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Forecasting the Global Demand for Preventive HIV Vaccines

IAVI Public Policy Department

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Publications Unit
International AIDS Vaccine Initiative
110 William Street, 27th Floor
New York, NY 10038 USA
Tel: + 1.212.847.1111
Fax: + 1.212. 847.1112
Email: pubs@iavi.org
Web: www.iavi.org

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IAVI's mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world.

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Forecasting the Global Demand for Preventive HIV Vaccines

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IAVI's Policy Research Working Paper series disseminates the findings of works in progress to promote the exchange of ideas about the effective development and global distribution of vaccines to prevent HIV infection.

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ACRONYMS & ABBREVIATIONS

AFRO	African Regional Office (World Health Organization)
AIDS	Acquired immunodeficiency syndrome
AMC	Advance market commitment
AMRO	Regional Office for the Americas (World Health Organization)
API	AIDS program effort index
CAGR	Compound annual growth rate
EMEA	European Medicines Agency
EMRO	Eastern Mediterranean Regional Office (World Health Organization)
EPI	(WHO-UNICEF's) Expanded Programme on Immunizations
EURO	European Regional Office (World Health Organization)
FDA	U.S. Food and Drug Administration
FSW	Female sex worker
GDP	Gross domestic product
GFATM	Global Fund to fight AIDS, TB and Malaria
GNI	Gross national income
HBV	Hepatitis B vaccine
HPV	Human papillomavirus
HIV	Human immunodeficiency virus
IAVI	International AIDS Vaccine Initiative
IDU	Injecting drug user
MMR	Measles, mumps, and rubella
MSM	Men who have sex with men
NGO	Nongovernmental organization
NPT	New preventive technology
NRA	National regulatory authority
OECD	Organisation for Economic Co-operation and Development
PrEP	Pre-exposure prophylaxis
PPP	Purchasing power parity
R&D	Research and development
SAGE	Strategic Advisory Group of Experts (World Health Organization)
SEARO	South East Asia Regional Office (World Health Organization)
STI	Sexually transmitted infection
SW	Sex worker
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
USD	United States dollars
VE_I	Vaccine effect on infectiousness
VE_P	Vaccine effect on disease progression
VE_S	Vaccine effect on susceptibility
WHO	World Health Organization
WPRO	Western Pacific Regional Office (World Health Organization)
WTP	Willingness to pay
WTV	Willingness to be vaccinated

EXECUTIVE SUMMARY

"Demand Forecasting refers to a process rather than a specific number" *(Longhi et al. 2006)*.

At of the end of 2005, approximately 40 million people worldwide were living with HIV/AIDS, most of them adults, 95% of them in developing countries. Although prevention programs have been implemented in many countries and have lowered the rate of new infections, more than 13,000 people became infected with HIV every day in 2005 (UNAIDS 2006), and about 3 million died of AIDS during that year. Hence there is an urgent need for stronger and more effective HIV prevention. New technologies are required to augment existing prevention efforts. An HIV vaccine could help reverse the pandemic and consequently save tens of millions of lives (IAVI 2005a; IAVI 2006). But to do so, it needs to be widely available and accessible and must be adopted and implemented quickly in the countries most affected. Long-term strategic demand forecasts are a valuable decision-making tool that can identify policy actions to help achieve these goals.

In this regard, the International AIDS Vaccine Initiative (IAVI) has conducted research to create a forecasting model for a preventive HIV vaccine. This work began with a review of previous academic and industry approaches to forecasting to explore their strengths and limitations and identify the key determinants of demand (IAVI 2005b). The review found that previous global HIV vaccine demand forecasts overlooked or only partially addressed a number of issues such as the effect on demand of vaccine characteristics, price, and vaccination strategies. More research was needed to address these shortcomings.

IAVI thus consulted with 80 expert stakeholders worldwide, including government policymakers, NGO personnel, pharmaceutical executives, academics, and vaccine researchers. IAVI sought the perceptions and preferences of these stakeholders with respect to the range of potential characteristics of a first-generation HIV vaccine, the current state and future course of the epidemic, vaccine adoption decisions, system capacity and funding constraints, the national vaccination strategies that might be employed, and the ability of these strategies to reach and cover target recipient populations.

The results from these consultations suggest that:

- HIV vaccines may need to be at least 50% effective before governments will initiate vaccination in the general population in countries with widespread ("generalized") epidemics, while efficacy may need to reach at least 70% to persuade officials to vaccinate the general adult population in countries where the epidemic is still focused in small pockets ("concentrated") epidemics.
- For use in populations at higher risk such as sex workers and their regular partners and injecting drug users, 30% may be an acceptable efficacy threshold for countries with generalized AIDS epidemics to endorse vaccine use, while 30% to 50% efficacy may be sufficient to convince officials to organize targeted vaccination campaigns in countries with concentrated epidemics.

The demand forecasts that were modeled upon the findings above indicate that, for a number of different scenarios:

- Average global annual demand for a first-generation preventive HIV vaccine could range between 28 and 142 million courses over a 30-year period, and demand could peak at between 38 and 152 million courses some seven to ten years after vaccine launch. (NB: One course is assumed to equal two doses in a prime-boost dosing regimen, key vaccine characteristics were varied: efficacy between 30% and 90%, duration from three to five years, and tiered pricing between US$2 and $100 per dose.
- These levels of demand could result in undiscounted global sales revenues of US$1.6 to $3.8 billion per year over a 30-year period, and up to US$2.5 to $5.5 billion in undiscounted peak annual revenues which would represent 5% to 13% of the total global vaccine market at that time. These revenues would come from sales in both developed and developing country markets.
- The 47 poorest (GAVI-eligible) countries might account for between 19% and 42% of total global demand by volume but only 4% to 9% of revenues; while the 47 wealthiest high-income (OECD) countries could absorb between 20% and 28% of total global demand but generate 64% to 72% of revenues. The remaining 97 low- and middle-income non-GAVI eligible countries were estimated to contain between 35% and 60% of demand by volume and account for 24% to 30% of revenues.
- Public markets might account for as much as three-quarters of global revenues if a high-quality vaccine candidate (with high levels of efficacy, duration, and other critical features) is developed and implemented. For low-quality HIV vaccine candidates, public demand is predicted to fall dramatically, with private markets accounting for up to 93% of revenues. Because of the higher prices paid for an HIV vaccine by private purchasers, the share of the private market in global revenues is expected to be disproportionately higher than its share of global volumes of vaccine demanded. For a high quality vaccine, private markets are estimated to account for a mere 6% of worldwide volume, and even for a lower quality vaccine, private markets are expected to make up 43% of the global total demanded.

These modeling projections have several important policy implications:

- Even partially effective preventive HIV vaccines may have considerable commercial potential because there could be a significant market for such a vaccine in affluent countries. Large volumes of demand in developing countries could also generate substantial revenues. Under these circumstances, it is unclear whether a pull mechanism such as an advance market commitment (AMC) would be needed or how large such mechanisms might need to be especially if significant vaccine demand materializes in high- and middle-income countries. The modeling presented here, however, assumes tiered pricing at between US$2 and $10 per dose for public sector markets in low-income countries. The upper end of this range is significantly higher than the prices for current GAVI-funded vaccines in these countries, so there may be a need for external subsidies to the poorest nations with high levels of HIV infection, in the form of AMC payments or GAVI purchase funding.

- Since expected demand is sensitive to vaccine characteristics and especially efficacy, investments in scientific innovations that can generate high-quality candidates could have a very large positive impact on future levels of demand. If the HIV vaccines currently being tested in large efficacy trials fall below the efficacy and duration thresholds mentioned above, considerable research and development (R&D) efforts will be needed to enhance these vaccines or develop novel approaches that work better. In either case, R&D policies including new incentive mechanisms to stimulate further scientific innovation could play a pivotal role.
- Demand for an HIV vaccine is not fixed or static – developing and developed country governments, international organizations, and AIDS advocates can do much to boost demand for, and access to a future HIV vaccine through a series of policy actions which are explored in this paper. Modeling indicates that governments might increase their uptake of an HIV vaccine by 40 million additional courses a year over a 30-year period, as compared with baseline projections, by: strengthening national regulatory systems, expanding health care infrastructure and programs to reach adolescents and vulnerable groups, and marshaling the political will and support to actively promote an HIV vaccine among their own citizens.

A caveat: the forecasting model used to generate these results is limited by available data and inherent uncertainty about the future. However, it can provide a framework for a longer-term dynamic forecasting process, as better data become available and assumptions are improved. Over time, lessons learned from the introduction of other new vaccines coming to market [e.g., human papillomavirus (HPV) vaccines] and the introduction of other new preventive technologies (e.g., male circumcision) may also improve our understanding of issues that must be addressed for widespread and rapid implementation of an HIV vaccine.

IAVI welcomes the opportunity to make this model and results available to interested stakeholders from developing countries, the biopharmaceutical sector, the private investment community, donors, and other multilateral groups/institutions [e.g., GAVI, WHO's Strategic Advisory Group of Experts (SAGE), WHO-UNAIDS HIV Vaccine Initiative, etc.].

An HIV vaccine is likely to take several more years to develop. However, given the long lead times involved in building demand, it is important to start addressing the policy environment now to maximize future demand and access. Such policy dialogue and action will help ensure the development of and eventual access to safe, effective, accessible, preventive HIV vaccines for use throughout the world.

1 INTRODUCTION

1.1 Background

Demand has historically been estimated for products that are close to or already on the market. However, assessing the demand for products still in an early phase of research and development (R&D) such as a preventive HIV vaccine is important because it can:

- Provide product developers with credible estimates of future market potential;
- Assist developers further along in the development process with R&D portfolio management decisions, decisions about financing raw materials and intermediate products, and capital investment decisions in new production facilities when rapid scale-up is required. Simply projecting health or product needs is insufficient to encourage this type of investment;
- Help donors design R&D incentives that include realistic market scenarios; and
- Provide information to health program officials to prepare delivery infrastructure for future vaccines well in advance of their introduction.

Demand assessments for early phase products are known as *long-term strategic forecasts* (Sekhri 2006). These forecasts are based on a set of early assumptions about product characteristics and are characterized by a long (10 to 30 years) time horizon.

Given the inherent uncertainty about the future, long-term strategic forecasts are designed to be flexible to changes in underlying assumptions. Such dynamic models are used to explore the effect on demand of different future scenarios, as defined by demographics, epidemiology, infrastructural and financial capacity and the associated policy environment, among other factors.

1.2 Previous Demand Research Associated with HIV Vaccines and Challenges to Conducting New Research

1.2.1 Previous Demand Research

The International AIDS Vaccine Initiative (IAVI) conducted a review of previous academic and industrial approaches to forecasting to explore the strengths and limitations of these studies and to identify the key determinants that influence demand (IAVI 2005b). We found that, until now, preventive HIV vaccine demand research has been:

- Based on product profiles (i.e., anticipated efficacy, mode of action, duration, etc.) that do not reflect current scientific opinion about the most likely profiles of the first-generation HIV vaccines in the R&D pipeline;
- Focused on global public sector demand or public sector demand in developing countries exclusively; and

- Limited in its consideration of how demand will vary over time from country to country, with respect to such factors as the extent and the nature of the epidemic, levels of political will, health care system capacity and effectiveness, and variability in vaccination strategies (Esparza 1993; Bishai et al. 2000; Esparza et al. 2003; IAVI 2005c; Shaffer et al. 2006).

Previous research suggested that developing a dynamic long-term strategic forecasting model for HIV vaccines would be challenging because of uncertainties about the vaccine's characteristics, who might use the vaccine, and how it might be implemented by the public sector.

1.2.2 Forecasting Challenges Related to Vaccine Characteristics

The likely characteristics of a first-generation HIV vaccine have a level of uncertainty and complexity that make demand forecasting difficult because they could reduce the vaccine's acceptability to both governments and individuals. A first-generation preventive HIV vaccine is likely to:

- Be only partially effective;
- Affect disease progression, infectiousness, and susceptibility to infection;
- Have a limited duration of protection; and
- Be expensive relative to the traditional vaccines currently delivered through the World Health Organization (WHO) - United Nations Children's Fund (UNICEF)'s Expanded Programme on Immunizations (EPI).

Understanding how the trade-offs between these characteristics affect government and individual preferences is therefore necessary to generate more realistic demand forecasts for an HIV vaccine.

1.2.3 Forecasting Challenges Related to Recipient Populations

Unlike most existing vaccines, which are targeted to children, an HIV vaccine will probably be recommended, at least initially, only for adolescents and adults. Moreover, in some instances, governments may achieve most of the benefit from HIV vaccination by targeting vulnerable populations at highest risk of exposure to HIV, such as sex workers (SW) and injecting drug users (IDU). Uncertainty remains however regarding the population subgroups that governments will actually want to target. Finally, it is unclear how likely the various target groups (adolescents, adults, and vulnerable and marginalized groups) are to agree to vaccination.

To generate the best possible forecasts, it is important to understand government preferences for targeting sub-populations, the underlying determinants of these targeting strategies, and the likely effectiveness (in terms of reach) of such strategies.

1.2.4 Forecasting Challenges Related to Vaccination Strategy

Together, the vaccine's characteristics and the intended recipient populations are likely to necessitate the development of vaccination strategies different from those currently used by the EPI.

Vaccination "catch-up" strategies for those who miss or are not eligible for routine annual programs may be necessary in many countries. Such broad vaccination strategies may be the most effective way to halt the progress of the epidemic, particularly in high-prevalence areas. In addition, if the vaccine's protection is of limited duration, regular revaccinations may be necessary to maintain levels of protection. Predicting how quickly such strategies can be implemented worldwide and estimating how effective they will be in reaching the intended recipents is difficult but necessary to generate forecasts for an HIV vaccine.

1.3 Research Overview and Scope

IAVI has undertaken policy research to identify the key determinants of demand for an HIV vaccine and to create a framework to conceptualize how these determinants affect demand. To understand how countries in developed and developing settings might adopt and implement a first-generation preventive HIV vaccine, we interviewed around 80 experts to assess the preferences and perceptions of those who make and influence policy (see Appendix I, pg. 42). We synthesized the interview findings along with published data to construct a forecasting model capable of creating HIV vaccine demand and revenues scenarios that could reflect the diverse market conditions in each country and across the world.

We did not attempt to address the following issues:

- Second-generation "follow-on" HIV vaccines, associated competitive dynamics, and the impact on market demand over time;
- The therapeutic use of an HIV vaccine designed, tested, and licensed for preventive use;
- The effect of other new preventive technologies (NPTs) such as microbicides, pre-exposure prophylaxis (PrEP), and herpes simplex virus suppression therapies on HIV vaccine demand, even though these other NPTs may be widely available by the time an HIV vaccine is launched; and
- The social, epidemiological, and financial impacts of HIV vaccine introduction.

