feasible even in low-resource environments with limited infrastructure [7]. Much of the delay in access to HAART can therefore be attributed to a lack of adequate financing and advance planning, including the development of global and national-level cost-effectiveness studies and delivery plans. Recognizing this delay, and in order to speed global access to HAART, WHO and UNAIDS declared a 'global health emergency' in September 2003 to focus attention and resources on delivering life-prolonging medicines to people living with HIV/AIDS throughout the world. In December 2003, WHO unveiled an ambitious plan, the *HIV/AIDS 3 × 5 Strategic Framework To Address The Global ARV Treatment Gap* ('the '3 × 5' Initiative'). The goal of this initiative is to develop the infrastructure, coordination and technical ability to provide HIV treatment to 3 million people by 2005.

To augment the global campaign against HIV, major investments are being made to research and develop new HIV prevention technologies, including HIV vaccines, microbicides, and prophylactic treatments [8]. These technologies might have particular importance for communities and countries in which existing prevention efforts are not yet succeeding. Therefore, efforts are being made to develop and evaluate HIV vaccines and other new technologies for their potential safety and use in populations with a high HIV incidence.

The first two phase III efficacy trials of candidate HIV vaccines based on the outer envelope protein of HIV-1 (gp120) derived from the HIV-1 genetic subtype BB' (VaxGen's AIDSVAX vaccines) in the USA, Canada and the Netherlands, and subtypes E and B in Thailand did not demonstrate any significant level of efficacy in study populations [9,10].

A third phase III trial, using a prime-boost regime (a Canarypox-HIV vector prime followed by gp120/VaxGen boost), is now underway, recruiting 16 000 participants in Thailand, with results expected by 2007. Several other candidate HIV vaccines are in development possibly to enter phase III efficacy trials in 2005 and 2006 [11,12]. It is widely recognized that candidate vaccines could produce substantial public health and personal benefits, even with only moderate efficacy for preventing HIV infection. This is particularly the case if the vaccines can also be demonstrated to reduce HIV viremia dramatically, thus delaying disease and reducing transmission [13,14]. This more comprehensive conceptualization of key vaccine effects has led to recommendations that vaccine effects on susceptibility (VE_s), infectiousness

(VE_i), and progression (VE_p) should be estimated for HIV vaccines [15].

Even if effective HIV vaccines are developed for global use, the rapid delivery and accessibility of the vaccines are not ensured. Delivery will be affected by existing public health capacity to deliver vaccines and healthcare to specific populations. Global immunization has so far been targeted mainly at infants through the Expanded Program on Immunization with the exception of vaccines delivered in endemic situations such as influenza, yellow fever and meningococcal A and C. Therefore, little practical experience exists for how to deliver a vaccine to age groups other than infants [16,17]. The logistical and practical barriers against delivering a vaccine to new at-risk populations [such as to commercial sex workers (CSW), injection drug users (IDU), or to adolescents and adults who are marginalized and living in resource-poor settings] are significant and raise a number of questions about immunization services in the future [18]. Delivery will also depend on the opinions of policy-makers, healthcare providers, and populations at risk of HIV about the potential costs and benefits of immunization against HIV.

Moreover, most vaccines developed so far have been relatively inexpensive to produce in bulk once large economies of scale have been achieved, but this may not be the case for newly developed vaccines against HIV or other diseases. In addition, global demand for future HIV vaccines is likely to exceed supply during the first years after efficacy is initially demonstrated [18,19]. Policy-makers in many countries will most likely face limited funding and healthcare infrastructure for scaling up HIV vaccination programmes [20]. Given the populations at risk of HIV infection, future HIV vaccines might also require innovative use and expansion of current vaccine delivery systems and providers [21]. Anticipating these challenges through careful policy analysis is essential for the rapid effective delivery of future HIV vaccines, and may have benefit for other national and global policy efforts related to public health vaccines.