2 METHODS

2.1 Demand Determinants and Methodological Framework

Key determinants or drivers of demand (Table 1) were identified after a review of prior studies (IAVIb 2005) and discussion with researchers. These determinants were incorporated into a methodological framework (Figure 1, pg. 10) that informed the structure of the forecasting model. The framework was based upon the notion that the determinants act as constraining factors that limit final demand to some fraction of the total population in need.

Table 1. Key determinants of demand

KEY DETERMINANT	DESCRIPTION
Need	Population requiring the intervention (e.g., not already infected, at most risk, etc.)
Vaccine characteristics	Product profile
Political will	Policymaker support
Capacity	Health care system capacity and effectiveness
Funding	Government (and donor) funding to pay for public sector vaccine demand, or private individuals' willingness to pay (WTP) for the vaccine
Acceptability	Individuals' beliefs and attitudes - their willingness to be vaccinated (WTV)
Targeting	The intended recipient population(s) for the public sector vaccination program(s)

The *need* for an HIV vaccine depends upon the national epidemiological and demographic situation. Need is described by incidence, prevalence, and disease burden in a country. Countries with higher prevalence, large disease burdens, and growing epidemics are those with the greatest need for a preventive HIV vaccine.

The *vaccine's characteristics* determine how well, for how long, and in which population subgroups the vaccine will work; how easy it will be to transport, store, and administer; and what it costs. These factors are important to policymakers because they influence the social benefit and risks as well as the cost of vaccinating a population. Such information often guides public sector decisions about whether to use the vaccine, and if it is to be used, for whom.

Political will plays an important role in prioritizing and implementing public health initiatives and therefore is a crucial determinant of demand. Among other things, a lack of political will can impede the licensure process of a vaccine, prevent rapid adoption and incorporation of vaccines into national public health initiatives, and limit funding for purchasing vaccines or financing delivery costs.

Capacity refers to the availability of resources (monetary or otherwise) for use in the health care system to introduce public health programs (e.g., vaccination campaigns) and deliver health technologies such as an HIV vaccine. Capacity determines the availability and ease of access to an HIV vaccine via public markets. From the introduction of other health care interventions, we

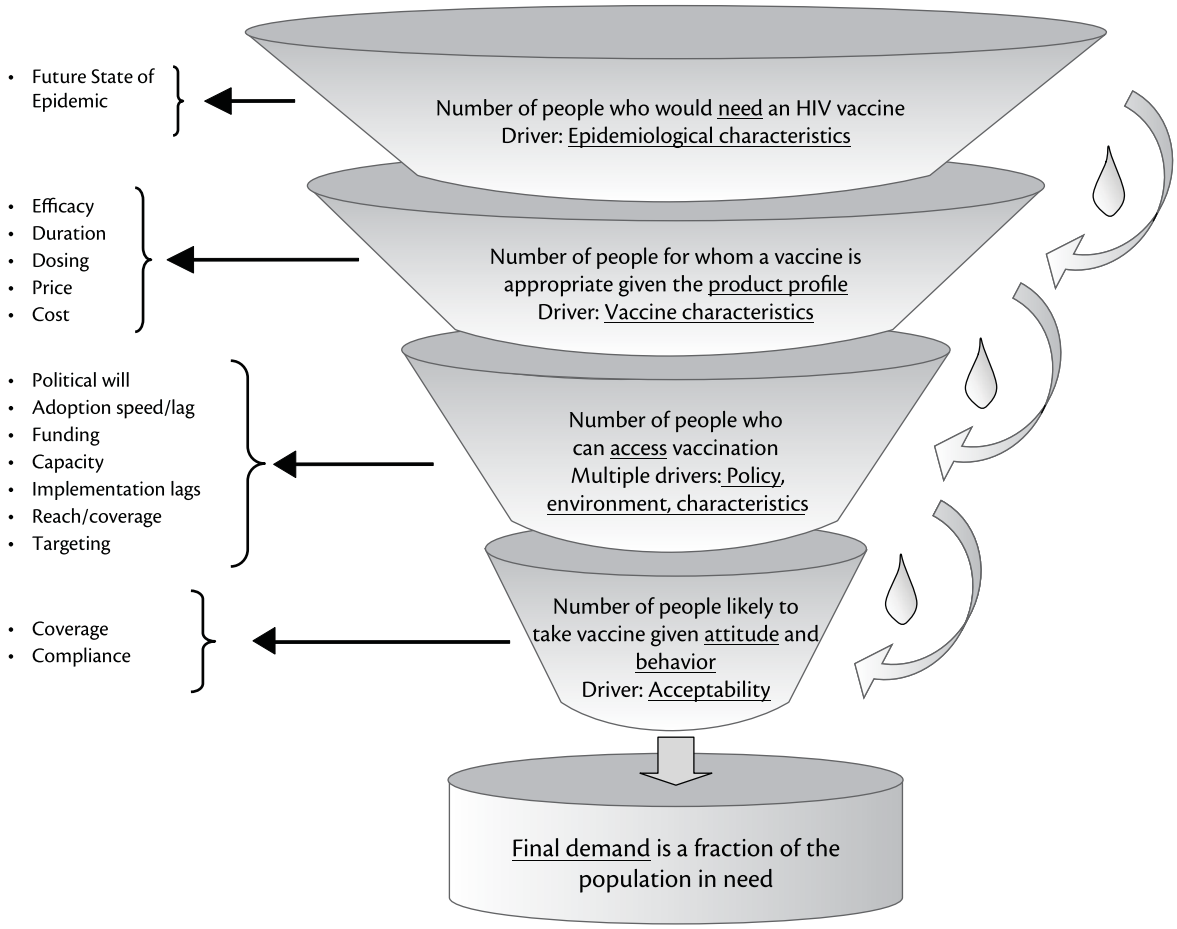
know that capacity constraints can cause some countries to receive vaccinations years later than countries in other parts of the world.

Funding from national governments or from international donors is essential to guarantee that desired levels of demand in public markets can be financed, especially in low- and middle-income countries. Funding constraints can affect the extent to which a public health care intervention is available and accessible. In privately funded markets, funding constraints are described by individuals' WTP.

Individuals' beliefs and attitudes play a large part in determining a vaccine's *acceptability*. Acceptability to individuals and wider society is an important determinant of utilization. Unless people are *willing to be vaccinated* (WTV), potential demand will not translate into actual utilization. A lack of acceptance may impede voluntary vaccination (resulting in lower *coverage*) or limit completion of a full multi-dose vaccine course (resulting in lower *compliance*).

The *targeting* and *vaccination strategy* employed by policymakers identifies the intended recipient population(s) for the vaccine and how these populations are reached. These will be based on policymakers' perceptions of the extent of the epidemic in a specific country and surrounding region, as well as preferences about the vaccine's profile (efficacy, safety, duration, price, etc.)

Figure 1. Methodological demand framework, from need to projected demand



2.2 Model Overview

IAVI created a model to estimate global demand based upon the aforementioned key determinants of demand and findings from the expert consultation. This model aims to reflect how each country might respond to the availability of an HIV vaccine. It therefore provides both a global and national picture of HIV vaccine demand, with outputs defined according to whether demand originates in public or private markets.

Assessing public and private demand is important because these markets respond differently to the determinants of demand. The timing, volume, and value of demand from each market may differ significantly and should be viewed separately.

Public market demand is described by two programs: (1) the high-risk population program, and (2) the low-risk population program. The private market is viewed as a single program. The contribution to demand by each of the programs is determined by three types of information: vaccine profile descriptors, country profile descriptors, and country-level behavioral parameters.

The model allows users to change the values for the descriptors and the parameters. Its flexibility enables users to explore the effects of changing the assumptions, the underlying data, and the predictive algorithms of the model. The basic assumptions and inputs presented in the following subsections are based upon a mixture of the preferences elicited in expert interviews as well as published data. See Appendix I for a comprehensive list of experts whom were consulted as part of this study.

2.2.1 Vaccine Profile Descriptors

Three key vaccine characteristics have been identified: efficacy, duration of protection, and cost (vaccine plus delivery costs). Different combinations of these characteristics were used to produce four vaccine profile scenarios (Table 2, pg. 12). These scenarios — Low, Baseline, Optimistic Baseline, and High — were assembled to represent the broad array of product profile characteristics for a likely first-generation preventive HIV vaccine.

In the Low Vaccine Profile Scenario (hereafter the Low scenario), we assume that the vaccine has a 30% level of efficacy, which vaccine experts regard as the lowest level that might be acceptable to regulators, and a duration of protection of three years. In the Baseline scenario, the efficacy is assumed to be 50%. In the Optimistic Baseline Senerio, the efficiacy is assumed to be 70%. In the High scenario, we assume that efficacy is 90% and the duration of protection is five years.

These vaccine profile scenario assumptions represent realistic and achievable but also aspirational goals. The ranges of efficacy and duration are certainly in line with current scientific expectations, although there is little certainty about the dosing regimen or the delivery and storage requirements. Ideally, the vaccine would require as few doses as possible and be stable at room temperature. However, scientific thinking suggests that first-generation HIV vaccines will require a prime plus boost combination (i.e., at least two doses). Many vaccines also require some sort of refrigeration.

Table 2. Efficacy and duration of protection, by scenario

		VACCINE PROFILE SCENARIOS			
		LOW	BASELINE	OPTIMISTIC BASELINE	HIGH
VACCINE EFFICACY[A]		30%	50%	70%	90%
DURATION OF PROTECTION		3 years	3 years	5 years	5 years
PRICE[B] PER DOSE	PRIVATE MARKET	US$10 - $100/dose			= to country government's maximum WTPs
	PUBLIC MARKET	US$2 - $50 /dose			
DOSING SCHEDULE (FOR A FULL VACCINATION COURSE)		2-dose prime-boost combination			
DELIVERY/ STORAGE REQUIREMENTS (upon which delivery costs are loosely based)		Single vial/cold chain of 2-8°C			
DELIVERY COST PER DOSE	PRIVATE MARKET	US$0.01 /dose			
	PUBLIC MARKET: HIGH RISK	US$3.00 /dose			
	PUBLIC MARKET: LOW RISK	US$2.00 /dose			

[A] The vaccine efficacy is assumed not to be clade-specific (i.e., the vaccine is effective against all strains/subtypes).
[B] Price dependent upon country's income classification (see Table 3 below).

In each of these scenarios (except the High scenario), it is assumed that the public and private market prices are tiered, varying according to the level of national income in each country (Table 3). The High scenario assumes that pricing is also tiered, but in this scenario, prices are set to each country's minimum acceptable price. This has the effect of removing any price constraint. Therefore, in the High scenario, the decision to adopt is based solely on vaccine efficacy and duration.

Table 3: Tiered pricing assumptions

COUNTRY INCOME CLASSIFICATION	PUBLIC MARKET PRICES	PRIVATE MARKET PRICES
Low Income	US$2/dose	US$10/dose
Middle Income	US$10/dose	US$50/dose
High Income	US$50/dose	US$100/dose

The prices chosen for this analysis are loosely based on current pricing structures for newly licensed vaccines such as Prevnar© and Gardasil©. These pricing assumptions may reasonably reflect the cost of investments and risks to producers of an HIV vaccine. However, these prices may seem very high compared to what less developed countries are used to paying for vaccines implemented through public programs. Regardless of income classification or market type (public or private), for the sake of simplicity, no price decline is assumed over time.

2.2.2 Country Profile Descriptors

The country descriptors underpin the model, describing the demographic, epidemiological, political, and financial situation in each country. These descriptors comprise data from published sources on:

- Demography: population, subpopulation sizes;
- HIV/AIDS epidemiology: prevalence, burden;
- Political will: AIDS Program Effort Index (API) score;
- Ability to pay: purchasing power parity (PPP)-adjusted Gross National Income (GNI) per capita;
- Health care system capacity: PPP-adjusted GNI per capita; and
- Funding: projected government and donor funding.

The demographic information is used to estimate the size of target populations. The epidemiological information is used to capture the extent of the epidemic and describe the need for the vaccine. Given that political will is difficult to quantify, the API score is an approximate measurement of a country's level of effort to implement AIDS treatment and HIV prevention programs. Income as measured by PPP-adjusted GNI per capita is used as a proxy for ability to pay, as well as a measurement of health care capacity. Finally, projected government funding is based on a proportion of national income, a proxy for budgetary constraints that might limit achievable demand.

The country profile descriptor data assume static values, some of which are categorized according to whether the value is high, medium, low or very low (Appendix III, pg. 47). This categorization is necessary for the application of the algorithms (Appendix IV, pg. 49) used to define the behavioral parameters.

2.2.3 Country-Level Behavioral Parameters

The behavioral parameters describe each country's public sector adoption (licensure) and implementation behavior, as well as private market demand and utilization behavior.

The public sector adoption and implementation behavior parameters describe the:

- Minimum acceptable levels of key vaccine characteristics (efficacy and duration) below which countries would not license and/or implement the vaccine;
- Maximum acceptable price above which countries would not license and/or implement the vaccine;
- Time to local regulatory approval;
- Time to initiate public vaccination programs;
- Vaccination strategy;
- Levels of achievable coverage; and
- Time it takes each country to achieve these levels of coverage.

The private demand and utilization behavior variables describe the:

- WTP for the vaccine;
- WTV; and
- Compliance.

The behavioral parameters can be defined by the user or by a set of algorithms (internal to the model) described in Appendix IV (pg. 49). The parameters that are used in the baseline analyses presented here are based on a mixture of both algorithm and specified values. The specified values used are based on findings from a wide consultation conducted by IAVI with about 80 experts.

2.3 Public Sector Adoption and Implementation Behavior Modeling Assumptions

2.3.1 National Implementation Decisions

Although implementation decisions are based on a variety of factors, including the risk-benefit profile of the intervention and the implications of this profile for cost-effectiveness and affordability, the model assumes that public sector implementation decisions are based solely on the acceptability of the vaccine's profile, in terms of efficacy, duration, and price per dose. If the vaccine profile meets minimum acceptable thresholds across all three profile dimensions, a national government will implement it in a particular target population.

The model assumes that the minimum acceptable level of efficacy (efficacy threshold) varies by target population. Therefore, given a particular level of vaccine efficacy, a national government might implement the vaccine in only the populations at higher risk of exposure to HIV. We assumed that these adoption thresholds are set at between 30% and 50% efficacy for populations at higher risk of exposure, and at 30% to 90% efficacy for lower-risk populations. The duration of protection and price adoption thresholds is not assumed to vary by target risk group. The minimum duration of protection for countries ranges between one to five years, while the maximum acceptable price ranges between US$1 to $50 per dose.

2.3.2 National Regulatory Approval Time

The model assumes that approval occurs first in North America and Europe following approval in the year 2015[i] by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). It is assumed that the regulatory approval time for developing countries is some two to five years after FDA/EMEA approval. This pattern of launching a vaccine in the developed world before the developing world is certainly more common, but not necessarily a given, as was recently shown in the case of GlaxoSmithKline's new rotavirus vaccine (Rotarix ©), which was licensed in Mexico before its licensure in the developed world.

The model assumes that the approval time depends on the vaccine's efficacy level. Vaccines with an efficacy of 30% or less have an approval time of one year longer than the baseline, while vaccines

[i] The year of licensure is an assumption made within the model – the chosen year is hypothetical, yet specifying it is necessary since the year is a crucial determinant of the size of populations around the world who might be targeted for vaccination.

with 70% or better efficacy would have an approval time of one year less than the baseline. National regulatory authorities (NRAs) may approve highly efficacious products more quickly because the clinical and scientific evidence is stronger and requires less scrutiny and time to assess We assume that the vaccine would need to demonstrate a minimum level of efficacy of 30% in any particular target population to be licensed anywhere in the world.

2.3.3 Vaccination Programs: Recipient Populations

Because current scientific opinion assumes that preventive HIV vaccines would be administered to HIV-uninfected individuals, the targeted population would ideally constitute those confirmed as HIV-negative. However, since HIV testing prior to vaccination will be logistically difficult and expensive, the starting population in this model is the total population. This assumes two distinct population groupings: populations at higher risk of exposure to HIV, and populations at lower risk of exposure.

2.3.3a Populations at higher risk of exposure to HIV

It is assumed that the populations at higher risk include female sex workers (FSWs), IDUs, and men who have sex with men (MSM). The size of these populations is based on three Joint United Nations Programme on HIV/AIDS (UNAIDS)-commissioned studies of prevalence in each of these populations (FSWs: Population Division of the Department of Economic and Social Affairs n.d.; IDUs: Vandepitte et al. 2006; MSM: Aceijas et al. 2004). These populations have been estimated for every country across the world within the model. Table 4 (pg. 16) provides examples of the projected population magnitudes for a handful of selected developed and developing countries during the year 2015. Although other target groups might also be potential recipients (e.g., migrant workers, truck drivers, health care workers), they are not included in our model, due to a lack of available data.

2.3.3b Populations at lower risk of exposure to HIV

For purposes of the baseline analysis, we defined populations at lower risk as those outside the higher-risk group and aged either 13 to 26 years or 13 to 49 years. The age range of the populations at lower risk for each country is determined by model according to the extent of the epidemic and the political will in each country; for example, countries with a higher prevalence of HIV and greater political will may target broader populations than countries with lower prevalence and less political will.

Table 4. Magnitude of high- and low-risk public market populations for selected countries

COUNTRY	WHO REGION[A]	TOTAL POPULATION SIZE (IN 2015)	% OF POPULATION AT HIGHER RISK (as percentage of total population)	POPULATION AT HIGHER RISK (absolute size)	BREADTH (AGE RANGE) OF LOW RISK PROGRAM	% OF POPULATION AT LOWER RISK WITHIN AGE RANGE	POPULATION AT LOWER RISK (absolute size)
Brazil	AMR	212,400,000	16.2%	34,400,000	13-26	18.4%	39,200,000
Cambodia	WPR	17,100,000	9.3%	1,600,000	13-26	18.1%	3,100,000
China	WPR	1,411,600,000	5.1%	72,400,000	13-26	18.5%	261,000,000
Germany	EUR	83,700,000	12.36%	10,300,000	13-26	16.7%	14,000,000
India	SEAR	1,282,100,000	10.2%	130,900,000	13-26	18.5%	237,300,000
Kenya	AFR	42,100,000	10.4%	4,400,000	13-49	43.6%	18,400,000
Nigeria	AFR	162,900,000	4.9%	8,000,000	13-49	43.2%	70,300,000
Peru	AMR	32,300,000	14.3%	4,600,000	13-26	18.1%	5,900,000
Russia	EUR	139,100,000	12.2%	17,000,000	13-26	17.6%	24,500,000
South Africa	AFR	53,400,000	6.4%	3,400,000	13-49	47.9%	25,600,000
Thailand	SEAR	70,100,000	9.5%	6,700,000	13-26	18.3%	12,800,000
UK	EUR	326,800,000	11.4%	7,000,000	13-26	17.0%	10,500,000
USA	AMR	326,758,485	12.6%	41,000,000	13-26	17.5%	57,100,000
Zambia	AFR	14,000,000	6.4%	900,000	13-49	40.8%	5,700,000

[A]WHO Region acronyms:

AFR African regions
AMR Americas region
EMR Middle-Eastern region
EUR European region
SEAR South-East Asian region
WPR Western Pacific region

2.3.4 Program Implementation Time Lags

Even after a vaccine has been approved for licensure by national regulatory authorities, there may be secondary implementation lags that further delay product emergence in public markets. These delays would occur because officials are waiting to learn from the experience of implementation in other countries or because of the time it takes for them to adequately scale up delivery infrastructure. Within the model, the lag to implement a particular public-sector vaccination program depends upon the population targeted. High-risk programs are assumed to be initiated first, between one to six years after regulatory approval/licensure.

These would then be followed by low-risk programs, which would begin one to three years after the high-risk programs. We assume that these lag values will vary by country, are additive, and are additional to the adoption lag.

2.3.5 Speed of Uptake after Adoption

Separate from the licensure approval decision and implementation lags is the speed or intensity with which the implementation of the vaccination strategy might occur. The uptake speed describes the time to reach the maximum achievable rate of coverage. In general, high-risk programs are assumed to achieve peak coverage as fast if not faster than low-risk programs, and routine vaccination strategies are assumed to achieve peak levels faster than catch-up vaccination strategies (see below for a description of potential vaccination strategies). Across all countries, we assume that it takes between five and 15 years to achieve the maximum level of coverage, depending on country, risk group targeted, and vaccination strategy employed.

2.3.6 Vaccination Strategy

In this model, three types of vaccination strategy are considered: a routine annual vaccination strategy, a catch-up vaccination strategy, and a revaccination strategy.

- *Routine vaccinations* refer to the approach employed to vaccinate new entrants to certain sub-populations in an annual program. For example, if adolescents 13 to 16 years old are the sole target group, then a routine strategy might involve a school-based program that vaccinates every 13-year-old in school each year. Alternatively, a routine strategy targeting IDUs might focus on individuals using needle exchange programs who had not already received an HIV vaccination.
- *Catch-up vaccinations* involve vaccinating those missed or ineligible for a routine vaccination. The catch-up strategy targets any residual population outside the routine recipient population(s). To continue the example from above, if adolescents 13 to 16 years old are the target group, then the catch-up strategy would attempt to vaccinate those 13-year-olds missed by the routine vaccinations offered that year, as well as those 14 to 16 years old who weren't vaccinated when they became eligible for a routine vaccination.
- *Revaccinations* are required when vaccines have a limited duration of protection. If an HIV vaccine is assumed to provide five years of protection, individuals will need to be re-vaccinated every five years while they are in the eligible target population. If a primary routine program involves an adolescent group 15 to 19 years old, with a five-year duration of protection, no revaccination is required. On the other hand, if the general population, aged 15 to 49 years, is targeted, then a vaccine with a five-year duration would involve up to seven revaccinations for each individual

There are two further assumptions regarding revaccination. First, in the absence of clinical evidence, revaccination is assumed to require only a single dose. Second, only 75% of people requiring a revaccination are assumed to return for each round of revaccination.

2.3.7 Reach, Coverage, Vaccine Acceptability, and Wastage

The model is designed to enable analysis of demand with respect to coverage, vaccine acceptability, compliance, and wastage by target population as well as by vaccination strategy.

However, due to lack of available data, we consider only coverage and wastage in the analyses presented here. In addition, the coverage rate assumed, which describes the proportion of the target population who receive a full course of vaccination, accounts to some extent for imperfect compliance to a multi-dose vaccination course.

Coverage rates in the model vary according to target populations (at lower and higher risk of exposure) and delivery strategies (routine and catch-up) and are assumed to range between 20% and 75%. We assume a wastage factor of 10% within the model across all countries and vaccination programs. Hence, for every 10 people who are fully vaccinated, one course is wasted.

Table 5 details the adoption and implementation parameter values assigned to 14 selected developed and developing countries. Similar information is embedded within the model for all 192 countries that make up our global analysis.

Table 5. Country-specific examples of adoption and implementation parameters

COUNTRY	ADOPTION THRESHOLDS				ADOPTION & IMPLEMENTATION LAGS (YEARS)			ADOPTION SPEED (TIME TO MAX. COVERAGE) AND MAX. COVERAGE FOR ROUTINE/CATCH-UP STRATEGIES			
	EFFICACY THRESHOLD		DURATION THRESHOLD (YEARS)	PRICE THRESHOLD (USD/ DOSE)	REGULATORY APPROVAL	HIGH RISK PROGRAM	LOW RISK PROGRAM	TIME TO PEAK COVERAGE (YEARS)		PEAK COVERAGE RATE (% OF TARGET POPULATION)	
	HIGH RISK	LOW RISK						HIGH RISK	LOW RISK	HIGH RISK	LOW RISK
Brazil	50%	70%	2	$10	1	1	0	3	5	75% / 60%	63% / 50%
Cambodia	50%	70%	2	$2	2	1	1	5	7	50%	63% / 50%
China	50%	80%	3	$2	3	1	1	3	5	50%	50%
Germany	50%	80%	3	$50	0	1	1	3	5	75% / 60%	63% / 50%
India	50%	70%	3	$10	2	2	1	5	5	40%	40%
Kenya	30%	30%	1	$10	1	1	0	5	5	50%	50%
Nigeria	30%	30%	1	$10	2	2	0	7	7	30%	30%
Peru	50%	80%	3	$10	1	2	3	5	5	75% / 60%	25% / 20%
Russia	50%	80%	3	$10	2	1	2	5	3	60%	40%
South Africa	30%	30%	1	$10	0	0	0	4	4	63% / 50%	50% / 40%
Thailand	30%	70%	2	$10	0	0	1	5	5	75%	60%
UK	50%	80%	3	$50	0	1	0	5	5	75% / 60%	63% / 50%
USA	50%	80%	2	$50	0	1	2	5	5	75% / 60%	63% / 50%
Zambia	30%	30%	1	$10	1	1	1	5	5	63% / 50%	50% / 40%

NB: The high-risk program implementation lag is in addition to the regulatory approval lag and the low-risk program lag is in addition to the high-risk program lag.

2.4 Private Market Modeling Assumptions

The private market for a vaccine is neither funded nor implemented by the public sector. It is driven by individuals who are willing and able to pay for the vaccine, and is likely to include firms purchasing the vaccine for their employees as part of health care benefits. However, due to a lack of information on all potential private markets, only individual private demand is considered here.

Licensure (Adoption) Decision: The thresholds for efficacy (30%) and duration (three years) in the private market are set to the minimum levels realistic for a first-generation vaccine. It is assumed that if a vaccine achieves these minimum standards, it would be licensed, and individuals would be able to buy the product via private markets, even in the absence of public programs.

An individual is assumed to be willing to pay a specified proportion of his or her income, irrespective of the vaccine profile. This threshold is set in the baseline so that the cost of a full course of the vaccine in the private market is always 50% or less of an individual's weekly income. Therefore, the proportion of persons in each country willing to pay for the vaccine depends upon the vaccine's price[ii] and income distribution in that country.

It is assumed that if a low-risk program is initiated in a given country, then 50% of those within the lower-risk target group who would otherwise be willing and able to pay for the vaccine via the private market would instead demand the vaccine via the public program, since rational individuals will seek to minimize their expenditures. Although governments could introduce means testing to ensure that the program is used only by lower-income individuals, this option has been ignored for the purposes of this model.

Regulatory Lag: The regulatory lag for private markets is the same length as for public initiatives in each country.

Private Program Lag: The model assumes no private program implementation lag.

WTV: The proportion of people within a particular country WTV in the private market represents those who believe they need the vaccine and are willing and able to pay for it. This proportion of people who might believe they need the vaccine is set at the same percentage used to describe the size of the populations at higher risk of exposure to HIV.

Maximum Coverage: In the private market, we assume that 100% of those who are willing to be vaccinated can be covered.

Uptake Speed: We assume that the uptake speed in the private market depends on each government's decision to implement the vaccine. If the vaccine is implemented in public programs, then we assume that uptake is fast. If the government does not implement the vaccine, as may be the case in some countries, particularly for low-efficacy vaccines (30%), then we assume uptake speed will be slow. These assumptions are based on the premise that without government endorsement, private individuals may be more cautious about using a low-efficacy vaccine

Compliance: We assume that 80% of those who choose to purchase an HIV vaccine through a private health care provider will complete a course of two or more doses.

[ii] The vaccine price in the private market varies by market (depending on the PPP-adjusted GNI/capita) between US$10 and $100 per dose, as described in tables 2 and 3.

Revaccinations: As in the public initiatives, the baseline forecasts in the model assume that 25% of those who require revaccination are lost to follow-up, and those who are revaccinated require only a single dose.

Table 6 illustrates the magnitudes of the private populations for the same range of developed and developing nations in the year that they adopt the vaccine in the Baseline scenario.

Table 6. Magnitude of private market populations for selected countries

COUNTRY	ASSUMED YEAR OF LOCAL LICENSURE [A]	TOTAL PEOPLE IN NATIONAL POPULATION [B]	PERCENTAGE OF POPULATION AGED16-49 YEARS	PERCENTAGE OF POPULATION WTP FOR VACCINE [C]	PERCENTAGE OF POPULATION WTV	PRIVATE MARKET POPULATION SIZE [D]
Brazil	2016	215,200,000	44.8%	7.4%	16.2%	1,200,000
Cambodia	2017	17,800,000	39.4%	7.4%	9.3%	50,000
China	2018	1,441,600,000	46.9%	7.4%	5.1%	2, 600,000
Germany	2015	83,700,000	44.0%	37.0%	12.3%	1,700,000
India	2017	1,321,100,000	42.2%	7.2%	10.2%	4,100,000
Kenya	2018	44,800,000	36.4%	7. 4%	10.4%	100,000
Nigeria	2016	166,400, 000	36.0%	7.4%	4.9%	200,000
Peru	2019	34,300,000	41.8%	7.4%	14.3%	200,000
Russia	2020	137,000,000	47.1%	7.5%	12.2%	600,000
South Africa	2015	53,400,000	42.6%	7.4%	6.4%	100,000
Thailand	2016	70,800,000	45.3%	7.4%	9.5%	200,000
UK	2015	61,500,000	43.9%	56.5%	11.4%	1,700,000
USA	2015	326,800,000	44.2%	72.6%	12.6%	13,200,000
Zambia	2015	14,000,000	33.7%	7.4%	6.4%	20,000

[A] Corresponds with year of availability on private market and based on the hypothetical assumption that the vaccine is first made available in 2015.
[B] In year of local licensure.
[C] That is, with adequate income to afford vaccine at private market prices.
[D] Population in age range, willing to pay, and willing to be vaccinated.