To avoid delayed or ineffective access to future potential HIV vaccines, WHO and UNAIDS have been advised to facilitate global and national-level policy work focused on the delivery and cost-effectiveness of future potential HIV vaccines [19]. This project has been initiated to complement other work related to global delivery and access to vaccines [22–25].

Methods

Research teams from five countries, Brazil, China, Kenya, Peru and Thailand, came together in 2003 to design and implement an international collaborative

project on public health perspectives for the future access and development of vaccination strategies with future HIV vaccines. The five countries represent a diversity of HIV epidemic experience. Each country team has broad research expertise and involvement in vaccine delivery, and each team has access to a wide range of governmental and non-governmental policy-makers and stakeholders.

The study is designed in three parts: (i) a survey on vaccine delivery to assess challenges and opportunities for country-level capacity to deliver potential future HIV vaccines; (ii) the collection of cost data associated with HIV vaccination and AIDS treatment; and (iii) a modeling exercise analysing the relative cost-effectiveness of potential HIV vaccination strategies. The combined study results will provide decision-makers with data and modeling analyses on vaccination strategies, and illuminate policy choices that will assist in developing country-level capacities for future HIV vaccine delivery in association with other HIV programme activities.

The study assumes that no future HIV vaccine candidate would be considered for global delivery unless it has a certain level of efficacy, has minimal side-effects or adverse events, and is safe for the intended populations. It is also assumed that similar vaccine efficacies will hold for various HIV subtypes and in all the at-risk subpopulations being considered for vaccination.

Part A: Assessing challenges and opportunities for HIV vaccine delivery capacity

The delivery survey questionnaire for the WHO-UNAIDS HVI-sponsored collaborative project was constructed to collect and map the priority challenges, opportunities and recommendations as described by key decision-makers and stakeholders in the five countries of Brazil, China, Kenya, Peru and Thailand. A structured, mostly closed-ended 30-question survey was developed in English, reviewed and pre-tested, and then translated into local languages for use in all five countries. Before and after pilot testing in each country, the survey questionnaire was back-translated into English and compared across countries to ensure common terminology and the meaning of all questions and responses.

Researchers in each country have piloted the survey, and are now implementing it among the following key informants: high-level government health officials; other government leaders and policy-makers; practitioners and others who implement vaccination programmes and other health promotion efforts; and community leaders, non-governmental organizationi representatives, and individuals from populations at high risk of HIV infection and in need of potential future HIV vaccines.

In most cases, the presentations and surveys are administered in a group 'workshop' setting, involving a maximum of 10 key informants in each group workshop.

In selected cases, the presentations and surveys are administered to individual key informants (when group workshops were not feasible). In both the groups and the individual survey sessions, key informants hear a standard educational PowerPoint presentation, have an opportunity to ask questions and hear clarifications about the presentation, and then are asked to complete the self-administered questionnaire.

By asking national leaders and community stakeholders about the potential delivery of future HIV vaccines, the study is specifically focusing on recommendations and the perceived relative importance of factors such as: the relative importance of general understanding by policy-makers and the public about basic concepts of HIV, HIV prevention, vaccines, and public health, given the sizes and susceptibilities of various subpopulations (CSW, IDU, etc.) at risk of HIV and the relative importance of those subpopulations for future HIV immunization; the relative importance of a country's ability to develop national policies and plans for immunization; the relative country-level capacity to achieve high immunization rates among subpopulations at risk of HIV through a variety of delivery systems (such as fixed sites or mobile outreach) and public and private providers; the relative importance of the level of stigma associated with HIV, HIV risk, and HIV immunization, the level of trust in public health vaccines and other interventions, and the effect of this stigma and trust on political support for HIV vaccine campaigns and on the targeting and use of HIV vaccines; the relative importance of projected vaccine effects in lowering vaccinee susceptibility to HIV infection (VE_S), in lowering the subsequent infectivity of those infected despite immunization (VE_I), and in slowing progression to AIDS in those infected despite immunization (VE_P); the maximum acceptable number of vaccine doses and boosters to achieve and maintain vaccine effects; the minimum quantity of vaccine that should be available before launching vaccine introduction; the maximum acceptable price of vaccine and cost of vaccine delivery; and the relative importance of the availability of national and international funding to cover this cost.