3 RESULTS AND DISCUSSION

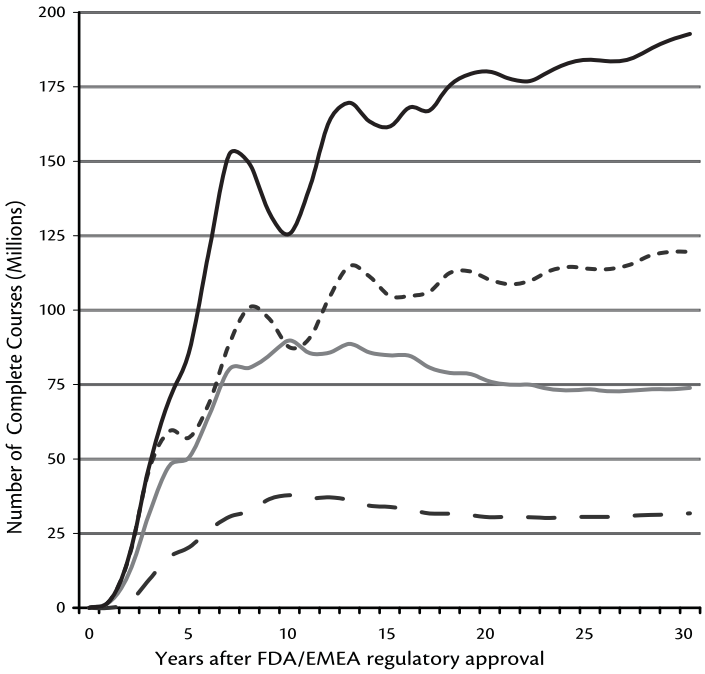
3.1 Model Results

The following results highlight the importance of the key determinants of demand and present some illustrative projections of future demand for an HIV vaccine generated by the demand forecasting model. It was not the intention to produce a single estimate of global demand. Rather, these results should be viewed as orders of magnitude of demand given a range of scenarios, based upon a variety of assumptions, including the likely first-generation vaccine characteristics, tiered pricing, government and donor funding, the extent of the epidemic, and a host of policy-related factors.

3.1.1 Baseline Scenario Results

In the first set of analyses, the four vaccine profiles described earlier are translated into the four global demand scenarios (Figure 2). These vaccine profile scenario outputs are based upon preferences elicited in expert interviews and modeling assumptions described in the Methods section. The interview findings suggested that HIV vaccines with an efficacy of at least 70% would be required for general population programs in countries with concentrated epidemics, whereas a minimum efficacy of 50% may be acceptable in countries with generalized epidemics. For use in high-risk populations, 30% to 50% efficacy would be sufficient in countries with concentrated epidemics, while 30% efficacy may be acceptable in countries with generalized epidemics.

Figure 2: Total annual global demand scenarios



Vaccine characteristics

HIGH
90% vaccine efficacy
5-year duration of protection

OPTIMISTIC
BASELINE
70% vaccine efficacy
5-year duration of protection

BASE
50% vaccine efficacy
3-year duration of protection

LOW
30% vaccine efficacy
3-year duration of protection

Price

National government's maximum willingness to pay

Tiered pricing

Assumptions

Country Income Classification	Market Price (US$ per dose)	
	Public	Private
Low	$2	$10
Middle	$10	$50
High	$50	$100

Additional assumptions:

- Dosing schedule (for a full vaccination course) is assumed to be a 2-dose prime-boost combination.
- The vaccine efficacy is assumed not to be clade-specific; i.e. the vaccine is effective against all strains/subtypes.

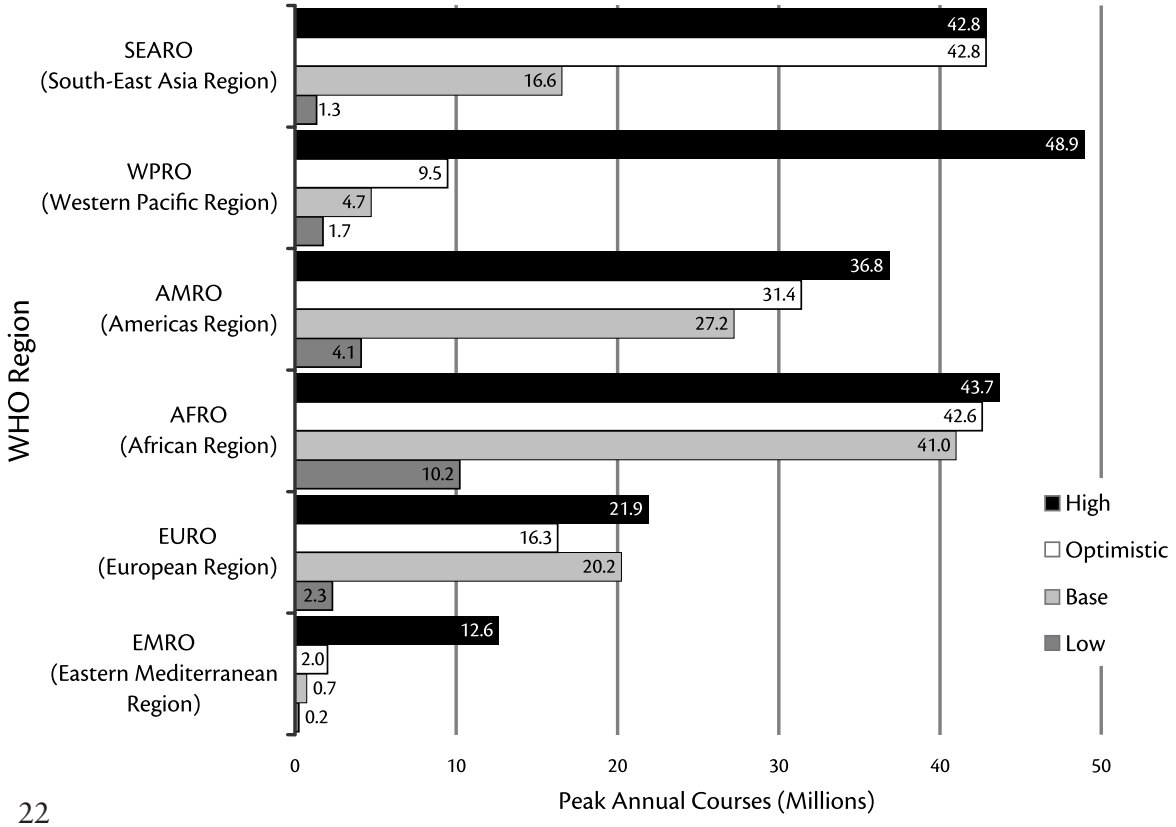
All scenarios are projected over a 30-year time horizon, and unless specified, assume no government or donor funding constraints throughout the period. These scenarios and results are presented in terms of the annual average demand, the peak demand, or the cumulative demand over this time horizon, and are split according to the vaccine profile assumed, the geographical contribution, the public versus private market split, and assumed vaccination strategy.

As Figure 2 (pg. 21) shows, vaccine profile assumptions have marked effects on overall global demand. Lower levels of efficacy and duration produce lower levels of demand worldwide. Setting the price threshold according to the level that countries are WTP (High scenario) greatly increases global demand, because this means that price is no longer a constraint in any country. Low-efficacy (30% or less) vaccines would generate peak demand of only around 40 million courses per year. However, at levels of efficacy at or above 50%, annual global demand volumes could be in the region of 100 to 200 million courses.

3.1.1a Geographical composition of demand

The regional breakdown (Figure 3) suggests that demand in the AFRO region would be relatively stable and insensitive to changes in the vaccine's profile, including its price. Demand in this region is not constrained by the preferences of decision makers with respect to efficacy at 50% or more or to duration; that is, the total amount of HIV vaccines demanded by African countries would be roughly the same (41.0 million, 42.6 million, or 43.7 million courses in the Baseline, Optimistic Baseline, and High scenarios), irrespective of vaccine characteristics. This occurs because the epidemic is mostly generalized across this region, and model parameters are set so that even medium-efficacy vaccines (50% and above) are acceptable for wide-scale use.

Figure 3: Demand by WHO region (in peak demand year for each scenario: years 10-15)



Demand in the SEARO region is sensitive to changes in the assumed vaccine profile; our analyses suggest that peak demand would change markedly depending on the profile of the vaccine that is eventually launched. In reality, much of this regional effect is due to India, and specifically can be largely attributed to a combination of the sheer size of the Indian population and the assumed adoption behavior of India (Tables 4 and 5, pg. 16 and 18). The government of India is assumed to have no desire to use an HIV vaccine through a public sector program if efficacy is less than 50%, and even then will only use it in a targeted fashion in populations at higher risk. Only when vaccine efficacy is at least 70% will the public sector be likely to implement the vaccine more broadly.

Demand in the WPRO region responds most dramatically to the High scenario and unconstrained price, reflecting China's dominant influence. This is because it is assumed that China would only implement an HIV vaccination program across its general population at a very low price (US$1/dose) and with a very high efficacy (90%).

In the EURO region, peak demand is slightly greater in the Baseline scenario than in the Optimistic scenario since, in the latter case, the vaccine profile has an increased duration of protection (five versus three years) and hence fewer revaccinations are required during the forecast period.

3.1.1b Composition of demand by program and strategy

The interview findings described above — particularly policymakers' preferences for various vaccine characteristics — have important implications for the relative contribution to global demand of private versus public initiatives, as well as the extent to which populations at lower or higher risk of exposure to HIV receive the vaccine. Table 7 details the relative public-private mixes in demand and the public market target populations in each of the four product profile demand scenarios.

Table 7. Relative contribution to cumulative demand of private versus public initiatives

		LOW SCENARIO	BASELINE SCENARIO	OPTIMISTIC SCENARIO	HIGH SCENARIO
Private Market		43%	17%	10%	6%
Public Market	High-Risk Population Program	15%	43%	27%	23%
	Low-Risk Population Program (% of all countries adopting in a broad population, either 13-26 years or 13-49 years)	42% (3%)	40% (16%)	63% (21%)	71% (21%)

The most striking thing is the large contribution of the private market in the Low scenario: 43% of demand for a low-efficacy vaccine. While many governments may not use a vaccine with low levels of efficacy, there are still many private individuals who might be willing and able to purchase the vaccine on the private market.

At higher levels of vaccine efficacy, more public initiatives would begin, and the contribution of the private market to total global demand is correspondingly smaller, dropping to only 6% of total demand in the high-efficacy case. This is due to the large size of the populations being vaccinated as part of public initiatives. The share of private demand also falls because it is assumed that people switch from more expensive private provision to cheaper public provision as the latter becomes available.

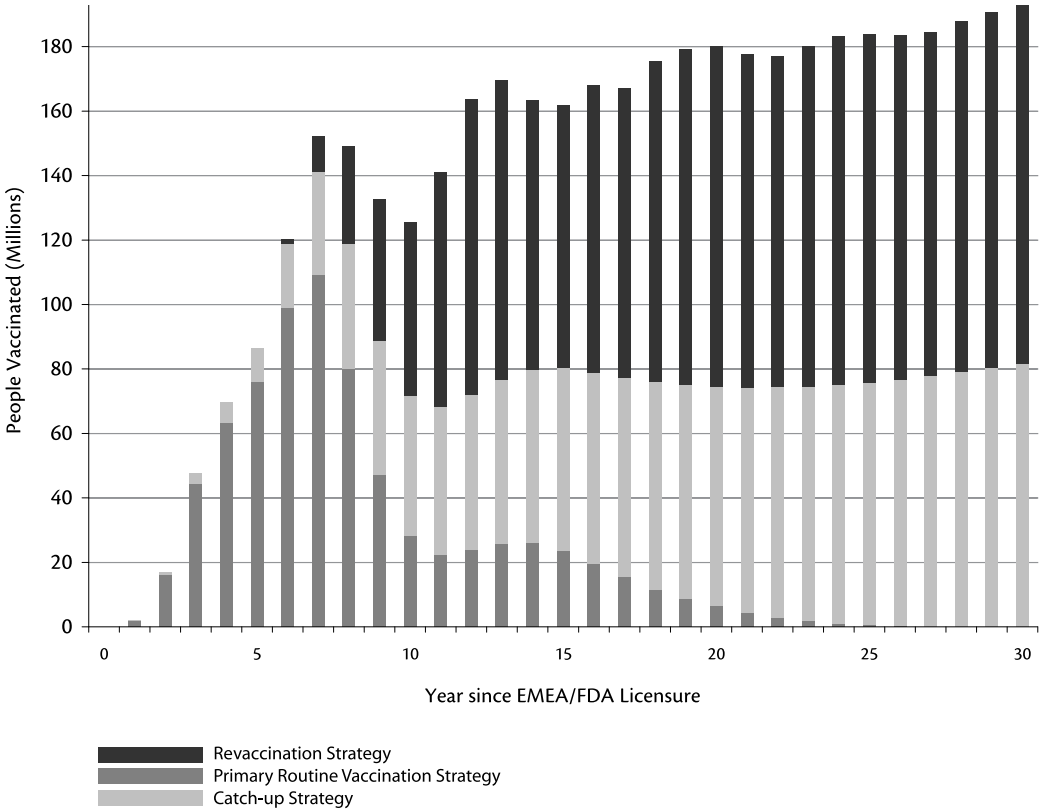
At higher levels of efficacy and longer vaccine duration, the model predicts that the share of demand in the public sector would rise from 58% (Low scenario) to 94% (High scenario). At the same time, a more efficacious vaccine would also be increasingly used by governments to cover their general adult population, including persons at lower risk of infection.

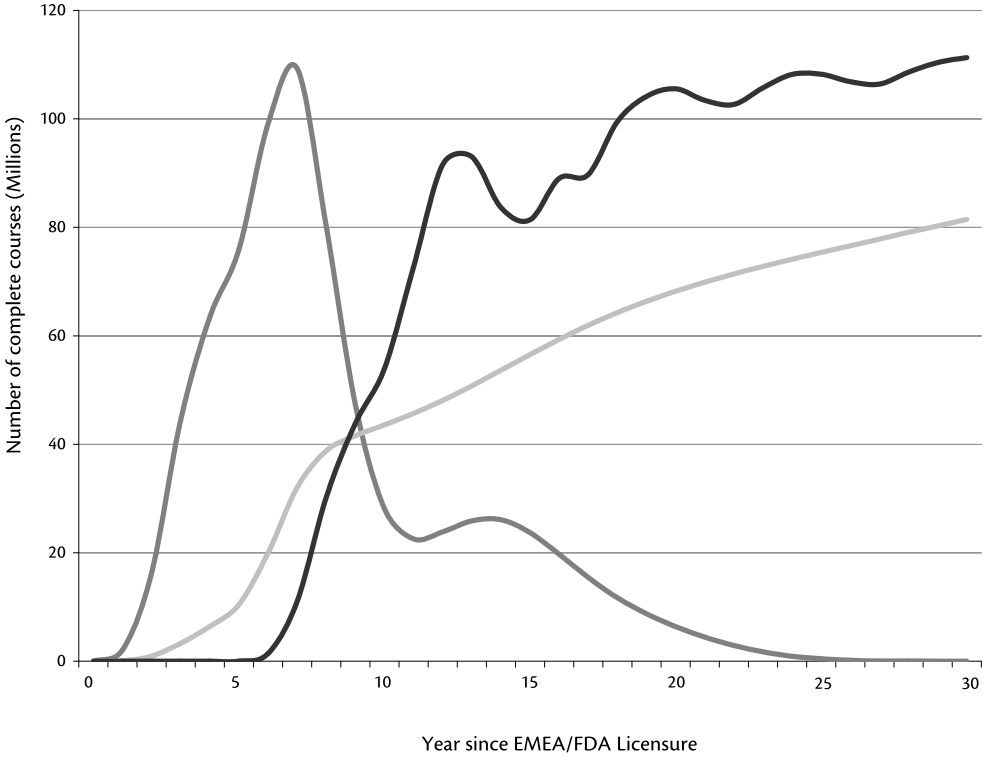
Figure 4 (parts i and ii) illustrates the relative contribution over time to global demand of catch-up strategies as compared with routine and revaccination strategies for the High scenario, and Table 8 details this information for each vaccine profile scenario. They show that demand is initially dominated by catch-up vaccination strategies. Over time, as more countries adopt the vaccine, revaccination strategies account for an increasing amount of global demand. This illustrates an important facet of demand for future HIV vaccines with limited duration of protection; the need for revaccination is the driving force behind longer-term demand volumes. Even with this conservative assumption that only 50% of those requiring revaccination are revaccinated, revaccinations account for 48% to 64% of cumulative demand (Table 8).

Table 8. Total cumulative global demand, by vaccination strategy

VACCINATION STRATEGY	TOTAL CUMULATIVE DEMAND OVER 30-YEAR TIME HORIZON IN MILLIONS OF COURSES (% CONTRIBUTION TO TOTAL CUMULATIVE DEMAND)			
	LOW SCENARIO	BASELINE SCENARIO	OPTIMISTIC SCENARIO	HIGH SCENARIO
Primary Routine Vaccination	131 (15%)	365 (17%)	512 (19%)	761 (17%)
Catch-up Vaccination	180 (21%)	411 (19%)	856 (31%)	1,531 (35%)
Revaccination	545 (64%)	1,322 (63%)	1,349 (50%)	2,123 (48%)
Cumulative Total	856 (100%)	2,109 (100%)	2,717 (100%)	4,414 (100%)

Figure 4 (i) & (ii): Total demand by vaccination strategy for High scenario





3.1.2 Improved Policy Scenarios: Implications for the Public Sector

If governments, vaccine advocates, and others work to improve the regulatory, political, and health system environment within the 20 countries with the highest burden of HIV/AIDS, the demand for an HIV vaccine could be substantially larger, according to the projections generated by the demand model (Table 9). The scenario specifications used to model each of these policy improvements are described within Appendix V (pg. 52).

Table 9. Peak demand for policy-enabled environmental scenarios, in millions of courses

	BASELINE SCENARIO	EXPEDITED REGULATORY APPROVAL	INCREASED COVERAGE & FUNDING	EXPEDITED PROGRAM IMPLEMENTATION & INCREASED POLITICAL WILL	COMBINED SCENARIO
Peak Year Demand	89.8m	90.8m	104.43m	119.7m	137.5m
(%) Change Peak Year Demand from Baseline	—	1.1m (1%)	14.6m (+16%)	29.9m (+33%)	47.7m (+53%)
Cumulative Demand(Years 1-10)	543.4m	585.0m	638.8m	716.5m	855.0m
(%) Change in Cumulative Demand (Years 1-10) from Baseline	—	41.6m (8%)	94.4m (+18%)	173.1m (+32%)	311.5m (+57%)
Total Cumulative Demand	2,108.9m	2,136.1m	2,390.0m	2,921.7m	3,361.0m
(%) Change in Cumulative Demand from Baseline	—	27.2m (+1%)	281.1m (+13%)	812.7m (+39%)	1,252.1m (+59%)
Average Annual Demand (over 30-year period)	68.0m	68.9m	77.1m	94.2m	108.4m
(%) Change in Average Annual Demand from Baseline	—	0.9m (1%)	9.1m (13%)	26.2m (39%)	40.4m (59%)

3.1.2a Expediting regulatory approval processes

Expediting regulatory approval might be achieved by expanding the participation of countries in discovery and development activities (especially future registration trials) for first-generation HIV vaccines. If locally generated data were available, this might reduce the lag between regulatory approval in the U.S. and Europe and subsequent approval in less developed countries. In addition, national and international regulatory processes could be streamlined using measures similar to those employed by the FDA to allow drugs for serious and life-threatening diseases to reach the market earlier.

Expediting regulatory approval has relatively little effect on global demand over the 30-year period: a 1% change over Baseline demand, equivalent to an additional 27.2 million complete courses administered. It does, however, shift the demand curve to the left, such that uptake starts earlier than in the Baseline scenario. The volume of demand is increased by almost 10% during the first 10 years as a result of expedited regulatory

approval. Since this is likely to be the period of market exclusivity, earlier regulatory approval could significantly increase the market potential of HIV vaccines.

3.1.2b Increased program coverage through health system improvements

Increased coverage is assumed to occur by scaling up vaccine outreach and delivery infrastructure for the expected target populations for an HIV vaccine. Since health services for populations at higher risk of exposure to HIV in developing countries are often delivered by NGOs, their "reach" would need to be extended. For populations at lower risk of exposure who would also be targeted in some of the scenarios, public sector vaccination infrastructure (mobile clinics, vaccination workers, cold chain, etc.) as well as information campaigns should be strengthened and capacity increased.

Increasing coverage through health systems improvements would also have a marked effect on cumulative global demand: a 13% increase over the 30-year period modeled, or an additional 281 million courses.

3.1.2c Expediting public vaccination program introduction and increased political will

Shortening the time to the advent of public vaccination programs might occur through advanced planning and preparation for HIV vaccines, and through learning from the experiences of other preventive and therapeutic technologies. For example, there could be valuable lessons to be learned from the introduction of other new adult/adolescent vaccines (such as an HPV vaccine) and other new preventive interventions such as male circumcision.

Stronger political commitment to HIV vaccines could emerge as leaders recognize the benefits of a vaccine in terms of infections averted, medical and other costs avoided, and lives saved. Under these circumstances, they would increase their relative prioritization of rapid HIV vaccine introduction. Some of the responsibility for generating stronger political support lies with advocates, community leaders, scientists, and others who can help to inform and influence policymakers about the importance of an HIV vaccine program.

Changes in political commitment have the largest single impact on cumulative demand over the Baseline scenario, an increase of 32% over the first 10 years and 39% over 30 years. It increases peak year demand by 33% over the Baseline scenario, resulting in demand during the peak year of 119.7 million courses.

3.1.2d Combining all of the policy interventions

The simultaneous and combined effects of all three of these policy changes (described above) is even larger than the additive effect of each of the policies alone: a 59% increase in cumulative and peak demand levels, as compared to the Baseline forecasts. However, 29% of potential demand in an environment without funding constraints would not be covered by government and donor funds, given the current funding

assumptions[iii]. Therefore, to realize the potential vaccination gains suggested by the model, national policymakers and international donors should consider carefully how to address potential funding constraints that might otherwise limit demand and access.

3.1.3 Results and Implications for Industry

3.1.3a Volume and timing of demand

Understanding the magnitude and timing of peak demand can help inform the future capital investment decisions of manufacturer of the scale of manufacturing facilities required and when they might need to have these facilities operating at full capacity. These decisions have historically been made as early as four to seven years before a vaccine is expected to be marketed because of the long lead times involved (Andre 2002; IAVI 2005d; Van Exan 2004). A more reliable estimate of demand can thus help to prevent possible delays or under/over supply of the vaccine.

In all four vaccine profile scenarios, demand peaks seven to 10 years after vaccine launch (Table 10). This is due to a combination of expected regulatory and implementation lags and the time to achieve maximum coverage.

Table 10. Volume of global demand across scenarios

	VACCINE PROFILE SCENARIOS			
	LOW SCENARIO	BASELINE SCENARIO	OPTIMISTIC SCENARIO	HIGH SCENARIO
Peak Year of Demand (Year of Initial Peak Annual Courses Demanded)	10	10	8	7
Demand During Peak Year (Millions of Courses)	37.9	89.8	100.9	152.3
Cumulative Total Demand Over 30 Years (Millions of Courses)	856	2,109	2,844	4,414
Average Annual "Steady-State" Demand Over 30 Years (Millions of Courses)	27.6	68.0	91.8	142.4

3.1.3b Baseline revenue scenarios

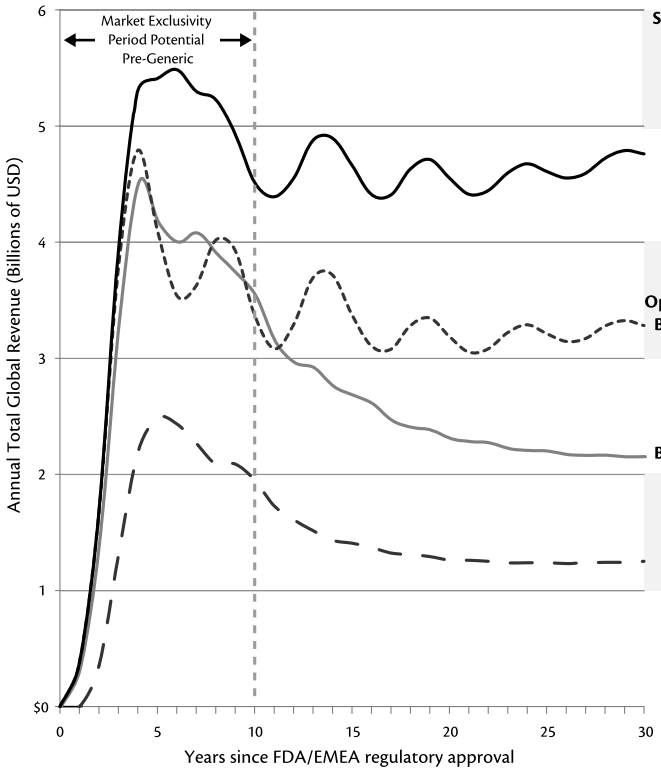
Based on the vaccine characteristic demand scenarios as well as the pricing assumptions detailed in Tables 2 and 3 (pg. 12), it is possible to generate a series of undiscounted sales revenue scenarios. While these are subject to additional uncertainties related to the future cost of manufacture and price of the vaccine, these revenue forecasts provide a second dimension of potential market opportunity with future HIV vaccines.

[iii] See Appendix III for details on the basic funding assumptions used within the model.

The two key results of interest are the average annual sales revenues and the peak sales revenues.

In the forecasts illustrated below, peak annual revenue is achieved four to six years after product launch for the four scenarios. Peak annual sales are US$2.5 to $5.5 billion, while average annual sales revenues range between US$1.6 and $3.8 billion (Figure 5).

Figure 5: Global sales revenue forecast scenarios (assuming tiered pricing)



Scenario	Peak Global Sales Revenue	Average Annual Undiscounted Sales Revenue (over years 0-10)	Average Annual Undiscounted Sales Revenue (over years 0-30)	Cumulative Undiscounted Sales Revenue (over 30-yr period)
High	5.49	3.83	4.34	134.37
Optimistic Baseline	4.79	3.02	3.17	98.39
Baseline	4.52	3.01	2.64	81.71
Low	2.48	1.56	1.41	43.83

All of the vaccine scenarios could be seen as describing blockbuster products, which are loosely defined as those products generating US$1 billion in revenues annually. Some of these revenue projections are of an order of magnitude similar to the forecasts undertaken in 1989-1990 by industry analysts at the Shearson Lehman Hutton and First Boston investment banks assessing the potential of the first HIV vaccine candidate (Cohen 2001).

To put the HIV vaccine revenue projections into context, published global vaccine market projections suggest that the market could reach a total value of US$15 billion by 2012 largely from advances related to cancer and adult vaccines (Kalorama Information 2007; Healthservicetalk 2007). Assuming a compound annual growth rate similar to those seen in the past few years (8% to 9%), the value of the global vaccine market would reach between US$26.5 to $31.1 billion in 2019-2021, the hypothetical years of peak sales revenues in the demand model. As such, the peak annual revenue projections suggest an HIV vaccine (US$2.5 to $5.5 billion) could represent 5% to 13% of the total vaccine market. To contextualize these absolute dollar values and market share estimates, it is worth bearing a few things in mind:

- In the year 2000, more than 50% of the vaccine market revenues came from five vaccines that each accounted for between 10% and 20% of global sales: hepatitis B at 19.5%, measles, mumps, and rubella (MMR) at 12%, flu at 12%, and hepatitis A at 9.8% (Gréco 2002).
- With the advent of newer, often more expensive vaccines, sales revenues for the vaccine market have grown significantly. Revenues for Merck's HPV vaccine (Gardasil) were US$358 million between January and March 2007 (Merck & Co. Inc. 2007), leading industry analysts to raise their annual revenue projections to US$1.4 billion for its first full year of sales (Mantone 2007).

Comparing Figure 2 (pg. 21) and Figure 5 (pg. 29), what seemed like very modest demand in terms of volume in the Low scenario still translates into significant peak year sales revenue. This can largely be explained by differences in tiered pricing and by public/private market volumes demanded in each scenario. In particular, 43% of the cumulative volume demanded in the Low scenario comes from the private market (Table 7, pg. 23), which translates into 93% of peak sales revenue, because of the higher price of the vaccine in the private market compared to the public sector (Table 11).