The survey instrument can be made available to interested researchers and policy-makers. All survey questionnaire data are now in the process of being collected and data

Table 1. WHO-UNAIDS HIV Vaccine Initiative: HIV Vaccine Delivery Survey status and timeline.

Country	Sample size of key informants and timeline
Brazil	100 KI to be interviewed November 2004 to April 2005
China	300 KI to be interviewed February 2005 to April 2005
Kenya	177 KI interviewed as of November 2004
Peru	100 KI to be interviewed January 2005 to April 2005
Thailand	144 KI interviewed as of November 2004

KI, Key informants.

processed in each country, with a national and globally centralized process for quality control and ensuring a uniformly coded dataset. The timeline and size of the five country studies are summarized in Table 1.

Part B: Collection of cost-effectiveness data for future HIV vaccination programmes

National governments and multilateral agencies must consider limited resources in selecting strategies to address HIV/AIDS and other health priorities, as well as different activities with the national HIV programmes. Cost-effectiveness analysis is a standard tool for guiding national and global public health policies and resource allocation. Systematic and comparative calculations of potential costs and resulting effects provide direction about the optimal use of limited resources.

Researchers in each of the five countries are now collecting AIDS treatment cost data and they are setting up different hypothesis for the costs of HIV vaccine delivery. The costs of AIDS treatment will largely be based on data already available. For HIV vaccine delivery, it is assumed that the cost will be comparable to that of other health service interventions, with some specific and measurable cost differences. The method for cost data analysis thus combines 'cost ingredient' calculations, such as specific personnel, supply and equipment unit costs and quantities, with cost extrapolations based on known data from other health service delivery cost research. Key indicators of the cost analysis include the size of different target groups, total costs of the HIV vaccination programme for different target groups and average costs per fully immunized individual.

Part C: Modeling cost-effectiveness of future HIV vaccine strategies

A number of mathematical models have been developed to shed light on potential strategies for future HIV/AIDS vaccines [26–30]. HIV VaccSim is a user-friendly computer simulation application designed to allow public health policy-makers and planners to investigate optimal vaccination programme strategies for HIV vaccines in various epidemic scenarios [31,32]. The HIV VaccSim model has been expanded to support modeling of the cost-effectiveness of various HIV vaccination strategies in the countries participating in this study. The HIV VaccSim model incorporates parameters that allow users to explore various hypothetical vaccine and vaccination programme characteristics including: vaccine effects lowering vaccinee susceptibility to HIV infection (VE_S); vaccine effects lowering the subsequent infectiousness from those infected despite immunization (VE_I); vaccine effects reducing progression to symptomatic AIDS of those infected despite immunization (VE_P); waning rates of VE_S , thereby creating requirements for boosters to maintain vaccine effects; specifiable quantities of vaccine availability during the vaccination programme; specifiable prices of vaccine and costs of

vaccine delivery; various subpopulation risk groups (e.g. CSW, IDU) with specifiable subpopulation sizes and susceptibilities (as determined by their contact rates and patterns, and transmission probabilities); a multistage representation of HIV/AIDS infection that supports the accurate depiction of variable infectivity and treatment costs associated with the stage of HIV infection; and specifiable levels of HIV vaccine acceptance over time among the at-risk subpopulations.

The HIV VaccSim model will be used to integrate the demographic, epidemic surveillance, policy-maker survey, and cost data in the cost-effectiveness analyses of potential HIV vaccination strategies in the participant countries. The HIV VaccSim model calculates several important economic and epidemiological outcomes over time, including total numbers of HIV infections, AIDS cases, and AIDS deaths prevented, and can provide these outcomes in terms of events prevented per vaccination course delivered or per vaccination programme resource costs expended in dollars (or local currencies).