Table 11. Relative contribution to cumulative peak sales revenue of public and private programs

SCENARIO		LOW SCENARIO	BASELINE SCENARIO	OPTIMISTIC SCENARIO	HIGH SCENARIO
PRIVATE MARKET		93%	49%	35%	25%
PUBLIC MARKET	High-Risk Population Program	2%	35%	26%	20%
	Low-Risk Population Program	5%	16%	39%	55%

As illustrated in tables 12 and 13, the contribution of the high-income (OECD) economies to total cumulative global demand is relatively stable under each of the four scenarios, at 20% to 28%, but because of the tiered pricing assumptions, their share of global sales revenues is much higher at 64% to 72%. Demand from the 47 GAVI-eligible low-income countries is forecast at 19% to 42%, depending on the vaccine profile assumed. Because of tiered pricing, however, the GAVI countries account for only 4% to 9% of revenues from HIV vaccine sales. The remainder (and majority) of global demand in volume terms comes from the 94 non-GAVI low- and middle-income economies.

Table 12. Relative contribution of developed versus developing economies to global demand across scenarios

COUNTRY GROUPING	NUMBER OF COUNTRIES PER GROUPING	TOTAL CUMULATIVE DEMAND OVER 30 YEARS, IN MILLIONS OF COURSES (% CONTRIBUTION TO TOTAL CUMULATIVE DEMAND)			
		LOW	BASELINE	OPTIMISTIC SCENARIO	HIGH
GAVI-eligible Countries	47	356 (42%)	720 (34%)	743 (26%)	851 (19%)
Low- & Middle-Income (Non-GAVI) Countries	94	304 (35%)	800 (38%)	1,474 (52%)	2,665 (60%)
High-Income (OECD) Countries	47	197 (23%)	589 (28%)	628 (22%)	897 (20%)

Table 13. Relative contribution of developed versus developing economies to global revenue across scenarios

COUNTRY GROUPING	NUMBER OF COUNTRIES PER GROUPING	TOTAL CUMULATIVE REVENUE OVER 30 YEARS, IN MILLIONS OF USD (% CONTRIBUTION TO TOTAL CUMULATIVE REVENUE)			
		LOW	BASELINE	OPTIMISTIC SCENARIO	HIGH SCENARIO
GAVI-eligible Countries	47	1,702 (4%)	3,478 (4%)	4,102 (4%)	11,774 (9%)
Low- & Middle-Income (Non-GAVI) Countries	94	13,008 (30%)	19,513 (24%)	30,753 (31%)	36,165 (27%)
High-Income (OECD) Countries	47	29,118 (66%)	58,716 (72%)	63,535 (65%)	86,461 (64%)

According to these revenue forecasts, there is not a large market incentive for companies to serve developing countries, at least relative to the potential revenues that can be earned in the developed countries. On the one hand, this suggests that manufacturers may not be very motivated to develop adequate manufacturing and supply capacity to meet the needs of the poorest countries. This could pose a special challenge for developing country leaders, public health experts, and AIDS advocates seeking rapid introduction of an HIV vaccine in Africa, South Asia, and other heavily affected regions. On the other hand, these revenue projections suggest that there may be an opportunity to broker a technology transfer between developers of the initial first-generation HIV vaccine and vaccine manufacturers in the developing world, since the vaccine technology may not have much commercial value for the originator company in the developing world.

3.2 One-Way Sensitivity Analyses

Sensitivity analyses were conducted to understand the extent to which certain vaccine profile or country-level behavioral parameters affect global demand. The sensitivity analyses conducted assess the effect on demand of using the upper or lower boundary of a particular parameter while

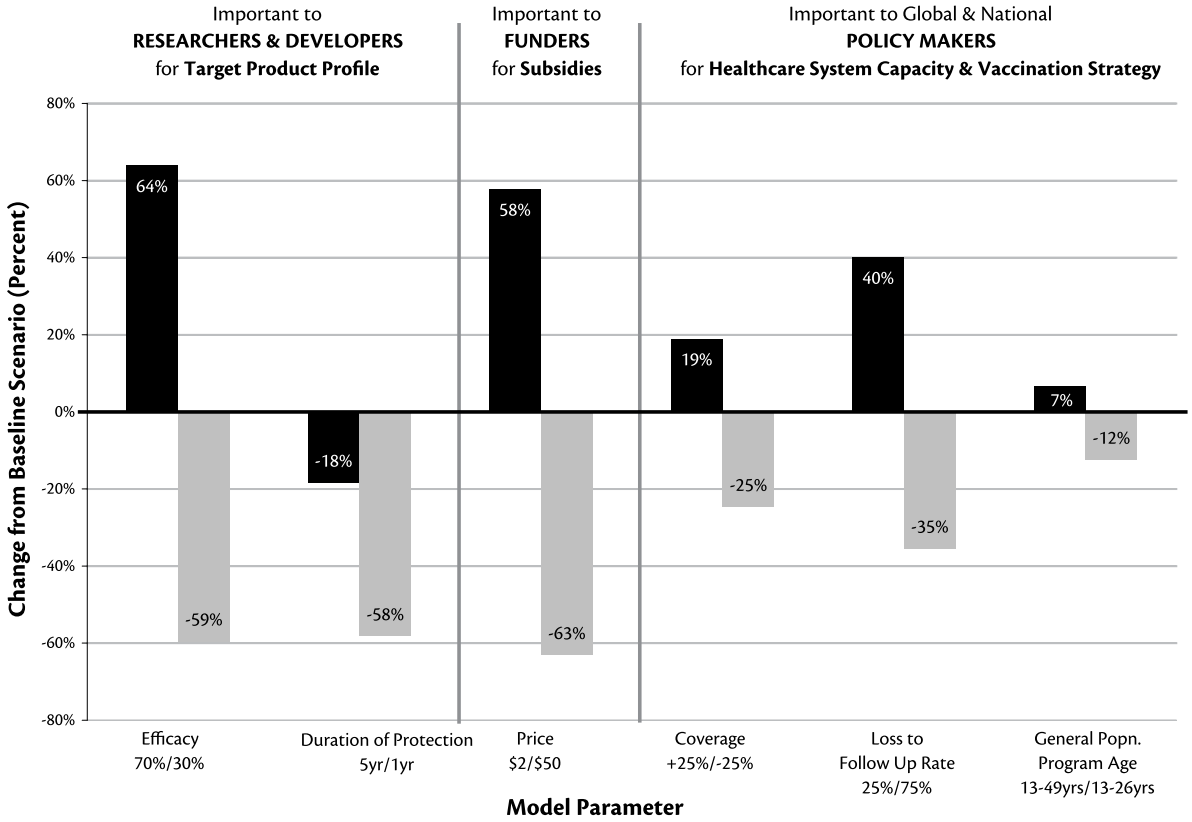
holding everything else constant (i.e., unchanged from the Baseline scenario). The boundaries or limits used for each sensitivity analysis are defined in Table 14, while the results of each of these analyses are illustrated in Figure 6.

Table 14. One-way sensitivity analyses of vaccine characteristics and coverage parameter

VACCINE PROFILE PARAMETER	UPPER BOUNDARY	LOWER BOUNDARY
Vaccine efficacy	70%	30%
Vaccine duration	5 years	1 year
Vaccine price (charged in all markets and countries)	US$2 per dose	US$50 per dose
Country-Level Behavioral Parameter	Upper Boundary	Lower Boundary
Coverage (% change from Baseline assumptions)	+25%	-25%
Loss To Follow Up Rate (for revaccination)	25%	75%
General Population Program Age Cutoff	13-49 years (Sexually active popn. only)	13-26 years (Adolescent & young adult popn. only)

NB: The sensitivity of demand to lags (both regulatory and program implementation) has not been assessed, since lags only affect the timing of peak demand.

Figure 6: Sensitivity analysis on vaccine profile and coverage parameters



Baseline scenario demand decreased by a large amount when vaccine characteristics were individually altered to reflect the lower bounds of a possible first-generation vaccine profile (Figure 6). Changes in demand were most striking with respect to changes in efficacy. This change reflects the findings from our consultation with policymakers and expert stakeholders, which indicated that very few governments would implement an HIV vaccine with low efficacy for use in populations at lower risk of exposure to HIV (e.g., the general population), while many more governments would use higher-efficacy vaccines in both populations at higher risk of exposure to HIV as well as in those at lower risk, such as adolescent and/or adult populations.

Reducing the assumed vaccine duration of protection causes the forecast levels of demand to fall, since shorter durations are not less preferred than longer durations. Even more surprising, increasing duration also had a negative effect on total demand. This is because vaccines with longer durations of protection require fewer revaccinations to keep populations protected. Changes to price, like efficacy, had a marked effect on demand. Demand increases considerably when the price of the vaccine is decreased to levels more often associated with EPI/childhood vaccines (US$2/dose). At these low costs, many countries may adopt and implement an HIV vaccine widely. Conversely, as one might expect, demand diminishes dramatically when the vaccine price is set closer to levels observed with newer vaccines (US$50/dose), since at these price levels, the budget impact may be above what a country (and in some cases, a donor) is willing or able to pay.

The fact that changing the vaccine profile may have such a pronounced effect on demand is important when developers consider the target product profile for their HIV vaccine candidates. On the basis of this forecasting model, lower efficacy and duration would dramatically reduce the market potential for a product. Similarly, from the perspective of funders/ and donors, if HIV vaccine prices are not tiered and relatively expensive (US$50/dose), and if developing countries' demand needs cannot be sufficiently subsidized, then there will be very limited demand and, by inference, access, particularly in the developing world, where populations are often those in greatest need of such a vaccine. This predicted outcome suggests that a first-generation HIV vaccine should be priced affordably through tiered pricing or sufficiently subsidized for those who need it most.

Baseline scenario demand estimates were affected to a lesser extent by changes in the coverage rates applied as well as by reductions to the loss of follow-up for revaccination. (NB: This latter rate is, in effect, a long-term coverage rate for revaccinations.) These results highlight the importance of coverage in determining demand. Moreover, the results illustrate how endeavors that lead to improvements in the initial and revaccination coverage of adolescents, adults, and vulnerable populations will have an important effect on maximizing future access and utilization of an HIV vaccine. This suggests that policymakers at both global and national levels should direct long-term efforts to building sufficient capacity in developing countries to deliver health care to the likely target populations for an HIV vaccine.

4 NEXT STEPS

There are currently a number of areas within the model that would benefit from additional research. Better information, further discussion with experts, and consultation with model users will assist future refinement and direct next steps.

Consultation and Feedback

IAVI welcomes the opportunity to work with interested stakeholders from the biopharmaceutical sector, the private investment community, donors, and other multilateral groups and institutions (e.g., GAVI, WHO SAGE, WHO HIV Vaccine Division, etc.), and officials from national vaccination programs to enable the principal customers of these forecasts the flexibility to re-specify assumptions, re-run analyses, and refine forecasts, as well as to ensure transparency with respect to the methods, assumptions, and results.

Strengthening Adoption Decision Modeling

Further discussion with developers and regulators will enable more sophisticated modeling of complex global regulatory processes. The time required to secure the range of regulatory approvals necessary to enable global access (e.g., EMEA, FDA, EMEA article 58, WHO SAGE recommendations, WHO Prequalification, etc.) deserves further assessment.

In addition, levels of regulatory acceptability are often viewed differently in North America and Europe as compared with the developing world. It may be that for a particular vaccine, the developed world countries will not want to license a partially efficacious, short-duration HIV vaccine because the risk-benefit profile does not suit the needs of those low-prevalence countries. This unacceptability does not automatically mean that this vaccine would remain unused. Understanding how regulators and decision makers in developing countries might react to such scenarios would help model these potential consequences.

It is not a given that the FDA/EMEA would be the first regulators to license a vaccine. As the case for the recent launch of a new rotavirus vaccine illustrates, a developing country (Mexico in this case) was first to license and adopt the vaccine. Discussions with regulators and manufacturers may enable us to better scope the range of possibilities for regulatory approval scenarios. Then, specification of different regulatory approval scenarios will enable exploration of the effects on global demand.

Consideration of Other Target Populations

Reliable estimates of the magnitude of populations at higher risk of contracting HIV by country are difficult to come by. The estimates currently used for FSWs, IDUs, and MSM, calculated using regional published data, could be improved. In addition, there are other potential recipient groups for an HIV vaccine, including migrant workers, truck drivers, clients of SWs, health care workers, military personnel, and sexually transmitted infection (STI) patients, which were not explicitly addressed within our model due to the lack of available data. Identification and incorporation of reliable estimates for the size of these groups would increase the model flexibility and better enable the model to be applied to different national settings.

Improving the Geographic Variability of Interviews

This work draws upon the expertise of stakeholders from a wide range of disciplines who inform or make health care and health financing decisions at national and regional levels. Future in-depth research in countries most affected by HIV/AIDS and/or with large population bases (e.g., Brazil, Kenya, South Africa, China, Russia, and many developed countries) would improve the model forecasts.

Use of a Static versus Dynamic (Epidemiological) Structure

This model uses estimates of prevalence and burden to categorize and describe each country's adoption and implementation behavior, but prevalence and HIV status do not directly inform the magnitude of target populations, and prevalence is assumed to be static in the model. Therefore:

- Targeting only HIV-negative individuals is not considered, although this could be a possible delivery strategy if suitable diagnostic technologies were available. From the perspective of this model, a scenario could be specified to explore what this would mean for uptake.
- The model does not consider how use of a preventive HIV vaccine would result in lower incidence, and hence lower prevalence in the longer term. This would change the levels of demand in the longer term, given that prevalence is one of the criteria used to describe adoption and implementation behavior.
- In addition, the model does not consider, in a dynamic fashion, how relative prevalence may actually decline over time due to the epidemiological impact of continued scale-up of current treatment and prevention technologies and the possible future adoption of other new prevention technologies (microbicides, PrEP, herpes simplex virus suppression, etc.), and thus will again change demand in the long run.

However, IAVI is supporting other activities to build global, regional, and country-specific impact scenarios for HIV vaccines (Stover 2005; Stover and Bollinger 2006). In addition, IAVI's partners are involved in research to explore the range of uncertainty and the resulting impact estimates (Barth-Jones et al. 2005; Barth-Jones and Longini 2002) associated with future preventive HIV vaccines. These concurrent efforts negate the need to redefine this demand scenario model with a dynamic epidemiological base, but underline the importance of future collaboration among researchers to make assumptions consistent and to illustrate the complementary nature of the various research, approaches, and models.

Lessons Learned from the Introduction of Other New Technologies

The introduction of new adult/adolescent vaccines coming to market (e.g., HPV vaccines) and the introduction of other new preventive technologies (e.g., male circumcision) will add lessons learned to improve understanding of issues that must be addressed for successful preparation and implementation of new health technologies in developing countries, particularly in adult/adolescent populations.

5 CONCLUSIONS

The characteristics of the HIV/AIDS pandemic make forecasting the demand for a preventive HIV vaccine challenging. HIV/AIDS is a global problem affecting those in developed and developing nations. As such, there are likely to be multiple public and private markets for a preventive vaccine in both rich and poor economies. Different population groups in different geographies have different risks of exposure to HIV (dependent on many factors) and therefore the level of need for a vaccine may vary from place to place and from group to group. This may mean a variety of targeting strategies and delivery mechanisms to identify and reach the groups perceived to be in need of the vaccine.

Moreover, the forecasting challenge posed for an HIV vaccine is particularly tricky due to the uncertainty and complexity of a future first-generation preventive HIV vaccine. Such a vaccine may be only partially effective in affecting disease progression, infectiousness, and susceptibility to infection; have a limited duration; and may be expensive. These uncertainties make assessing vaccine's acceptability to both governments and individuals difficult. Understanding government and individual preferences for and trade-offs among these characteristics is therefore important for generating more realistic demand forecasts for an HIV vaccine.

Our research attempts to create a conceptual framework to handle and structure the complexity and uncertainty associated with this forecasting problem. The findings suggest that demand for an HIV vaccine is likely to be highly dependent on the vaccine's characteristics, especially its efficacy and price. Other determinants of demand, outside of the vaccine profile, are also important, including the extent and trajectory of the epidemic, funding from national health care systems, capacity and effectiveness to reach and vaccinate target recipients, and levels of political will.

From the perspective of national and global policymakers, our analyses suggest that efforts to address regulatory, infrastructural, financial, and political constraints could vastly increase uptake of an HIV vaccine. Our analyses and model could also assist donors and global health policymakers with strategic decisions about the magnitude of future R&D incentives and financing mechanisms and the specifics of potential tiered pricing structures for future HIV vaccines.

From the perspective of private sector developers and financiers, our analyses and model provide evidence of the extent of market opportunity for an HIV vaccine as well as the critical success factors or constraints that will enable or hinder these opportunities. On the basis of the assumptions presented here, it is clear that global demand volumes will be highly sensitive to the quality of the vaccine developed, and that most of these volumes are likely to originate from low- and middle-income countries. However, as an artifact of the tiered pricing assumptions, the majority of global sales revenues are likely to originate from the wealthy high-income economies.

While there are still considerable scientific challenges and an HIV vaccine is still likely to take several more years to develop, it is important to start changing the policy environment now to maximize future demand and access, by engaging vaccine developers, manufacturers, private financiers, public donors, and health care system officials on their respective R&D, funding, and preparatory endeavors. This forecasting model can assist these decision makers with both immediate and long-term strategic action and investment decisions.

Like all modeling endeavors, this forecasting model is limited by imperfect information and the inherent uncertainty of the future. However, we believe that this research has created the framework for a long-term dynamic forecasting process. As further information is collected, existing data updated, assumptions improved, and lessons learned from the introduction of new vaccines and other preventive technologies, the dynamic nature of this model will enable IAVI to continually improve the forecasts. In the meantime, IAVI welcomes the opportunity to make our model available to and to work with interested stakeholders from the biopharmaceutical sector, the private investment community, donors, and other national/multilateral organizations and government health officials, to give these principal customers of demand forecasts the flexibility to evaluate assumptions, re-run analyses, and refine forecasts.

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APPENDIX I: List of Interviewees and Collaborators

TITLE, FIRST, SURNAME	POSITION/AFFILIATION
Dr. Dinesh Agarwal	Team Leader and Technical Advisor. Reproductive Health, UNFPA, New Delhi
Dr. Martha Ainsworth	Senior Economist, The World Bank, Washington, D.C.
Dr. Jon Andrus	Chief, Immunization Unit, Pan American Health Organization, Regional Office of the World Health Organization, Washington D.C.
Dr. David Apuuli	Director-General, Uganda AIDS Commission, Kampala
Dr. Christian Baeza	Acting Director, Health, Nutrition and Population Division, The World Bank, Washington D.C.
Dr. Dan Barth-Jones	Assistant Professor, Center for Healthcare Effectiveness Research and the Department of Internal Medicine, Wayne State University
Dr. Simon Barton	President, British Association for Sexual Health and HIV (BASHH) and Clinical director, HIV and Genitourinary Medicine Unit, Chelsea and Westminster Hospital, London
Prof. Ramesh Bhat	Professor, Finance and Accounting and Public Systems Group, Indian Institute of Management, Ahmadabad
Professor David Bishai	Associate Professor, Johns Hopkins School of Public Health, Baltimore, Maryland
Dr. Ricardo Bitrán	Founding Partner and President, Bitrán & Asociados, Santiago de Chile
Dr. Lori Bollinger	Vice President, Futures Institute, Glastonbury, Connecticut
Dr. Nirupa Borges	Project Director, Mumbai District AIDS Control Society
Dr. Denis Broun	Country Coordinator, UNAIDS, New Delhi
Dr. James Curran	Dean and Professor of Epidemiology, Rollins School of Public Health, Emory University, Atlanta
Dr. Prakash P. Doke	Director, Health Services, Government of Maharashtra
Mr. Ravi Duggal	Coordinator, Centre for Enquiry into Health and Allied Themes (CEHAT), Mumbai
Dr. Agnes Dzokoto	Senior Technical Officer, Action for West Africa Region-HIV/AIDS (AWARE-HIV/AIDS) Project, Accra
Dr. John Edmunds	Head of Unit, Modelling and Economics Unit, Centre for Infections, Health Protection Agency (HPA), London
Dr. Laura Efros	Senior Director, Vaccine Public Policy, Merck Vaccine Division, Merck & Co., Inc., West Point, Pennsylvania
Dr. Jose Esparza	Senior Advisor, HIV Vaccines, HIV, TB, & Reproductive Health, The Bill and Melinda Gates Foundation, Seattle, Washington
Dr. John Fitzsimmons	Senior Technical Officer and Manager, Pan American Health Organization's Revolving Fund, Washington D.C.
Mr. A.K. Ganesh	Project Manager, YRG Care for AIDS Research and Education, Chennai
Ms. Vidhya Ganesh	Chief, HIV/AIDS, UNICEF, New Delhi
Prof. N. K Ganguly	Director General, Indian Council of Medical Research, New Delhi
Mr. Gopi Gopalakrishnan	Country Director, Janani/DKT International, Mumbai
Ms. Anjali Gopalan	Executive Director, NAZ Foundation, New Delhi

TITLE, FIRST, SURNAME	POSITION/AFFILIATION
Mr. Anand Grover	Project Director, Lawyers Collective, HIV/AIDS Unit, Mumbai
Dr. Indrani Gupta	Head, Health Policy Research Unit, Institute of Economic Growth, Delhi
Dr. M.D. Gupte	Director, National Institute of Epidemiology, Chetpet, Chennai
Prof. Andrew Hall	Chair of Joint Committee on Vaccines & Immunizations (JCVI), UK Department of Health; and Professor of Public Health, the London School of Hygiene & Tropical Medicine (LSHTM), London
Dr. Raymond Hutubessy	Economist, WHO-UNAIDS HIV Vaccine Initiative, Immunizations, Vaccines & Biologicals, WHO, Geneva
Dr. Shahid Jameel	Group Leader, Mammalian Biology and Virology, International Centre for Genetic Engineering and Biotechnology, New Delhi
Dr. Amar Jesani	Coordinator, Centre for Research in Ethics and Rights, Mumbai
Dr. Pontiano Kaleebu	Assistant Director, Uganda Virus Research Institute (UVRI), Entebbe
Dr. S.V. Kapre	Executive Director, Serum Institute of India, Pune
Dr. Ashok Khar	Head (R&D), Shanta Biotech
Dr. P. Krishnamurthy	Project Director, AIDS Prevention and Control Project , Chennai
Dr. Sanjeev Kumar	Head, Social Consulting, Hindustan Latex Family Planning Promotion Trust, New Delhi
Dr. Raj Kumar	Director, Immunisation - PATH India, New Delhi
Dr. Ruth Levine	Vice President for Programs and Operations, Center for Global Development, Washington D.C.
Dr. Homayoun Madjrouh	Managing Director, Sanofi Pasteur, New Delhi
Mr. Manoj Gopalakrishna	CEO, Hindustan Latex Family Planning Promotion Trust, New Delhi
Dr. P. Manorama	Director, Community Health Education System, Chennai
Dr. M. Martin	AIDS Action Executive Director, Washington D.C.
Dr. R.A. Mashelkar	Former Director General and Secretary, Council of Scientific & Industrial Research, New Delhi
Ms. Susan McKinney	Senior Technical Advisor for Immunization, United States Agency for International Development (USAID), Washington, D.C.
Mr. Rajiv Misra	Former Secretary, Health, Ministry of Health and Family Welfare, Government of India, Delhi
Dr. S.N. Misra	Deputy Director, Clinton Foundation, New Delhi
Dr. Michael Montgomery	Division Chief, Office of AIDS, California Department of Health Services, California
Dr. Carlos Morel	Scientific Coordinator, Centre for Technological Development in Health (CDTS), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro
Dr. Peter Mugyenyi	Director, the Joint Center for Clinical Research (JCRC), Kampala
Dr. Pem Namgyal	Medical Officer, Immunization and Vaccine Development, WHO-SEARO, New Delhi
Ms. Angeline Nanni	Director, Vaccine Finance and Supply, GAVI's Pneumococcal ADIP, Baltimore, Maryland
Dr. Abdulsalim Nasidi	Director, Special Projects, Nigerian Federal Ministry of Health, Abuja
Dr. Jean-Marie Okwo-Bele	Director, WHO Department of Immunization, Vaccines and Biologicals, Geneva

TITLE, FIRST, SURNAME	POSITION/AFFILIATION
Dr. Saladin Osmanov	Coordinator, WHO-UNAIDS HIV Vaccine Initiative, Immunizations, Vaccines & Biologicals, WHO, Geneva
Dr. R.K. Pal	National Programme Officer (Hep. B), WHO-India, Delhi
Dr. Samiran Panda	Vice President, Society for Positive Atmosphere and Related Support to HIV/AIDS (SPARSHA), Kolkata
Mr. Manoj Pardesi	President, Network of Maharashtran People Living with HIV&AIDS (NMP+), Mumbai
Dr. George Pariyo	Senior Lecturer and Head of Department, Health Policy, Planning and Management Department, Institute of Public Health, Makerere University, Kampala
Dr. Mrudula Phadke	Vice Chancellor, Director, Medical Education & Research, Mumbai
Dr. Ciro de Quadros	President Emeritus and Director of International Programs, the Sabin Vaccine Institute, Washington, D.C.
Dr. Wiwat Rojanapithayakorn	Team Leader, UNAIDS Asia Pacific Inter-country Team, and HIV/AIDS Team Leader, World Health Organization (WHO), Beijing, China
Lt. Gen. D Raghunath	Principal Executive, Sir Dorabji Tata Centre for Research in Tropical Diseases, Bangalore
Ms. Patricia Atkinson-Roberts	Senior Officer, Commercialization and Corporate Partnerships, Malaria Vaccines Initiative (MVI), Bethesda, Maryland
Mr. Askok Row Kavi	Chairman, The Humsafar Trust, Mumbai
Ms. Supriya Sahu	Joint Secretary, Department of Health and Family Welfare, Government of Tamil Nadu, Chennai
Dr. N.M. Samuel	Professor and Head of Department, Dept. of Experimental Medicine, The Tamil Nadu Dr. M.G. R. Medical University, Chennai
Dr. Sanjay Sawant	Deputy Secretary (Employment), Government of Maharashtra, Mumbai
Mr. Ezio Távora dos Santos Filho	Vice-President, Grupo Pela Vidda/Forum of AIDS-NGOs, Rio de Janeiro
Mr. D.G. Shah	Secretary General, Indian Pharmaceutical Alliance, Mumbai
Mr. Ranjit Shahani	Vice Chairman & Managing Director, Novartis India Limited, Mumbai
Dr. Suneeta Singh	Senior Public Health Specialist, The World Bank, New Delhi
Dr. Suniti Solomon	Director, Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE), Chennai
Dr. Chutima Suraratdecha	Health Policy and Economics Officer, PATH Japanese Encephalitis Project, Seattle, Washington
Dr. Soumya Swaminathan	Deputy Director, Tuberculosis Research Centre, Chennai
Dr. Roberto Tapia-Conyer	Vice-Minister of Health, Mexico, Mexico City And Senior Professor in the School of Medicine of the Universidad Nacional Autonoma of México (UNAM)
Dr. A. Vaidyanathan	Former Director of Madras Institute of Development Studies, Chennai
Dr. Ravi K. Verma	Senior Programme Associate, Horizons/Population Council, New Delhi
Dr. Wabwire- Mangen	Associate Professor of Epidemiology, Institute of Public Health, Makerere University, Kampala
Dr. Neff Walker	Senior Project Officer, Strategic Information Section of UNICEF, New York

TITLE, FIRST, SURNAME	POSITION/AFFILIATION
Dr. Roy Widdus	Project Manager, Initiative Public-Private Partnership Projects Global Health Futures Network, London
Dr. Paul Wilson	Assistant Clinical Professor of Population and Family Health, Mailman School of Public Health, Columbia University, New York
Mr. Peter Young	President and Chief Executive Officer, AlphaVax Inc., North Carolina

APPENDIX II: First-Generation HIV Vaccine Profile Specification

Table A1 describes the lower and upper bounds of vaccine characteristics to describe possible first-generation vaccines. These were developed through informal discussion with scientific experts and were used to guide discussion during the expert consultations.