By simultaneously running parallel models with and without hypothetical vaccination programmes, the number of HIV infections and AIDS deaths averted by the HIV vaccine programme can be estimated and the relative cost-effectiveness can be calculated at varying levels of vaccine price and delivery cost. Conducting cost-effectiveness analyses with such modeling methods is imperative, because the use of dynamic epidemic models allows policy makers to assess the potentially profound impacts of herd immunity [31,33]. As is the case for other infectious diseases, the indirect protection from HIV infection afforded to individuals who do not receive the preventative intervention (e.g. vaccination) but who are nonetheless protected by the intervention can be dramatic. In many cases, the indirect protection may far exceed the direct protection provided by the intervention, and health economic evaluations that fail to consider these effects have been demonstrated almost always to underestimate the true cost effectiveness of the intervention [34].

Country-specific validation, uncertainty and sensitivity analyses will be conducted as part of the cost-effectiveness analyses. Validation analyses use HIV epidemic surveillance data from the participating countries to ensure that the simulation parameters and model configurations selected can reproduce the antecedent HIV/AIDS epidemics in the country [35]. The validation process for the epidemics includes the consideration of the quality of the reporting information, potential biases and the precision of the estimates available. This information is synthesized to determine plausible ranges of longitudinal prevalence levels and incidence rates for HIV infections, AIDS cases and AIDS deaths for each country. The simulation model is then

used to restrict the parameter space that will be further explored in the uncertainty, sensitivity and optimization analyses. Only parameter sets producing results that are compatible with the antecedent epidemic data are retained for further analyses.

Because many of the input parameters for the simulation model will be imprecisely known and many combinations of these parameters will be capable of reproducing the antecedent HIV/AIDS epidemics in the scenario countries, it will be important to evaluate the effect of this uncertainty on the policy optimization analyses and the associated conclusions. Uncertainty and sensitivity analyses examine the variability in the objective functions and policy optimization results that occur because of the uncertainty in the input simulation parameters. This is accomplished by use of the Latin Hypercube Sampling method [36]. This method has been used frequently for policy evaluations using epidemiological models, providing some assurance regarding the generalizability of the policy recommendations in spite of the uncertainty in the model parameters [31,32,36,37]. Sensitivity analyses are used to examine the relationships of the input parameters and the outcome variables produced in the simulations. Such analyses identify those input parameters that have large effects on the objective functions and optimal distributions. These analyses help policy-makers in evaluating policy recommendations by clarifying the implications that uncertainties in the different parameter value assumptions have for vaccination programme recommendations [31,32]. When clearly superior strategies can not be determined because of uncertainty in the model parameters, such sensitivity analyses will help to identify future epidemiological and behavioral research critical for distinguishing the superiority of competing vaccination strategies.

Discussion and next steps

Based on progress and preliminary results from this study, the WHO-UNAIDS HIV Vaccine Initiative believes that a resource tool will be developed that would assist policy makers in making evidence-based decisions on future potential HIV vaccine immunization strategies, taking into consideration country-specific costs and HIV epidemiology in the context of other ongoing HIV/AIDS prevention, treatment and care strategies. In addition, there is a need for a long-term forecast of financial requirements to sustain the HIV vaccination programme.

The WHO-UNAIDS HIV Vaccine Initiative plans to make this resource available to the broadest possible range of stakeholders in the public and private sectors to help advance policy and capacity related to future potential HIV vaccines. Guidelines and user-friendly tools will be

developed to enable policy makers and health professionals easily to assess their own national capacity to deliver future HIV vaccines, the cost-effectiveness of an HIV vaccine in any given country, to project total resource requirements of a hypothetical HIV vaccination programme, and to identify resource gaps and potential actions to be taken now. The WHO-UNAIDS HIV Vaccine Initiative and the collaborating researchers in this endeavor welcome any comments or questions.

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