Table A1. Lower and upper bounds of vaccine profile

PARAMETER	ASSUMPTIONS	VACCINE CHARACTERISTIC	
		LOWER BOUNDS	UPPER BOUNDS
Efficacy & Mechanism of Action	1. Vaccine is imperfect (partially efficacious) 2. Vaccine prevents infection in those vaccinated prior to exposure by a fixed percentage (VE_S) 3.Vaccine also lowers infectiousness after being infected (VE_I) by same magnitude as VE_S 4. Assume VE_S/VE_I effects work differentially in low- and high-risk groups	VE_S/VE_I = 30% efficacy in preventing infection in low-risk groups	VE_S/VE_I = 70% efficacy in preventing infection in low-risk groups
		VE_S/VE_I = 15% in high-risk groups	VE_S/VE_I = 35% in high-risk groups
	5. Vaccine doubles time of disease progression to AIDS after being infected (VE_P).	VE_P = 200%[iv]	
Duration of Protection (and effect on revaccination)	1. Duration of effect would be 2 years or longer 2. Vaccine effect lasts for a certain number of years and doesn't wane before then 3. Revaccination would be required every 2-5 years 4. Assume that for revaccination, only a single dose is required	2-year duration	5-year duration
Price per Dose	1. Based on pricing of a range of old and new existing vaccines 2. Assessed global prices for Hepatitis B vaccine (HBV), new pneumococcal conjugate vaccine, and EPI vaccines 3. No price decline from launch needs to be assumed	$2	$50
Dosing Schedule (including revaccination requirements)	Two dosing schedules hypothesized • 3-dose vaccine represents less favorable dosing profile • 2-dose schedule is viewed as more optimistic of the two scenarios •1-dose revaccination	Prime + 2 boosters 0, 1-, 6-month schedule	Prime + 1 booster 0, 1-year schedule
Clade Specificity	All vaccine profiles considered would be effective against any strain prevalent in any country	Complete and uniform cross-clade protection for all countries and populations	
Safety	No serious adverse effects (SAEs)	Similar to a placebo	
Delivery/ Storage Requirements and Delivery Costs	Single vial cold chain of 2-8ºC	US$1 per full vaccition course (McGreevey 2004)	US$6 per full vaccination course (McGreevey 2004)

[iv] During the consultation interviews, it because clear that many respondents found it difficult to appreciate the different mechanisms of vaccine effect (VE_I, VE_S, and VE_P); thus, disease-modifying effects (VE_P) were removed and are not considered within these analyses.

APPENDIX III. Country Profile Descriptor Information and Assumptions

CRITERION	PROXIES	SOURCE(S)	ASSUMPTIONS AND/OR CUT-OFFS (HIGH/MEDIUM/LOW)
Demography	N/A	CIA World Factbook (CIA n.d.), UN Population Division World Population Prospects (Population Division n.d.); Sexually Transmitted Infections Supplement on the Data, Methods, & Tools Used to Produce the 2005 UNAIDS / WHO HIV/AIDS estimate (Vandepitte 2006, Aceijas 2004, Caceres 2006).	Assumes a compound annual growth rate (CAGR) of 1.5% per annum to calculate population magnitudes in 2015. As current scientific opinion assumes that preventive HIV vaccines would be administered to uninfected individuals, the starting population constitutes those whose HIV status has been confirmed as HIV-negative. However, pre-vaccination HIV testing is likely to be logistically difficult and expensive. Therefore, the starting population in the model is derived from the total population, irrespective of HIV status (CIA n.d.).
Need	Prevalence per capita	UNAIDS-WHO: 2006 Report on the Global AIDS Epidemic (UNAIDS 2006).	Assumes a flat CAGR for rate in 2015 • High: >5% • Medium: between 1%-5% • Low: between 0.2%-1% • Very Low: ≤ 0.2%
Political Will	AIDS Program Effort Index (API)	UNAIDS- USAID-WHO-POLICY Project; 2003 (USAID 2003).	Scores vary between 0 and 100. • High: API 67 • Medium: API 55 - 66 • Low: API 54
Capacity and Ability to Pay	National Income per capita - PPP adjusted	World Bank data (World Bank n.d.)	Assumes a CAGR of 6.9% per annum for rate in 2015. Based on World Bank cut-offs for 2005 in USD: • High: $10,066 • Medium: $826-10,065 • Low: $825

CRITERION	PROXIES	SOURCE(S)	ASSUMPTIONS AND/OR CUT-OFFS (HIGH/MEDIUM/LOW)
Projected government funding on health care budget & predicted allocation to HIV/AIDS and HIV vaccine	National Income	World Bank data (World Bank n.d.)	**Assumes:** • 6.9% Gross Domestic Product (GDP) growth per annum • 1.19% of GDP spent on health • 1% of health budget spent on HIV/AIDS • Maximum of 25% of HIV/AIDS budget spent on HIV vaccine • Based on government attitudes toward the vaccine profile, some proportion of the HIV vaccine funding "pot" is actually spent on vaccine. On the basis of the vaccine profiles described in Table 2 above: o Low Profile =15% of funds o Medium Profile = 50% of funds o High Profile = 73% of funds spent on HIV vaccine
Projected donor funding allocation to HIV vaccines	The Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM)		**Assumes:** • Only GAVI-eligible countries[v] would receive international donor support. • All international donor support would be committed by the GFATM alone. • GFATM funds follow the same growth trajectory as for 2006-2007. •This is differs from the actual growth projections of the Global Fund from 2010 onwards, which currently assume that there is no growth in new program approvals; i.e. 'flat' funding growth from 2010 on wards (Global Fund 2007). • Maximum of 25% of the GFATM donor funding for each country would be spent on an HIV vaccine. • Based on donor attitudes toward the vaccine profile, some proportion of the GFATM HIV vaccine funding "pot" is spent on vaccine. On the basis of the vaccine profiles described in Table 2 above: o Low Profile =15% of funds o Medium Profile = 50% of funds o High Profile = 73% of funds spent on HIV vaccine

[v] i.e., those countries with a GNI per capita of less than $1000

APPENDIX IV. Algorithms to Define Endogenous Country-Level Behavioral Parameters

Tables A2-A5 describe how the model transforms the Country Profile Descriptors to define the Country Behavioral Parameters for the minimum acceptable thresholds of efficacy and duration of protection and maximum acceptable level of price for government adoption of an HIV vaccine.

Table A2: Efficacy: Adoption threshold matrix for high-risk program

POLITICAL WILL (API SCORE)		PREVALENCE (%)			
		VERY LOW	LOW	MEDIUM	HIGH
		<0.20%	0.20 - 0.99%	1.00 - 4.99%	>5.00%
LOW	≤ 54	50%	50%	50%	50%
MEDIUM	55 - 66	50%	50%	30%	30%
HIGH	≥ 67	50%	50%	30%	30%

Table A3: Efficacy: Adoption threshold matrix for general program

POLITICAL WILL (API SCORE)		PREVALENCE (%)			
		VERY LOW	LOW	MEDIUM	HIGH
		<0.20%	0.20 - 0.99%	1.00 - 4.99%	>5.00%
LOW	≤ 54	90%	80%	70%	50%
MEDIUM	55 - 66	80%	70%	50%	50%
HIGH	≥ 67	70%	50%	50%	30%

Table A4: Duration of Protection: Adoption threshold matrix

POLITICAL WILL (API SCORE)		PREVALENCE (%)			
		VERY LOW	LOW	MEDIUM	HIGH
		<0.20%	0.20 - 0.99%	1.00 - 4.99%	>5.00%
LOW	≤ 54	5 yrs	3 yrs	3 yrs	3 yrs
MEDIUM	55 - 66	3 yrs	3 yrs	2 yrs	1 yrs
HIGH	≥ 67	3 yrs	2 yrs	1 yrs	1 yrs

Table A5: Price: Adoption threshold matrix

INCOME (PPP-ADJUSTED GNI/CAPITA)		PREVALENCE (%)			
		VERY LOW	LOW	MEDIUM	HIGH
		<0.20%	0.20 - 0.99%	1.00 - 4.99%	>5.00%
LOW	≤$825	$1	$2	$10	$10
MEDIUM	$826-10,065	$2	$10	$10	$10
HIGH	≥ $10,066	$50	$50	$50	$50

Table A6 describes how the model transforms the Descriptors (in this case, need [prevalence] and political will [API score]) to define the regulatory lag by country.

Table A6: Regulatory/Licensure Lag matrix

POLITICAL WILL (API SCORE)		PREVALENCE (%)			
		VERY LOW	LOW	MEDIUM	HIGH
		<0.20%	0.20 - 0.99%	1.00 - 4.99%	>5.00%
LOW	≤ 54	5 years	5 years	4 years	3 years
MEDIUM	55 - 66	4 years	3 years	2 years	1 years
HIGH	≥ 67	4 years	2 years	1 years	1 years

Tables A7-A9 describe the calculation process for determination of the High-Risk Program Implementation Lag.

The model takes a composite score, derived by adding values for levels of political will (API), need (prevalence), and income (GNI/capita):

Table A7: API - Prevalence - GNI scores

API SCORE	VALUE	PREVALENCE	VALUE	GNI/CAPITA	VALUE
Low	1	Very Low	1	Low	1
		Low	2		
Medium	2	Medium	3	Medium	2
High	3	High	4	High	3

This composite score informs an intermediate lag value.

Table A8: Intermediate High-Risk Program Implementation Lag Value

COMPOSITE SCORE	INTERMEDIATE LAG VALUE #1
1	6 years
2	6 years
3	6 years
4	5 years
5	4 years
6	3 years
7	2 years
8	1 years
9	1 years
10	1 years

A second intermediate lag value is derived from the year of hepatitis B vaccine adoption.

Table A9: Hepatitis B adoption

YEAR OF ADOPTION	INTERMEDIATE LAG VALUE #2
1900	0 years
1997	1 year
2003	2 years

The summation of these two intermediate lag values (Value #1 + Value #2) provides the high-risk program lag.

Table A10 describes the Low-Risk Program Implementation Lag calculation.

A third intermediate lag value is derived from the API, prevalence, and GNI values only (listed above) and used to inform the low-risk program lag.

Table A10. Intermediate Low-Risk Program Implementation Lag Value.

COMPOSITE SCORE	INTERMEDIATE LAG VALUE #3
1	3 years
2	2 years
3	1 years

The low-risk program lag is the sum of the intermediate lag value #3 and the high-risk lag (described above).

Table A11. describes how the model transforms the Descriptors (in this case, need [prevalence] and political will [API score]) to define the upper age limit of the low-risk target group.

Table A11. Upper Age Limit of Low-Risk Target Group matrix

POLITICAL WILL (API SCORE)		PREVALENCE (%)			
		VERY LOW	LOW	MEDIUM	HIGH
		<0.20%	0.20 - 0.99%	1.00 - 4.99%	>5.00%
LOW	≤ 54	26 years	26 years	49 years	49 years
MEDIUM	55 - 66	26 years	26 years	49 years	49 years
HIGH	≥ 67	26 years	26 years	49 years	49 years

APPENDIX V. Improved Policy Scenerio Specifications

POLICY CHANGES	MODEL SPECIFICATION[vi]
Expedition regulatory approval	Reduce regulatory lag in public and private markets by 1 year in the 20 countries with the highest burden of HIV/AIDS (as measured by absolute prevalence).
Increased coverage and funding	Increase the proportion of government funding available for an HIV vaccine from 25% to 50% of the national HIV/AIDS budget; and increase maximum coverage rate across all public programs by 20% -- in the 20 countries with the highest burden of HIV/AIDS.
Expedited public vaccination programme introduction and improved will	Decrease the time to introduce public vaccination programmes following national regulatory approval (i.e. reduce implementation lag) by 1 year in both the programs targeting populations at higher and lower risk of exposure to HIV; and increase political will classification from 'medium' to 'high'. (changing the API score, a proxy for political will from 57 to 67) -- in the 20 countries with the highest burden of HIV/AIDS.
Combined policy changes	All of the above modifications.

[vi] Only specific variables where different from Baseline values

GLOSSARY

TERM	DEFINITION/EXPLANATION
Adoption lag	The time between licensure of the vaccine by the FDA or EMEA and licensure in a country outside the jurisdiction of these regulatory agencies.
Behavioral disinhibition	When vaccinated individuals believe they are protected from HIV infection and therefore engage in behaviors that put them at greater risk of exposure to HIV.
Catch-up vaccination strategy	A vaccination strategy aiming to vaccinate those missed or not eligible for a *routine vaccination*. A catch-up strategy targets any residual population outside of the routine recipient population(s).
Determinants of demand	Enabling factors and constraints that facilitate or limit demand.
First-generation preventive HIV vaccines	The first set of preventive HIV vaccines that are licensed for use.
High-risk vaccination program	Public vaccination programs implemented to target (vaccinate) populations at greater risk of exposure to HIV.
Implementation lag	The time between licensure of a vaccine and commencement of a public vaccination program.
Long-term stable demand	The level of total annual doses or courses of a vaccine at which demand is stable (i.e., when there is no significant change from year to year in levels of demand).
Loss to follow-up	The proportion of those vaccinated who do not return for a needed revaccination.
Low-risk vaccination program	Public vaccination programs targeting certain populations at lower risk of vaccination program exposure to HIV.
Public vaccination program	Vaccination programs targeting certain populations at lower risk of exposure to HIV.
Peak yearof demand	The year during the forecasting period when demand reaches its highest level.
People fully vaccinated	The total number of people who receive a complete course of the HIV vaccine within a given period. This is equivalent to the total number of courses (not doses) received.
Political will	The level of policymaker support for public policy initiatives.
Private market	The market for a vaccine that is not funded or subsidized by public funds and not implemented as a public health program. In this analysis, the private market represents individual demand from those willing and able to pay for the vaccine and also willing to be vaccinated.
Program implementation lag	See “Implementation lag”.
Public market implementation lag	Vaccine demand or utilization funded by the public sector.

TERM	DEFINITION/EXPLANATION
Regulatory lag	See "Adoption lag."
Revaccination strategy	The vaccination strategy employed to maintain protection when a vaccine with a limited duration is used.
Routine vaccination strategy	The vaccination strategy employed to vaccinate new entrants to certain sub-populations as part of an annual program. The routine vaccination strategy may vary in approach depending on the sub-population (e.g., school-based vaccination or adolescent programs, harm reduction programs for IDUs, or outreach/condom promotion programs for sex workers).
Targeting	The selection of specific population groups for vaccination based on such criteria as risk of exposure, age, etc.
Vaccine profile	The key vaccine characteristics that describe the vaccine, including efficacy, duration of protection, price per dose, dosing regime, and clade-specificity.
Wastage factor	The amount of vaccines lost due to inefficiencies in storage, transport, or usage (e.g., poor cold chain system, faulty syringes, etc.).

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IAVI—East Africa
PO Box 340 KNH
Nairobi, 00202
Kenya

IAVI—Europe
Herengracht 208
1016 BS Amsterdam
The Netherlands

IAVI—Headquarters
110 William Street, Floor 27
New York, NY 10038-3901
USA

IAVI—India
193 Floor 1, Jorbagh
New Delhi, 110003
India

IAVI—Southern Africa
Postnet Suite 099
Private Bag X11
Craighall 2024
South Africa